Retrospective studies in mesenchymal tumours:

clinical implications for the future

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Introduction

Cancer is one of the leading causes of death in the world. In The Netherlands, the incidence in 2016 was approximately 650 patients/100.000 inhabitants/year.[1] Most of these incident cases are carcinomas, *i.e.* cancers originating from the epithelial layers of the body. In contrast, sarcomas, *i.e.* cancers originating from the mesenchyme, are very rare. The mesenchyme is the embryonal layer giving rise to amongst others connective tissue, fat, muscles, synovium and bones. These tumours account for approximately 1-2% of all cancers (6 patients/100.000 inhabitants/year).[1] These sarcomas are split up in more than 50 histological entities.[2] Besides the malignant tumours of the mesenchyme, the sarcomas, there are also several so-called intermediate, locally aggressive or rarely metastasizing, mesenchymal tumours.[2] Prospective studies are difficult because the number of sarcoma patients is too low to study the different subtypes. Moreover, randomized phase III trials in all soft tissue sarcoma patients together need to be multicentre, and multinational, taking several years to complete. Therefore, it is important that the available data of historical patients is used to generate hypotheses that can be tested in these prospective studies. In this thesis, results from retrospective studies on various aspects of these tumours are reported with the objective of improving daily sarcoma patient care and generating hypotheses and background data for future studies.

Mesenchymal tumours

Before elaborating on the outline of this thesis, a short summary of the different mesenchymal tumours is important. The earlier cited WHO classification of Bone and Soft Tissue Tumours defines the different mesenchymal tumours and divides them in benign, intermediate and malignant.[2] The intermediate group is further subdivided in locally aggressive tumours and rarely metastasizing tumours, i.e. metastasizing in less than 2 percent of patients.

Benign tumours

The most common category are the benign tumours. Tumours in this category are for example lipomas, fibromas, elastofibromas, localized type tenosynovial giant cell tumours and leiomyomas. In general, these tumours only need treatment in case of complaints or diagnostic uncertainty (differential diagnosis of a malignant tumour). The combination of radiology and pathology can often make the distinction between benign and malignant tumours and so, resection is not always necessary.

Intermediate category; locally aggressive and rarely metastasizing tumours

Locally aggressive tumours are for example desmoid-type fibromatosis and atypical lipomatous tumour/well-differentiated liposarcoma. These tumours do not metastasize, but have a clinical behaviour resulting in compression of surrounding organs or local

invasion of other structures and they thereby disturb normal anatomy. Treatment is often necessary to prevent or diminish symptoms caused by these tumours.

Rarely metastasizing tumours have the potential to metastasize, but do this rarely (<2%). However, the risk of metastases might be one of the reasons to opt for resection of these tumours. An example of such a tumour is Kaposi sarcoma.

Tumours can also have characteristics of both categories, e.g. giant cell tumour of bone (GCT-B).

Below, this introduction will elaborate on both desmoid-type fibromatosis and giant cell tumour of bone belonging to this category.

Malignant tumours

The last category of mesenchymal tumours are the overt malignant tumours, which are called sarcomas. These tumours do metastasize and need surgical resection, often combined with radiotherapy to get local control. Radiotherapy can be used either neo-adjuvant or adjuvant and both have their risks and benefits. In case of locally advanced disease or distant metastatic disease, the goal of treatment is prolongation of survival and palliation, in which case chemotherapy is a possibility as treatment. However, in case of oligometastatic disease, the goal of treatment can still be curative. In this situation, the treatment often consists of more than one modality and more than once surgery.

Specific tumours

After this short introduction of the different groups of mesenchymal tumours regarding biologic behaviour, the current diagnostics and treatment of the main tumours studied in this thesis will be discussed, *i.e.* desmoid-type fibromatosis, gastro-intestinal stromal cell tumours, the complete variation of soft tissue sarcomas, giant cell tumours of bone and osteosarcomas.

Soft tissue tumours

Desmoid-type fibromatosis

Desmoid-type fibromatosis are rare, locally aggressive, tumours. In the Netherlands, the incidence was 5.36 patients per million inhabitants per year in 2013.[3] The peak age of patients is between 30-40 years of age.[3,4] Clinical behaviour varies between spontaneous regression, long time stable disease and rapid progression.[5] Although death due to progression of desmoid-type fibromatosis is rare, it can be a very debilitating disease. As it can be localised intraabdominal, in the chest and abdominal wall and in the extremities, complaints vary according to localisation. If localised

intraabdominal, the disease can result in obstructive symptoms of intraabdominal organs such as the intestine, resulting in an ileus, and of the bile ducts resulting in cholestasis. When localised in the abdominal or chest wall and in the extremities, it can result in pain, cosmetic complaints and impairment of mobility. So, although not full blown malignant, it can have a big impact on quality of life.

Histologically, tumours consist of spindle cells with nuclear expression of β-catenin. Genetically these tumours harbour either a somatic *CTNNB1* mutation (either T41A, S45F or S45P) or a germline APC mutation.[6,7] These mutations are mutually exclusive. In case of an *APC* (adenomatous polyposis coli) mutation, patients often have a full blown familial adenomatous polyposis (FAP) syndrome with a colon full of adenomatous polyps and a high risk of developing colorectal cancer. The combination of FAP and desmoid-type fibromatosis is also called Gardner syndrome. The *CTNNB1* mutation is predictive of the clinical behaviour to some extent, with the S45F mutation having a more aggressive behaviour.[6,7]

Treatment of desmoid-type fibromatosis was long dominated by surgery, with complete removal of the tumour as goal of therapy. Due to the unpredictable behaviour sometimes resulting in spontaneous complete regression, currently patients are followed up to see the natural behaviour of the tumour.[8,9] Although surgery can cure patients, there is always a risk of disease recurrence. Although there is a suggestion that microscopically positive resection margins are associated with local recurrence, this finding is not consistent.[10–13] The *CTNNB1* S45F mutation is associated with an increased risk of recurrence after surgery.[6,7,14–16] Other treatment options are radiotherapy and systemic treatment with selective oestrogen receptor modulators, non-steroidal anti-inflammatory drugs (NSAID), tyrosine kinase inhibitors (TKI), chemotherapy or a combination of these.[8] Radiotherapy was studied in a study by Keus *et al.,* showing that radiotherapy has a local control rate of 81.5%, but has also adverse events, such as skin fibrosis and impaired wound healing.[17] The evidence for systemic treatment is based on case reports, case series and single arm phase II studies, which is in this disease a problematic design because of the unpredictable natural behaviour of these tumours. Recently, for the first time a randomised phase III trial was published, reporting an increased 2-year progression-free rate for patients treated with sorafenib 400mg once daily versus placebo (81% vs. 36%).[18]

Gastro-intestinal stromal cell tumour

Gastro-intestinal stromal cell tumours (GISTs) are the most common mesenchymal tumours of the gastro-intestinal tract.[19] The incidence of GIST has been estimated to be between 7.8 and 21.1/million inhabitants per year.[20–26] These tumours occur throughout the whole gastrointestinal tract, but most of them are located in the stomach.

When GISTs are small, they often are asymptomatic and it is also a frequent finding during surgery for other indications. Symptoms of GISTs can be bleeding and obstruction.

Microscopically, GISTs are tumours consisting of spindle or epithelioid cells. Immunohistochemistry is often positive for CD117 and/or DOG-1 (discovered-on-GIST-1).[27-31] As most of the GISTs harbour a *KIT* or *PDGFRα* (platelet-derived growth factor receptor alpha) mutation, mutational analysis can also help to confirm the diagnosis of GIST in immunohistochemical CD117 negative cases.[27] It is possible to predict clinical behaviour based on primary localisation, tumour size, mitotic index and tumour rupture.[27] Different risk classification systems exist, but they all use these same parameters. In 2002 the first risk classifications were developed by Fletcher *et al.* and another was developed at the same time by Miettinen *et al.*[32,33] Thereafter, risk classifications were published by Miettinen, Joensuu and Gold.[34-36] These classifications predict the chance of development of metastases and are mainly used for the indication of adjuvant imatinib, the most effective tyrosine kinase inhibitor (TKI) used in GIST treatment. The response to imatinib and progression-free survival depend on mutational status.[37,38] Mutations in *KIT* are most frequent (80%), followed by *PDGFRα* (7.5%).[31,39] Other GISTs are associated with succinate dehydrogenase complex deficiency or neurofibromatosis type 1. [28,40-43]

Primary treatment consists of surgery with in case of a high risk of recurrence adjuvant treatment with imatinib.[27] Both the 5-year recurrence free survival (65.6% vs. 47.9%) and 5-year overall survival (92.0% vs 81.7%) are higher in patients treated with 3 years of adjuvant imatinib compared with 1 year of adjuvant imatinib.[44] In patients with locally advanced disease, imatinib can be used as induction treatment.[45] If unresectable, treatment with imatinib improves the overall survival of these patients with a 2-year progression-free survival of 44% for imatinib 1dd 400 mg.[27,46-48] Second-line palliative treatment consists of sunitinib with a time to progression of 27.3 weeks with sunitinib (50 mg/day 4 weeks and 2 weeks off) versus 6.4 weeks with placebo.[49] In another study a continuous schedule of 37.5 mg/day was shown to be active.[50] Third, and currently last, line treatment for GIST is regorafenib with a progression-free survival of 4.8 months when treated with regorafenib 160mg daily 3 out of every 4 weeks versus 0.9 months with placebo.[51]

Soft tissue sarcomas

Multiple studies in this thesis consider the systemic treatment of soft tissue sarcoma. As already mentioned, soft tissue sarcomas comprise approximately 1-2% of all patients with cancer. It is a broad spectrum of tumours comprising amongst others liposarcoma, synovial sarcoma, leiomyosarcoma and malignant peripheral nerve sheath tumours. All these tumours have a different clinical behaviour and differ in their tendency to give distant metastases, risk of local recurrence, response to radiotherapy and to systemic

treatment. However, because of the rarity of these tumours, the different histologic subtypes are often studied within one trial without stratification by histology.

Primary treatment, if possible, is complete surgical resection. Based on risk factors for local recurrence, such as high grade, origin deep to the fascia, probability of incomplete resection and/or other high risk features, neo-adjuvant or adjuvant radiotherapy is considered.[52] The benefit of neo-adjuvant radiotherapy is the lower dose of radiotherapy and the smaller volume of healthy tissue irradiated, but with adjuvant treatment the indication is more clear.[53,54] Neo-adjuvant or adjuvant treatment with chemotherapy is still under debate because some studies suggest benefit of systemic treatment to prolong overall survival while others do not.[55-59]

If distant metastases occur, first line treatment consists of doxorubicin monotherapy or doxorubicin/ifosfamide.[52] In Europe, doxorubicin monotherapy is standard of care and combination therapy is used if rapid response is essential in case of induction chemotherapy or when complaints exist.[52] In the EORTC (European Organisation for Research and Treatment of Cancer) 62012 trial, overall survival in patients treated with doxorubicin monotherapy was 12.8 months and with doxorubicin/ifosfamide was 14.3 (difference not significant).[60] More recently studies comparing doxorubicin with gemcitabine/docetaxel showed improved overall survival data with 17.6 months for doxorubicin and 15.5 months with gemcitabine/docetaxel.[61] Moreover, in SARC021 the median overall survival was 18.4 months with doxorubicin/evofosfamide versus 19.0 months with doxorubicin monotherapy.[62] Second line treatment can be ifosfamide monotherapy, gemcitabine/docetaxel, trabectedin for leiomyosarcomas and liposarcomas, eribulin for liposarcomas and pazopanib for all soft tissue sarcomas except liposarcomas.[63-69]

As already mentioned, most of these studies in soft tissue sarcoma do not differentiate between the different histologic subtypes or different disease stages. This hampers the development of histotype tailored treatment. Some progress was made over the last decades, e.g. GIST and dermatofibrosarcoma protuberans (DFSP), previously included in these general studies, were found to be responsive to imatinib.[46,47,70,71] Due to the low number of patients, no distinction is made in these studies between different disease stages (such as locally advanced tumours and distant metastatic disease). Also, other prognostic factors cannot be accounted for.

To improve overall survival of patients with metastatic soft tissue sarcoma several strategies are evaluated. First, new drugs are tested, for example olaratumab, a PDGFRa antibody. The results of this study were recently shown to be negative.[72] Second, new combinations are considered. Last, maintenance treatment would be an option to improve both overall and progression-free survival. To design such trials of maintenance

therapy, data on overall and progression-free survival after the completion of doxorubicin therapy would support the development of adequate trials.

Pazopanib is one of the drugs used in later line treatment of metastatic soft tissue sarcoma. It has no significant improvement in overall survival (pazopanib 12.5 months versus placebo 10.7 months), but showed a significant improvement in progression-free survival (4.6 months versus 1.6 months) in the phase III PALETTE study.[65] The benefit of pazopanib is that it is an oral drug, which can be used at home. The side effects of pazopanib are, amongst others, diarrhoea, liver function abnormalities, fatigue, nausea and hypertension.[65] Liver function abnormalities are a common reason for decreasing the dose of pazopanib and discontinuation of pazopanib treatment. The incidence of a grade ≥2 elevated alanine aminotransferase (ALAT) was 10% (placebo 3%) and aspartate aminotransferase (ASAT) was 8% (placebo 2%) in the PALETTE study.[65] The addition of prednisolone to pazopanib treatment could be a way to continue pazopanib in the presence of pazopanib induced liver injury.[73]

Bone tumours

In the second part of this thesis we focus on tumours that arise primarily in bone. Also, in this type of tumours benign, intermediate and malignant tumours exist. The, in this thesis studied, giant cell tumour of bone is an example of a locally aggressive, rarely metastasizing tumour. On the other hand, osteosarcoma is an example of a high-grade malignant bone tumour. Other examples of malignant bone tumours are Ewing sarcoma and chondrosarcoma. These last two tumours were not studied in this thesis.

Giant cell tumour of bone

Giant Cell Tumours of Bone (GCT-B) are locally aggressive, rarely metastasizing tumours. GCT-B are composed of large osteoclast-like giant cells and sheets of mononuclear cells. These tumours primarily affect the metaphysis of long bones.[74] The expression of the receptor of nuclear factor kappa-B ligand (RANKL) is one of the import pathophysiologic mechanisms of this disease.[75,76] The incidence of GCT-B is currently not exactly known, but these tumours are extremely rare. Approximately 5% of all bone tumours are GCT-B and the incidence is estimated between 1.03-1.33 per million per year based on doctor-driven registries.[74,77,78] It affects patients in all age groups but the median age ranges between 20 and 40 years of age, with an equal distribution between the sexes or a slight female predominance.[74,77,78]

Typical symptoms are pain, swelling, often decreased joint movement and sometimes a pathological fracture.[74,79] It is known to be locally aggressive and rarely metastasizes.[74] Treatment of GCT-B can consist of curettage, curettage with an adjuvant treatment or resection with joint replacement.[80] As surgical treatment can be mutilating, it often results in loss of quality of life. In GCT-B local recurrence rate is 6-42%.[79,81] Recently

denosumab, a human IgG2 monoclonal antibody against RANKL, was registered for use in GCT-B and showed tumour response in two phase II studies.[82,83]

Osteosarcoma

The last tumour discussed in this thesis is osteosarcoma. It is the most common, but still rare, primary bone malignancy. The age of osteosarcoma patients has a bimodal distribution with adolescents and patients of advanced age being affected. Osteosarcoma can arise at any site, but most tumours develop in the long bones with the distal femur (30%), proximal tibia (15%) and proximal humerus (15%) as most common sites.[84] Osteosarcoma has several subtypes, *i.e.* conventional, teleangiectatic, chondroblastic and small cell.[2]

The intent of treatment in case of local disease or local disease with pulmonary metastases consists of chemotherapy and surgery. The 3-year event free survival is approximately 60-70%.[85-88] The first line chemotherapy in most of the Western world consists of methotrexate, doxorubicin and cisplatin. Although studies in this rare disease are difficult, the EURAMOS study tried to improve cure rate in high risk patients by the addition of ifosfamide and etoposide to the perioperative regimen of methotrexate, doxorubicin and cisplatin.[89] However, this study failed to reach its primary endpoint, but resulted in a higher rate of adverse events.[89] Currently, approximately 40% of all osteosarcoma patients develop local recurrence or distant metastatic disease after first line treatment. In this situation cure is still possible, when the recurrence and/or metastases are still limited and surgery is possible.[90,91]

When the intent of treatment is no longer cure, different chemotherapeutic regimens can be considered, but which to use is not well defined. Regimens consisting of e.g. ifosfamide, etoposide, ifosfamide/etoposide and gemcitabine/docetaxel were reported, but in small, single arm, studies.[92-98] None of these studies were randomized. Ifosfamide/etoposide was tested in first line and had a response rate of 48-59%.[92,93] Response rates for gemcitabine/docetaxel and for etoposide ranged between 12.5% and 17%.[94,95] Progression-free survival (PFS) for gemcitabine/docetaxel was 3.5 months.[95] Ifosfamide as second line treatment was studied in several small studies (between 6 and 19 patients per study) studying varying ifosfamide doses, ranging from 5 g/m^2 in one day to a total of 14 g/m^2 continuously over 7 days.[96-99] None of these studies reported the overall survival (OS) and/or PFS. Overall response rates varied between 24% and 44%.

During the years, several studies were done with in the end ineffective drugs. These studies can be used to determine a reference standard to compare new drugs with. A retrospective analysis of 7 Children's Oncology Group studies, all with inactive drugs (according to the study criteria), by Lagmay *et al.* showed an event free survival (which is usually called PFS) of 12% at 4 months, which can be used as reference for new single arm studies.[100] In a recently published small randomised phase II study, including 43

patients, regorafenib was shown to have an 8 weeks PFS of 65% versus 0% for the placebo group.[101]

Outline of the thesis

This thesis studies several aspects of various mesenchymal tumours and is split in two parts. The first part studies soft tissue tumours and the second part bone tumours.

Soft tissue tumours

In this first part of the thesis, desmoid-type fibromatosis, GIST and soft tissue sarcomas in general are discussed.

As described above, the treatment of desmoid-type fibromatosis has changed during the past years from surgical treatment to non-surgical management, i.e. watchful waiting, radiotherapy and systemic treatment. Although some studies are reported, data of real-world patients treated in first line is scarce. In **chapter 2** the outcome of first line treatment of patients in The Netherlands is reported.

Radiotherapy has proven activity in desmoid-type fibromatosis with a local control rate of 81.5%, but has also adverse effects, such as skin fibrosis and impaired wound healing.[17] Although extremely rare, radiotherapy can also cause the development of a malignancy. In **chapter 3** we studied whether radiotherapy induced sarcomas developing after radiotherapy for desmoid-type fibromatosis developed from the tumour or from the healthy tissue surrounding it.

In 2004 a nationwide survey was performed in the Netherlands to estimate the incidence of GIST in 1995 and 1998 to 2003.[20] In **chapter 4** this study was repeated for the period between 2003 and 2012. Because the diagnosis is well established now, well-known to pathologists and effective treatments exist, the aim of this study was to estimate the current incidence of GIST, incidence of risk categories, frequency of various mutations, immunohistochemical markers and histological subtypes. Also, daily practice of pathology reporting was compared with the current ESMO (European Society for Medical Oncology) guidelines.

Imatinib is first-line treatment in GIST and is in general well tolerated. It is a TKI, which amongst others binds KIT and PDGFRA. The drug is also used in chronic myeloid leukaemia and a frequently described side effect is neutropenia in CML (chronic myeloid leukaemia). The frequency of this side effect is much lower in GIST, but we retrieved 4 patients from 3 reference centres which had a neutropenia due to imatinib treatment for GIST. In **chapter 5** the management of this side effect in GIST patients is described.

The last chapters **(chapters 6-9)** of this first part discuss several studies in soft tissue sarcomas. In **chapter 6** the results of an EORTC database study are reported studying the difference between patients with locally advanced disease, distant metastatic disease or both locally advanced and distant metastatic disease. Differences in overall and progression-free survival, overall response rate and prognostic factors were studied. These results are important for daily practice when considering palliative treatment and for designing studies.

In **chapter 7** the results of a second EORTC database study are reported, in which all patients are studied who completed 6 or more cycles of doxorubicin-based therapy and the overall survival and progression-free survival is calculated. These data are important when designing studies with maintenance therapy after doxorubicin palliative treatment.

Chapter 8 and 9 study two complications of pazopanib treatment. Pazopanib is an oral tyrosine kinase inhibitor used in later line palliative treatment of soft tissue sarcomas. **Chapter 8** is a case report discussing a way to manage liver function abnormalities. Besides, the patient was diagnosed with an endometrial stromal cell sarcoma and showed a remarkable response. In **chapter 9** patients suffering from pneumothorax due to pazopanib treatment are discussed and a possible mechanism for the development of this complication is postulated.

Bone tumours

The incidence of tumours is important for health care planning and the design of studies. As the incidence of giant cell tumours of bone is only based on doctor-driven cancer registries, this incidence was studied in a national pathology database in **chapter 10**.

In the last chapter of this thesis, **chapter 11**, the results of the palliative systemic treatment of osteosarcoma patients with ifosfamide treatment is reported. It is important to know the overall survival, progression-free survival and overall response rate of this treatment when discussing the start of palliative treatment with patients. It also can be used as a reference treatment during development of new drugs.

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PART *I*

Soft tissue tumours

Outcome of non-surgical management of extra-abdominal, trunk and abdominal wall desmoid-type fibromatosis:

a population based study in the Netherlands

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Abstract

Introduction

Non-surgical management of patients with desmoid-type fibromatosis (DF) is increasing. This study tries to provide insight on type, usage and outcome of first-line non-surgical management strategies.

Patients and Methods

From the Dutch Pathology Registry (PALGA) patients with extra-abdominal or trunk/abdominal wall DF, diagnosed between 1993 and 2013, were identified. First-line treatment was analysed. Best response (BR) using RECIST-criteria from start of treatment/surveillance until change of treatment or last follow-up was analysed.

Results

Ninety-one of the 1141 identified patients had first-line non-surgical management. The percentage of patients treated non-surgically increased from 0.6% in 1993-1998 to 12.8% in 2009-2013. Thirty-seven patients had surveillance (41%), 35 radiotherapy (38%) and 19 systemic treatment (21%). BR for surveillance was complete response (CR) in 2/37, partial response (PR) 4/37, stable disease (SD) 21/37, progressive disease (PD) 5/37 and unknown 5/37 patients. BR for radiotherapy was CR in 4/35, PR 11/35, SD 16/35 and unknown 4/35. BR for systemic treatment was CR in 1/19, PR 1/19, SD 10/19, PD 2/19 and unknown 5/19. Totally, 91% of patients did not progress.

Discussion

Given the low percentage (9%) of PD of non-surgical management, these data can be used in shared decision making with the patient regarding optimal treatment.

Introduction

Desmoid-type fibromatosis (DF or aggressive fibromatosis) is an intermediate grade soft tissue tumour that does not metastasize, but can be locally aggressive.[1] For long, surgery has been the primary treatment for resectable tumours, with or without additional radiotherapy. Currently, a more conservative approach is applied based on reports of disease stabilization and spontaneous regression, and on documented progression after surgery as radical resection may be difficult to achieve.[2,3] An epidemiological study conducted in extra-abdominal and trunk/abdominal wall DF patients in the Netherlands reported an increase in the use of non-surgical modalities over the past decade.[4]

A European consensus on the management of DF has recently been published, advocating active surveillance as the initial treatment modality, with systemic treatment, surgery or radiotherapy in case of tumour progression.[5] Despite a trend towards conservative treatment, knowledge on the outcome of different management modalities as first-line treatment is limited.

Studies on radiotherapy have described disease stabilization and tumour regression.[6-8] Literature on systemic treatment is limited, with a variety of treatment regimes, often applied at different stages of disease presentation.[9-18] Active surveillance is currently being investigated in a prospective setting by three different groups; a French group (NCT01801176), an Italian group (NCT02547831) and a Dutch group (NTR4714).[19] Non-surgical management of patients with DF is increasing. Population-based studies are needed to gain insight into the actual implementation of non-surgical treatment in daily practice. This retrospective study provides insight in the application and outcome of all first-line treatment modalities in a nationwide cohort of DF patients during routine clinical care.

Patients and Methods

From the PALGA database, the nationwide network and registry of histo- and cytopathology in the Netherlands, patients diagnosed between 1-1-1993 and 31-12-2013 having extra-abdominal or trunk/abdominal wall DF were identified. The PALGA database contains encoded excerpts of all nationwide pathology examinations obtained by diagnostic procedure, including tissue biopsy or resection since 1971 in selected laboratories and expanded to nationwide inclusion in 1991.[20] Due to incomplete data registration, patients with disease presentation before 1993 were excluded. Excerpts contained standardized information: an encrypted patient identification, date of pathology report, age and gender of the patient, and the conclusion of the pathology reports. Reports were scored as biopsy, resection or re-resection. Patients with diagnostic biopsy of DF, without excision specimens within 6 months of biopsy were selected. Patients with excision specimens within 6 months of biopsy were considered

to have initial surgical treatment. Exclusion criteria were intra-abdominal DF, recurrent disease at presentation, uncertain diagnosis and initial surgical treatment.

Hospitals with more than 10 patients were contacted for information. Data collection was performed in seven tertiary referral centres, as most patients were referred to these centres after diagnosis. In addition to the PALGA database, centre-based registrations were searched for patients. For all selected patients in these seven centres medical records were reviewed. From the excerpts and the medical records, data was collected on age, gender, year of diagnosis, localization, size, nuclear Beta-catenin, *CTNNB1* mutations, *APC* mutations, treatment modalities, date of start of treatment, response to treatment and toxicities. Only the first-line of treatment was documented.

Tumour localization was categorized as: head/neck, trunk (including thoracic wall, breast and back), abdominal wall, extremity or groin. Type of systemic treatment was categorized as: non-steroidal anti-inflammatory drug (NSAID), anti-hormonal (HT), chemotherapy (ChT) or tyrosine kinase inhibitors (TKI).

Reports from all available imaging studies were reviewed. Best response to treatment was classified using RECIST 1.1 as complete response (CR), partial response (PR) in case of $\geq$30% decrease of the largest diameter, stable disease (SD) or progressive disease (PD) in case of $\geq$20% increase of largest diameter based on reported measurements.[21] Date of the start of treatment was defined as the date of visit with the physician in which the treatment modality was initiated or date of start radiotherapy. In most patients, active surveillance was initiated within 3 weeks after diagnosis. Results are shown as best response and time to progression (TTP). TTP was defined as the period from start of treatment to radiological PD as classified by RECIST 1.1. Follow-up period for each treatment was documented as time of start treatment or active surveillance until change of treatment or last documented follow-up visit, whichever came first.

Late toxicity after radiotherapy was retrospectively scored using RTOG-EORTC criteria.[22]

Statistical analysis was performed using IBM SPSS Statistics 21. Continuous variables are shown as median with interquartile range (IQR), and categorical variables as numbers with percentages.

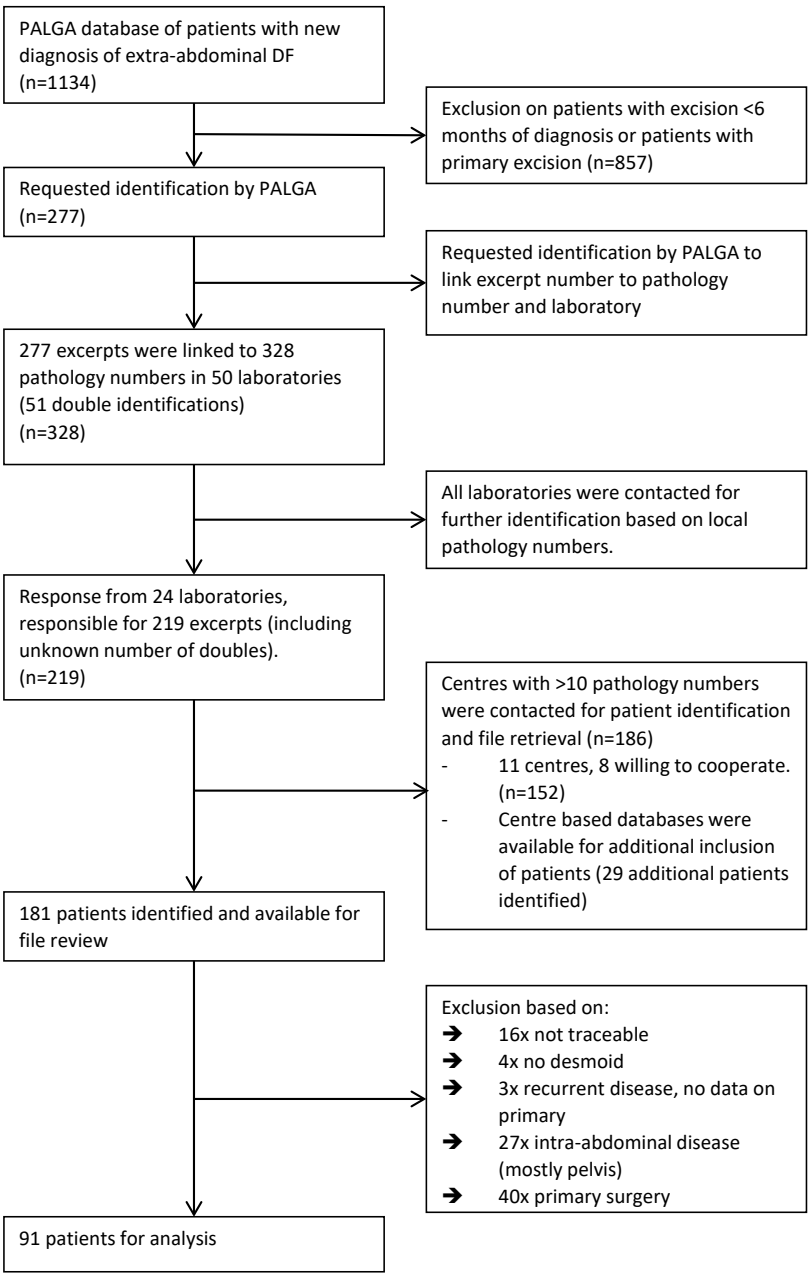

Figure 1. CONSORT diagram of patient selection

Table 1. Baseline characteristics.

	All patients		Active Surveillance		Radiotherapy		Systemic treatment	
	N	%	N	%	N	%	N	%
Gender								
Male	30	33	9	24.3	12	34.3	9	47.4
Female	61	67	28	75.7	23	65.7	10	52.6
Age (years)								
Median (IQR)	39 (33.1-52.2)		36 (31.2-51.6)		43.6 (39.4-52.4)		34.8 (23.3-46.3)	
Localization								
Head/Neck	9	9.9	3	8.1	6	17.1	-	-
Thorax/back	35	38.5	13	35.1	13	37.1	9	47.4
Abdominal wall	25	27.5	17	45.9	1	2.9	7	36.8
Extremity	21	23.1	4	10.8	15	42.9	2	10.5
Other*	1	1.1	-	-	-	-	1	5.3
Size								
<5 cm	25	27.5	16	43.2	7	20.0	2	10.5
5-10 cm	48	52.7	18	48.6	19	54.3	11	57.9
>10 cm	15	16.5	2	5.4	8	22.9	5	26.3
Missing data	3	3.3	1	2.7	1	2.9	1	5.3
Beta-catenin (nuclear)								
Positive	56	61.5	28	75.7	16	45.7	12	63.2
Negative	10	11	3	8.1	6	17.1	1	5.3
Unknown	25	27.5	6	16.2	13	37.1	6	31.6

N=number of patients. Cm=centimetres. IQR = interquartile range. *groin.

Results

The PALGA search covering the period between 1-1-1993 and 31-12-2013, identified 1134 patients with extra-abdominal and trunk/abdominal wall DF. Patients were selected using in- and exclusion criteria (see Figure 1). Of these 1134 patients, 277 fulfilled the inclusion criteria for our study and 181 of these patients were treated in one of the seven hospitals selected for our study. Their files were reviewed for details on tumour characteristics and treatment modalities. After chart review 90 additional patients were excluded, because the chart review revealed additional information not available in the pathology report. Centre-based registrations provided data on additional patients (diagnosed in 2014). In total, 91 patients were included for further analysis based on in- and exclusion criteria. Baseline characteristics are listed in Table 1. Details on beta catenin (*CTNNB1*) and *APC* gene mutation status were reported sporadically. To our knowledge, 6 patients with *APC* gene mutation were included. Due to the scarce data, these factors were not included in further analyses.

Based on initial management patients were divided in 3 groups: active surveillance, radiotherapy and systemic treatment. Outcomes for each group are listed in Table 2. Median follow-up for active surveillance, radiotherapy and systemic treatment was 16 months (IQR 7-31), 44 months (IQR 24-62) and 5 months (IQR 2-12) respectively.

Table 2. Outcome of non-surgical treatment, using best response according to RECIST

	CR		PR		SD		PD		Unknown		Total
	N	%	N	%	N	%	N	%	N	%	N
Active surveillance	2	5.4%	4	10.8%	21	56.8%	5	13.5%	5	13.5%	37
Radiotherapy	4	11.4%	11	31.4%	16	45.7%	0	0%	4	11.4%	35
Systemic treatment	1	5.3%	1	5.3%	10	52.6%	2	10.5%	5	26.3%	19

N=number of patients. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease.

There is a clear increase in the use of non-surgical management over the years, from 0.6% in 1993 -1998 up to 12.8% in 2009-2013 (Table 3). Table 3 also presents data of 7 additional patients diagnosed in 2014, which were found during chart review.

Table 3. First-line non-surgical treatment per 5 year time period.

	1993-1998	1999 - 2003	2004 - 2008	2009 - 2013	2014	Total
	N	N	N	N	N	N
PALGA registration[4]	180	185	331	438		1134
First-line treatment	1	5	22	56	7	91
Stratified treatment						
Active surveillance	0	0	5	26	6	37
Radiotherapy	0	1	13	20	1	35
Systemic treatment	1	4	4	10	0	19
Percentage*	0.6 %	2.7%	6.6%	12.8%		8.0%

N=number of patients. * Percentage of non-surgical treatment compared to overall diagnoses as documented in the PALGA registration

Active surveillance

Thirty-seven patients had active surveillance after diagnosis. Tumour localization was as follows: 3 patients with head/neck tumours, 13 patients with truncal tumours, 17 patients with abdominal wall tumours and 4 patients with extremity tumours.

Best response during that period was spontaneous CR for 2 patients (5%), PR for 4 patients (11%), SD for 21 patients (57%) and PD for 5 patients (14%). For 5 patients, images required for RECIST were not available. CR was documented after 12 and 17 months, PR after 5, 10, 12 and 36 months. During the follow-up period, 13 patients had progressive disease with a median TTP of 7.3 months (IQR 4.1 – 11.9). In total, 22 patients (63%) were still under active surveillance at the date of last follow-up after a median of 16 months, including all patients with CR or PR (median duration of active surveillance for patients with CR and PR was 22 months, IQR 13-46). Of the 21 patients with SD as best outcome, 3 ended active surveillance due to complaints related to the tumour without actual progression and 5 patients ended due to progression (<20%). Thirteen patients with SD continued active surveillance till end of follow-up. Of the 5 patients with PD, 1 patient continued active surveillance. Two patients with unknown outcome continued active surveillance till end of follow-up.

Radiotherapy

Initial treatment was radiotherapy for 35 patients. Tumour localization was categorized as follows: 6 patients with head/neck tumours, 13 patients with truncal tumours, 1 patient with abdominal wall tumour and 15 patients with extremity tumours.

Most patients (n=34) received 56 Gy in 28 fractions of 2 Gy or 25 fractions of 2 Gy and 2 fractions with 3 Gy. One patient with a tumour on the head/neck received 54 Gy over 30 sessions of 1.8 Gy.

Ten patients had no toxicity, 11 patients had grade 1 (mild joint stiffness, slight atrophy, pigmentation change), 10 patients had grade 2 (patch atrophy, moderate fibrosis, moderate joint stiffness) and one patient had grade 3 toxicity (severe joint stiffness). Of three patients insufficient data were available.

Best response to radiotherapy was CR in 4 patients (11%), PR in 11 patients (31%) and SD in 16 patients (46%). For 4 patients, no images were available to determine outcome according to RECIST. CR was documented after 12, 17, 26 and 29 months, PR after median 15.5 months (range 4-56 months). During follow-up, 2 patients developed PD with TTP of 31 and 47 months.

Systemic treatment

Nineteen patients received initial systemic treatment. This consisted of non-steroid anti-inflammatory drugs (NSAID) in 10 patients, anti-hormonal therapy (HT) in 5 patients, chemotherapy (ChT) in 1 patient, a tyrosine kinase inhibitor (TKI) in 1 patient and a combination of HT and TKI in 1 patient. Details were missing for 1 patient.

Tumour localization was categorized as follows: thoracic/back in 9 patients, abdominal wall in 7 patients, extremity in 2 patients and groin in 1 patient.

Best response during initial systemic treatment was CR for 1 patient (5%), PR for 1 patient (5%), SD for 10 patients (53%), PD for 2 patients (11%) and unknown for 5 patients (26%). CR was documented after 12 months, PR after 24 months. The female patient with CR received HT. The patient with PR received an NSAID. The 10 patients with SD were on NSAIDs (n=7), HT (n=2) and TKI (n=1). PD was seen after an NSAID (n=1) and ChT (n=1). During follow-up, 3 patients developed PD with TTP of 6.3, 7.1 and 7.2 months.

After initial systemic treatment, multiple systemic treatments were given to 10 patients in different regimens. Seven patients received 2 treatment regimens and three patients received a total of 4 treatment regimens.

Discussion

The change in treatment strategies from initial surgery with or without radiotherapy to initial non-surgical management has been fuelled by several studies and increasing expertise about this disease with its unpredictable behaviour. The level of evidence is limited by the rarity of this disease. The Dutch cohort represents a unique and large group of patients with data on real life practice. Within this group, analyses show that a

25% response rate and 52% stable disease rate was achieved using initial non-surgical management.

Over the past 20 years, first-line non-surgical management has increased up to 12.8%. Although the ratio between the time periods might be biased by several factors (such as limited numbers and registration), the trend towards non-surgical management is evident and is expected to increase, as more specialists adhere to the current guidelines. Although there is an increase in non-surgical management, still most patients are managed by surgery. Complaints such as pain or cosmetic reasons are reasons to do a resection. A resection could also have been performed for diagnostic purposes. Finally, limited experience with non-surgical treatment in non-referral centres could explain this high incidence of surgical excisions. As only chart review was done for patients with first line non-surgical treatment we can only hypothesize about the reason for surgical management.

Literature on first-line non-surgical management is limited and most studies are reports from specialized centres. Retrospective studies with combined data from the French and Italian research groups reported promising results for all tumour localizations.[23-25] The present study was designed to provide more insight in common practice for this rare disease on a population based level. In a national database of 1134 patients, the number of non-surgically treated patients is small, but definitely increasing. Obviously, surgery has remained the first-line treatment over the last 20 years, but a paradigm shift towards active surveillance can be observed. The surveillance cohort is the largest group among patients managed non-surgically. Radiotherapy was the second used treatment modality. In general, radiotherapy is indicated only in serious cases where progression of the tumour can lead to serious morbidity.[6] The risk of acute and late toxicity, including secondary malignancy, restricts its application, particularly in the young age group and in those patients with abdominal locations. Compared to the study by Colombo, et al., the current study showed a high frequency (38%) of patients treated with radiotherapy compared to 3% in the French/Italian study.[23] No other studies are available and the reason for this high number of primary irradiated tumours is unknown. Compared to the surveillance cohort, there is a relative high number of patients with an extremity localization in the radiotherapy group. Although we do not exactly know, it could be that patients with an extremity tumour are less likely to be referred and when they are referred they are symptomatic and therefore prone to have surgery or radiotherapy. The small numbers of patients who received systemic treatment reflect the limited evidence for any of the treatment options and lack of clinical studies in the Netherlands. This study was not designed to compare the outcome of the different treatment modalities, merely to report common practice over the years.

Overall, outcome of first-line non-surgical treatment was good with a 25% response rate and 52% stable disease rate. Of all evaluable patients 90% did not have early progression

of disease. Among patients under active surveillance, 16% showed spontaneous regression and 57% disease stabilization. These results might be biased because in many cases choice for first-line treatment was made after referring the patient to a tertiary referral centre which enabled the physicians to observe the natural behaviour of the tumour, thereby selecting patients for either active surveillance or more aggressive treatments. As referring these patients to a tertiary referral centre is common practice in the Netherlands, this reflects the common practice in the Netherlands. For radiotherapy, the patients in the present study received radiotherapy at the recommended dose of 50-56 Gy.[6-8,26] Results of radiotherapy showed a response in 43% and SD in 46% of the patients. During the follow-up period (median of 44 months (IQR 24-62) only 2 patients had disease progression with long TTPs of 31 and 47 months. These results are promising and might seem to advocate radiotherapy. However, radiotherapy might be considered an aggressive treatment for this intermediate grade tumour, usually reserved for patients with advanced disease. Especially in younger patients, given the low, but present long term risk on irradiation induced sarcomas radiotherapy is not deemed as first line treatment. When systemic treatment is chosen, a large variety of possible agents and regimens are applied (despite the lack of a specific registration for DF), such as hormonal agents, NSAIDS, chemotherapy and angiogenesis inhibitors, making comparison impossible. Although the group in the present study was small and diverse, results show stabilization and response in 63% of patients. Again, due to the large variety, no conclusions can be made for on preference of specific agents or regimens.

Given the lack of randomized studies, treatment decisions should be made during multidisciplinary expert meetings. Decision making should take into account location and growth of the tumour, but in particularly the symptoms of the patient. A recent study by the French Patients advocacy group SOS desmoid, showed that 63% of patients that participated in a survey reported pain.[27]

The optimal first-line non-surgical management of DF has been discussed by many groups, predominantly based on expert opinions and specific treatment modalities. The European consensus, reported by Kasper et al.[5] advises to start with active surveillance and switch to active treatment in case of 3 subsequent reports of progression, and that treatment should be guided by tumour localization. There is no staging system available to predict outcome at the time of diagnosis. Predictive factors have been described, such as age, tumour localization and *CTNNB1* mutations.[28-33] Recent data on *CTNNB1* mutations show different behaviour for tumours with different mutations. In the future, these mutations could play an important role when deciding to initiate specific treatment modalities. Moreover, it is increasingly important to recognize the lack of association between radiological volume and symptoms.[34-36] Given the chronic condition and the spontaneous fluctuations of the disease this should be taken into account in any decision that will be taken.

By the use of PALGA, the Dutch pathology registry, and the long study period, we have tried to be as inclusive as possible. Because referral for a desmoid-type fibromatosis to one of the sarcoma referral centres is standard practice in the Netherlands, we consider this overview as unbiased. However, a part of the patients identified from PALGA, were not included because they were treated outside the referral centres. The referral of these patients is essential to develop expertise in the treatment of this rare disease.

A limitation of the study is it retrospective nature. As a result, details on symptoms during or after treatment are lacking, which could have provided insight in the way decisions to either management had been taken. Therefore, no comparisons can be made between the different strategies. The natural behaviour of these tumours is variable, varying from spontaneous regression to long-term disease stabilization and rapid progression. In the absence of randomization, no clear recommendations can be given.

Conclusion

Desmoid-type fibromatosis remains a rare disease, for which several treatment modalities are available. Active surveillance seems to be a good and safe initial treatment, with options for active treatment in case of progression. Importantly, expected benefits from therapy should be well balanced against potential treatment-induced chronic and late effects.

Data availability

Requests for the raw data will be considered by the corresponding author.

Conflict of interest statement

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Radiation induced sarcomas occurring in desmoid-type fibromatosis are not always derived from the primary tumour

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Abstract

Desmoid-type fibromatosis is a rare, highly infiltrative, locally destructive neoplasm which does not metastasize, but recurs often after primary surgery. Activation of the Wnt/β-catenin pathway is the pathogenic mechanism, caused by an activating mutation in exon 3 of *CTNNB1* (85% of the sporadic patients). Radiotherapy is a frequent treatment modality with a local control rate of approximately 80%. In very rare cases this may result in the development of radiation induced sarcoma. It is unclear whether these sarcomas develop from the primary tumour or arise de novo in normal tissue. In four tertiary referral centres for sarcoma, six cases of desmoid-type fibromatosis that subsequently developed sarcoma after radiotherapy were collected. The DNA sequence of *CTNNB1* exon 3 in the desmoid-type fibromatosis and the subsequent post-radiation sarcoma was determined. Sarcomas developed 5-21 years after the diagnosis of desmoid-type fibromatosis and included two osteosarcomas, two high grade undifferentiated pleomorphic sarcomas, one fibrosarcoma and one undifferentiated spindle cell sarcoma. Three patients showed a *CTNNB1* hotspot mutation (T41A, S45F or S45N) in both the desmoid-type fibromatosis and the radiation induced sarcoma. The other 3 patients showed a *CTNNB1* mutation in the original desmoid type fibromatosis (two with a T41A and one with a S45F mutation), which was absent in the sarcoma. In conclusion, post-radiation sarcomas that occur in the treatment area of desmoid-type fibromatosis are extremely rare and can arise through malignant transformation of *CTNNB1* mutated desmoid fibromatosis cells, but may also originate from *CTNNB1* wild-type normal cells lying in the radiation field.

Introduction

Desmoid-type fibromatosis (ICD-O 8821/1) is a rare, locally aggressive (myo-) fibroblastic neoplasm that arises in deep soft tissues.[1] It does not metastasize, but is characterized by infiltrative growth and it may recur in a high proportion of cases after primary surgery.[2-4]

Desmoid-type fibromatosis may occur in the context of familial adenomatous polyposis (FAP) (OMIM #175100), which is caused by an inactivating mutation of the adenomatous polyposis gene (*APC*). The product of the *APC* gene is part of the destruction complex of β-catenin and consequently *APC* inactivating mutations result in activation of the Wnt/β-catenin pathway. An alternative mechanism for activation of this pathway is a mutation in exon 3 of *CTNNB1*, the gene encoding β-catenin, which results in stabilization of the protein. *CTNNB1* mutations occur in 85% of the sporadic desmoid-type fibromatoses.[5] Activating mutations are located at the GSK3β phosphorylation sites located in the N-terminus of β-catenin and alter the functionality of these sites, thereby preventing degradation of the protein.[6] Stabilization of β-catenin facilitates its translocation to the nucleus where it associates with a member of the TCF family of DNA binding proteins and subsequently causes transcription activation of target genes such as *MYC, CCND1* and *AXIN2*. Activation of this so-called canonical Wnt signal transduction pathway can be assessed by nuclear immunohistochemical staining for β-catenin. When β-catenin is not activated by canonical Wnt signalling, it is degraded in the cytoplasm or can be found at the membrane as part of the cadherin mediated adherens junctions.[7]

The treatment of desmoid-type fibromatosis is under debate, because the natural course of the disease varies between spontaneous regression, stable disease for a long time and rapid progression.[8,9] A policy of wait and see is now the first line option in many patients and in cases where local therapy is considered to lead to high morbidity, medical treatment is considered a first line option.

Until recently, desmoid-type fibromatosis was preferably treated by surgery with a wide margin. However, these lesions often are poorly circumscribed and may infiltrate in the surrounding tissue, which hampers adequate surgical excision. If surgery is not possible or insufficient to eradicate the entire tumour, radiation therapy is effective with a local control rate of approximately 80%.[10] For general cancer treatment, the incidence of radiotherapy-induced sarcoma was estimated to be 0.06%.[11] Three case reports were found in literature describing the occurrence of a radiotherapy-induced sarcoma in patients with desmoid-type fibromatosis.[12-14] It is unclear whether these sarcomas developed from the primary tumour or arose *de novo* in normal tissue. To assess this issue, we determined whether post-radiation sarcomas arising in desmoid-type fibromatosis contain mutations in *CTNNB1*. We examined six cases from four tertiary

sarcoma reference centres and determined the DNA sequence of exon 3 in the desmoid-type fibromatosis and the subsequent post-radiation sarcoma.

Methods

Cases

Cases were obtained from the institutional cancer databases of four tertiary referral centres for sarcoma. Slides of the desmoid-type fibromatosis and sarcoma were reviewed to confirm the diagnosis. Radiation induced sarcoma was defined as a sarcoma occurring in the previously irradiated fields.

CTNNB1 mutation analysis

DNA was isolated from formalin-fixed paraffin-embedded tissue using a previously described protocol.[15] Exon 3 of *CTNNB1* gene was sequenced as described.[16] Immunohistochemical staining for b-catenin was done routinely. Staining for p53 was performed using an antibody from Dako (Carpinteria, CA, USA, clone DO-7, dilution 1:500, antigen retrieval pH 9, positive control normal skin).

Results

Brief case descriptions

Patient 1 was a 12-year-old boy, when he was diagnosed with a desmoid-type fibromatosis of the right shoulder, which was resected and recurred approximately 40 months after the resection. (This case was previously described in a study of post-radiotherapy histologic changes in desmoid-type fibromatosis.[17]) The recurrence was treated with radiotherapy, total dose 60 Gy. Almost sixteen years after radiotherapy, a radiotherapy induced fibrosarcoma was found, and treated with a forequarter amputation.

Patient 2 was a 16-year-old woman, when she developed a large desmoid-type fibromatosis of the right leg and thigh, which was treated with surgery multiple times and external radiotherapy. At age 32, 16 years after the first diagnosis of the desmoid-type fibromatosis, she received iridium 192 as brachytherapy 25 Gy over approximately 50 hours minimum tumour dose. This was preceded by one hour of hyperthermia at 42 to 43 degrees Celsius. Two years later, at age 34 years, she was diagnosed with an osteosarcoma of the midshaft of the right femur for which she was treated with a hemipelvectomy. She was lost to follow up in 2011 at the age of 49 with no evidence of disease, at which point it had been 17 years since her osteosarcoma was treated.

Patient 3 was a 60-year-old woman, when she developed a desmoid-type fibromatosis tumour of the left side of the neck treated by surgery and radiation therapy. Six years

later she developed an osteosarcoma of the left scapula. Because this case was diagnosed in 1977, we could not retrieve any additional information.

Patient 4 was a 21-year-old male, when he was diagnosed with a desmoid-type fibromatosis of the left shoulder. He was treated medically with a non-steroidal anti-inflammatory drug (NSAID) (stopped because of progression) and later on a combination of an anti-oestrogen treatment and a selective COX-2 inhibitor, and had radiotherapy twice, first of the left shoulder 4 years before the development of the sarcoma (56 Gy) and then the second time for a recurrence at the distal field border 1.5 years before the development of the sarcoma (56 Gy). Six years after the primary diagnosis, biopsy of a progressive lesion in the left axilla showed a high grade undifferentiated pleomorphic sarcoma, for which a forequarter amputation was performed. He died 3 months later of pleural and pulmonary metastases.

Patient 5 was a 32-year-old male, who was diagnosed with a desmoid-type fibromatosis of the right shoulder/neck. He was treated with repeated surgery, medical treatment, i.e. NSAID/anti-oestrogen treatment, MTX/vinblastine and an oral VEGFR tyrosine kinase inhibitor, and twice radiotherapy (11 years before development of the sarcoma 46 Gy + 14 Gy boost and 1.5 year before 56 Gy). He was diagnosed 11 years after the initial diagnosis with an undifferentiated pleomorphic sarcoma in the radiotherapy fields with pulmonary metastases, for which he was treated with doxorubicin/ifosfamide without effect and died 6 months later of progressive disease.

Patient 6 was a 24-year-old female diagnosed with desmoid-type fibromatosis of the left upper arm. This tumour was excised with clear margins, but recurred and 18 months later was again treated with resection of what was now a 10 cm mass. As margins were microscopically positive, she received radiotherapy and subsequently received methotrexate, vinblastine, and capecitabine. When her desmoid again recurred, she was given sorafenib. Five years after her initial desmoid surgery (and three years after her radiation therapy at the site of recurrence), she developed an undifferentiated spindle cell sarcoma within the prior radiation site. This was resected with limb sparing surgery followed by treatments with doxorubicin and ifosfamide. Chemotherapy was complicated by cardiotoxicity and development of a pulmonary embolism. Approximately 3 months ago, she presented with adjacent local recurrences of both her desmoid and the undifferentiated spindle cell sarcoma for which she is currently under treatment.

Table 1: Clinical characteristics, mutation analysis and immunohistochemistry results

Patient	Age at diagnosis of sarcoma	Sex	Localisation	Type of sarcoma	Years between diagnosis of desmoid and sarcoma	Years between radiation therapy and sarcoma	CTNNB1 mutation in		B-catenin immunohistochemistry	
							Desmoid-type fibromatosis	Sarcoma	Desmoid-type fibromatosis	Sarcoma
1	33	Male	Shoulder	Fibrosarcoma	21	16	T41A	T41A	Nuclear	Membranous
2	34	Female	Right femur	Osteosarcoma	18	18	T41A	None	Nuclear	Membranous
3	66	Female	Left scapula	Osteosarcoma	6	6	T41A	None	Negative	Membranous
4	27	Male	Left shoulder	Undifferentiated pleomorphic sarcoma	6	4	S45F	None	Nuclear	Membranous
5	43	Male	Right shoulder and neck	Undifferentiated pleomorphic sarcoma	11	11	S45F	S45F	Nuclear	Membranous/ nuclear
6	29	Female	Left upper arm	Undifferentiated spindle cell sarcoma	5	3	S45N (unusual mutation)	S45N	Nuclear	Membranous/ patchy nuclear

Histology and immunohistochemistry

Representative photographs of the histology of the desmoid-type fibromatosis and the corresponding radiation induced sarcoma per patient are shown in figure 1. The diagnosis of desmoid-type fibromatosis was confirmed by nuclear beta catenin staining in five of six cases. Two out of six radiation induced sarcomas revealed nuclear staining for beta-catenin, while nuclear staining was absent in the remaining four sarcomas. (Figure 2, table 1)

Immunohistochemistry for p53 revealed overexpression in the sarcoma of patient 5, while staining in the sarcomas of patients 1, 4 and 6 revealed a wild-type pattern. (Figure 3) The sarcomas developed 3-21 years after radiation therapy.

CTNNB1 mutation testing

In all six cases a *CTNNB1* mutation was detected in the desmoid-type fibromatosis. Three patients had a T41A mutation, two a S45F mutation and one a S45N mutation. In three patients the mutation was not present in the radiation-induced sarcoma. In the other three cases the T41A, S45F and S45N mutation were also present in the radiation-induced sarcoma. (Table 1)

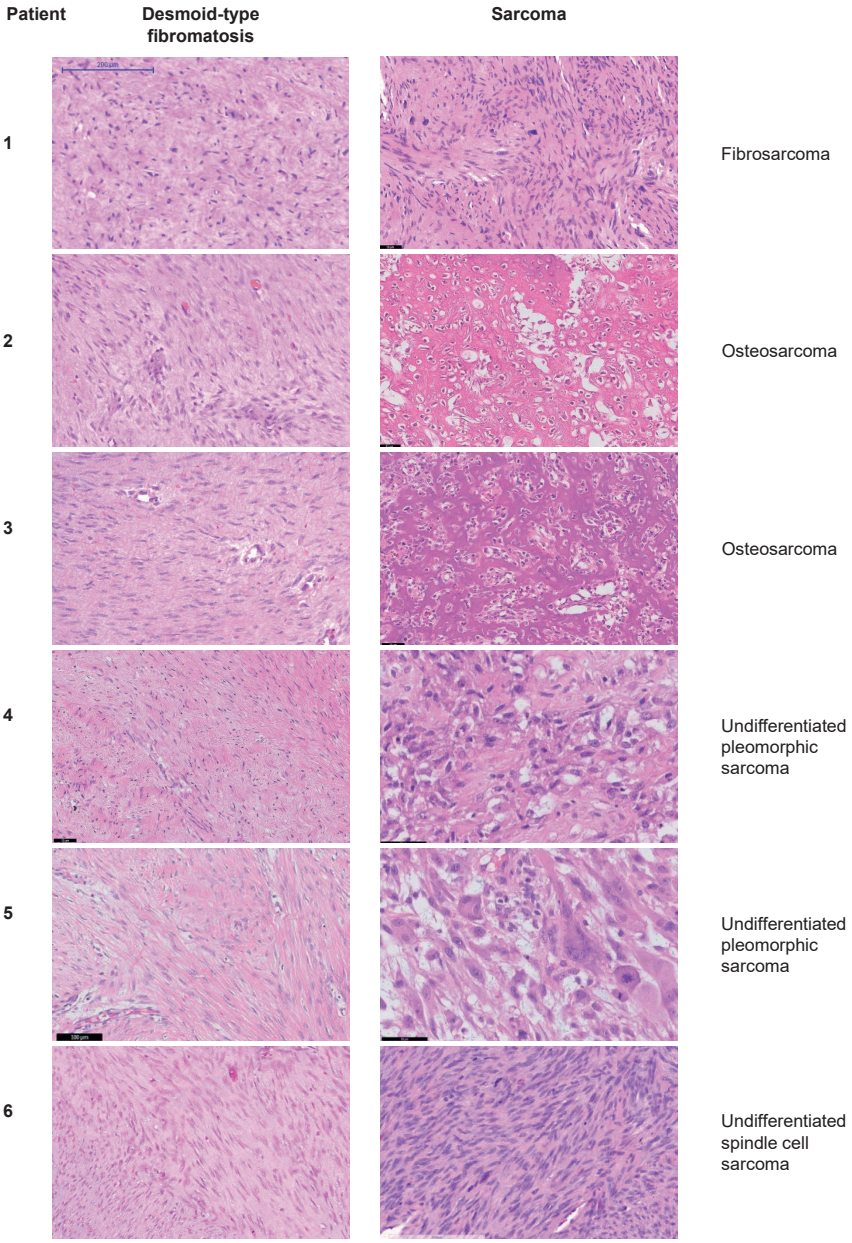

Figure 1: Hematoxylin and eosin stained slides of both desmoid-type fibromatosis and radiation induced sarcoma of all patients.

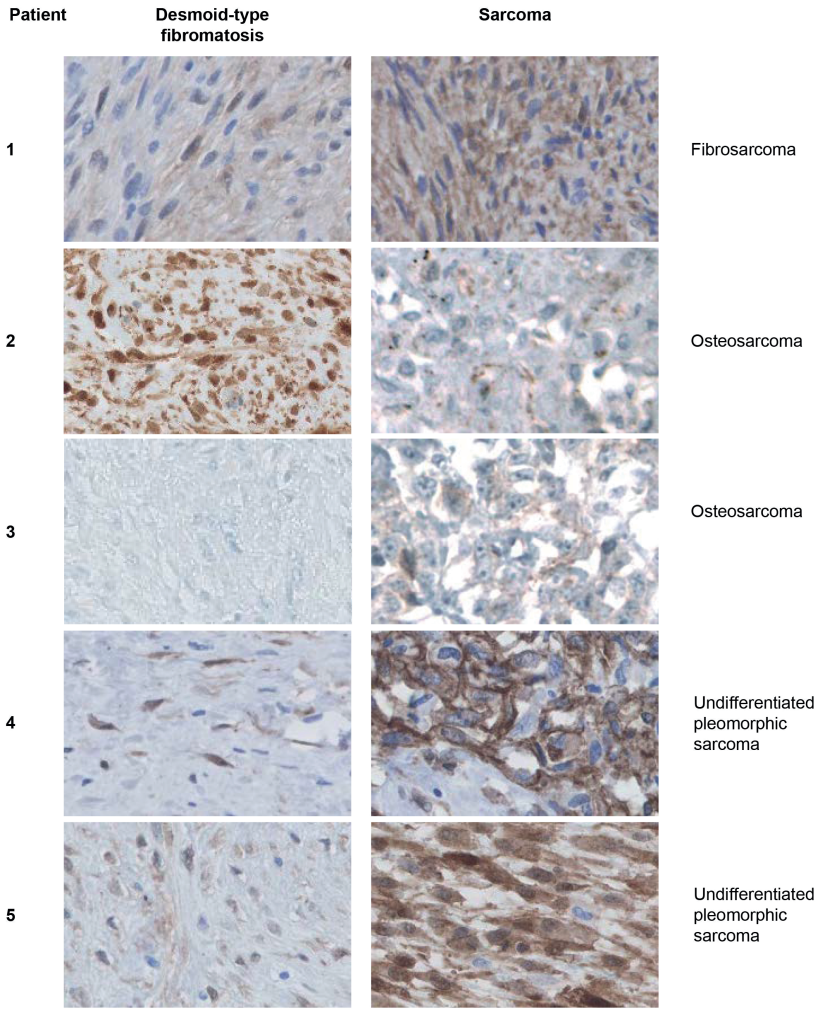

Figure 2: Immunohistochemical staining for B-catenin, which shows nuclear expression of B-catenin in desmoid-type fibromatosis of all patients, except for patient 3. B-catenin showed also nuclear positivity in the sarcoma of patient 5. All other sarcomas had a membranous localisation of B-catenin.

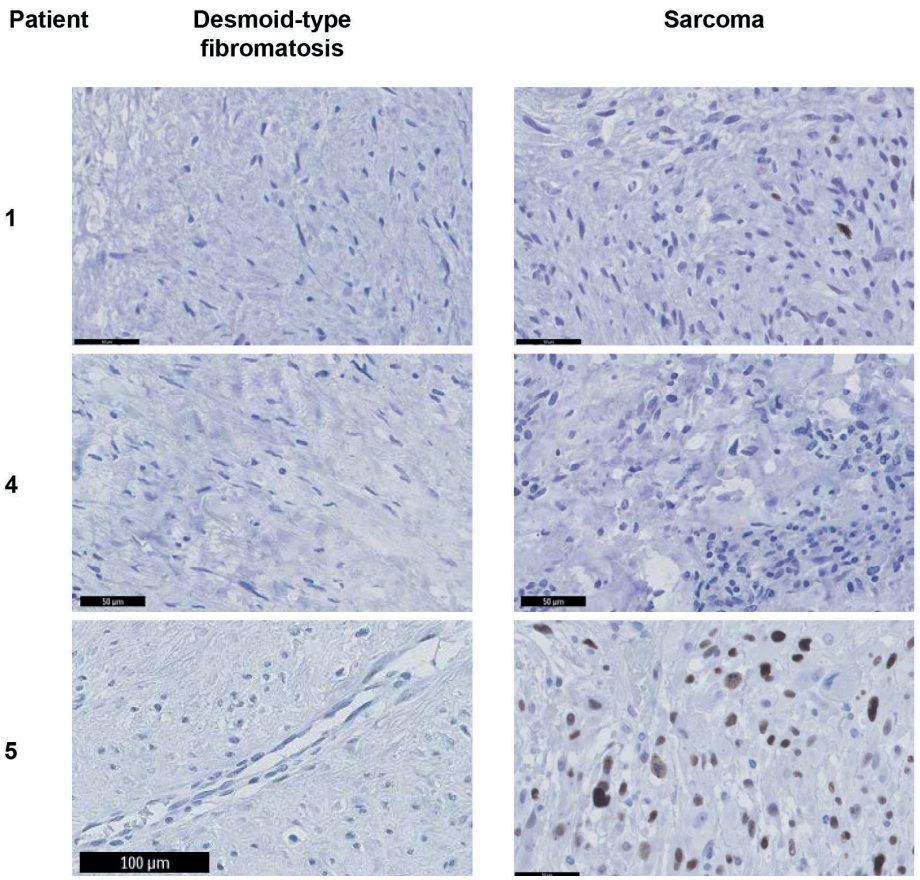

Figure 3: Immunohistochemical staining for p53, which shows nuclear expression of p53 in the radiation induced sarcoma of patient 5. All other tumours were negative for p53. Patient 6 also had a wild-type pattern, but photographs were not available.

Discussion

The high recurrence rate of desmoid-type fibromatoses (14-64%)[2-4] when only surgery is used, together with the difficulty to achieve complete resection without positive margins, has led to the use of adjuvant or alternative treatments of this locally aggressive but non-metastatic tumour. Radiation therapy has been used both as an adjuvant to surgery or as first-line single modality treatment and has shown local control rates of 80% with an average dose of 56 Gy.[10] There were no morphological and immunophenotypical differences when comparing desmoid-type fibromatoses before and after radiation therapy, which suggests that histomorphologic alterations attributable to the effects of ionizing radiation in desmoid-type fibromatosis are usually minimal.[17]

In the current study we show that the development of a sarcoma in desmoid-type fibromatosis after radiotherapy is extremely rare, as we have collected six such cases from four different referral centres. For instance, in the Leiden University Medical Centre, 57 patients were treated with radiotherapy for desmoid-type fibromatosis of which two developed a radiation induced sarcoma (patients 4 and 5). A *CTNNB1* hotspot mutation in exon 3 is the hallmark of sporadic desmoid-type fibromatosis and was indeed found in all desmoid-type fibromatosis tumours analysed in this study. The sarcomas presented 3-21 years after radiotherapy, and histological subtypes included osteosarcoma, fibrosarcoma and undifferentiated sarcoma. We show that radiation induced sarcomas can develop as a new primary, lacking *CTNNB1* mutations, as well as result from malignant transformation of the desmoid-type fibromatosis, retaining the *CTNNB1* mutation.

It has been suggested that desmoid-type fibromatosis patients with a S45F mutation are at higher risk for recurrence than those with T41A or no mutation in *CTNNB1*[5,18]; however other studies did not find this difference.[19,20] Although our series is small, different mutation types, including a rare variant (S45N) were found in the desmoid-type fibromatosis that preceded the radiation induced sarcomas, so it seems unlikely that mutation type is associated with malignant transformation. The S45N mutation of case 6 is caused by two nucleotide substitutions, i.e. TCT to AAT. It is not reported as mutation in the COSMIC database (http://cancer.sanger.ac.uk/cosmic), however it was reported as a mutation in *CTNNB1* recently, and personal communication with the authors confirms that it was detected in a case of fibromatosis.[21]

Only one out of four sarcomas, for which we could perform immunohistochemistry for p53, revealed overexpression of the protein, suggestive of a TP53 mutation. Therefore, it seems unlikely that TP53 plays a major role in the development of radiation induced sarcoma in desmoid-type fibromatosis.

In conclusion, postradiation sarcomas are rare though may arise in the treatment area of desmoid-type fibromatosis either *de novo*, lacking the *CTNNB1* mutation characteristic of the original desmoid-type fibromatosis, or may arise from malignant transformation of pre-existing desmoid-type fibromatosis cells, retaining the *CTNNB1* mutation.

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The incidence, mutational status, risk classification and referral pattern of gastro-intestinal stromal tumours in the Netherlands:

a nationwide pathology registry (PALGA) study

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Abstract

Introduction

Symptomatic Gastrointestinal Stromal Tumours (GIST) are infrequent with an incidence of 12.7 per million inhabitants in the western population. We studied whether the incidence of GIST has further increased between 2003 and 2012 and assessed the frequency of mutations, risk groups, histological subtypes and immunohistochemistry results.

Methods

From PALGA, the nationwide Dutch Pathology Registry, pathology excerpts from all patients with a GIST or GIST-like tumour between 2003 and 2012 were retrieved to calculate incidence rates. Full pathology reports were retrieved of resections in 2011 and 2012 to study the frequency of mutations, risk groups, histological subtypes and immunohistochemistry results.

Results

The incidence of GIST increased to 17.7 per million inhabitants in 2012 with a median age of 67 years. Mutational analysis was performed in 33.9% of patients with a resection between 2011 and 2012 (KIT mutation 67.5%, PDGFRA 16.3%, wild-type 11.4%). The percentage of high-risk patients in the different risk classifications varied from 19.9% to 38.0% depending on the used classification. Only 35.9% of patients had diagnosis or revision of pathology diagnosis within three months in a designated GIST referral centre. No increase in proportion of central pathology reviews was found. Proportion of patients with mutational analysis increased over the years.

Conclusion

The registered incidence of GIST, 17.7 per million inhabitants in 2012 in the Netherlands, is still rising. Despite incorporation in the ESMO GIST guidelines since 2008 for mutational testing and since 2010 for central review of pathology, both are performed in a minority of patients.

Introduction

The most common mesenchymal tumours of the gastrointestinal tract are Gastrointestinal Stromal Tumours (GISTs).[1] Clinical behaviour is predicted by primary localisation, tumour size, mitotic index and tumour rupture.[2] The differential diagnosis contains gastrointestinal leiomyoma and leiomyosarcomas, desmoid-type fibromatosis and schwannoma.[3] The estimated incidence of GIST in the Netherlands was 12.7 per million inhabitants in 2003.[4] Studies in other countries report incidences between 7.8 and 21.1/million.[5-10] Most studies were non-nationwide, doctor-driven cancer registry studies.[11]

Primary treatment remains surgery and when non-resectable, imatinib has considerably improved prognosis of these patients.[2,12-15] Response to imatinib and progression free survival depend on mutational status.[16,17] KIT is the most commonly mutated gene (76.2-83.6%), followed by PDGFRA (3.2-11.2%).[18,19] A significant subset of the 10-15% of GISTs that lack mutations in KIT or PDGFRA, are associated with loss of function of the succinate dehydrogenase complex, the so called SDH deficient GIST, which has specific histological features.[20-24]

The diagnosis of GIST is based on morphology and CD117 and/or DOG1 immunohistochemistry.[2,18,22,25,26] Mutational analysis is considered standard of care in the diagnostic work-up for GIST for the first time in the 2008 ESMO guidelines and after 2010 confirmation by an expert pathologist is recommended.[2,27,28] These recommendations are incorporated in the Dutch guidelines.[29]

In 2004 a nationwide survey was performed in the Netherlands to estimate the incidence of GIST in 1995 and 1998 to 2003.[4] We repeated this study for the following ten years (2003-2012) during which the diagnosis GIST was well established. Our primary objective was to estimate the incidence of GIST and the classification into the different risk categories, the frequency of the various mutations, immunohistochemical markers and histological subtypes. The secondary aim was to compare the current daily practice of pathology reporting with the actual ESMO guidelines.

Methods

Patients

From PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands,[30] all excerpts were retrieved matching the following search criteria: GIST or metastasis of GIST OR ((malignant) leiomyoma (i.e. leiomyoma, leiomyosarcoma, leiomyoblastoma etc.) AND gastrointestinal tract). A second search was performed with the following criteria (used earlier by Goettsch *et al.*[4]): (gastro-intestinal tract OR abdomen OR retroperitoneal OR abdominal wall) AND (liposarcoma OR desmoid-type

fibromatosis OR solitary fibrous tumour OR schwannoma OR malignant peripheral nerve sheath tumour). The standardized excerpts contain encrypted patient identification, age at diagnosis, sex, the date of arrival of the pathology specimen, whether the analysis was done in a clinical centre active in GIST (defined below) and the conclusion of the pathology report. Patients with a first, incident GIST were included. AJV extracted the data and uncertain pathology conclusions in the reports were discussed with HG and JVMGB. For uncertain cases, full pathology reports were retrieved. Because not all questions could be answered with the information in the excerpts, full pathology reports were retrieved for all patients with a primary resection for a GIST in 2011 or 2012.

A clinical centre active in GIST was defined as a centre with more than 15 new pathology diagnosis of GIST per year and a dedicated multidisciplinary sarcoma team. Five Dutch centres met these criteria: the Erasmus Medical Centre, Rotterdam, the Antoni van Leeuwenhoek hospital, Amsterdam, the University Medical Centre Groningen, the Radboud University Medical Centre, Nijmegen, and the Leiden University Medical Center.

Data collection

Data was collected on age at diagnosis, sex, year of diagnosis, localisation, tumour size, mitotic rate, immunohistochemical staining results (CD117, DOG-1, SDHB, desmin, smooth muscle actin and CD34), mutation analysis and surgical resection margins. Tumour size *and* mitotic rate were categorized into to the categories used in the various risk classifications, *i.e.* <2, 2-5, 5-10, >10 cm *and* 0-5, 6-10, >10 mitoses per 50 HPF or 5 mm^2, depending on what was reported.

Risk stratification scores

For the analysis of the different risk stratification scores patients were grouped according to the criteria of Fletcher[31], Miettinen 2002[32], revised Miettinen/AFIP[33], Joensuu[34] and Gold nomogram[35]. Most risk classifications give a long-term indication of the risk of recurrence, but the Gold nomogram specifies the 2- and 5-year recurrence free survival (RFS) after surgery. For the comparison the 5-year RFS was used. RFS rates were categorized to a low risk group (Gold nomogram 5-year RFS 90-100%), moderate risk group (75-90%) and high-risk group (<75%), which are comparable to percentages given in the revised Miettinen/AFIP criteria. Because it is not possible in the RFS calculation to have a RFS >96%, no very low risk group was identified.

Statistical analysis

The incidence rate of GIST was calculated per million inhabitants, also standardised for 5 year age groups and sex for the Dutch population of 2012 and standardized to the WHO and European (ESR) standard population.[36,37] Time trends for incidence were either tested for significance with regression analysis or a Mantel-Haenszel X^2–test for trend.

Spearman's rank correlation coefficient was used to test the correlation between the different risk classifications.

Results

Figure 1 shows the search strategy and numbers of patients identified. In total 2456 patients were included for incidence analysis and 489 patients were included for full pathology report analysis.

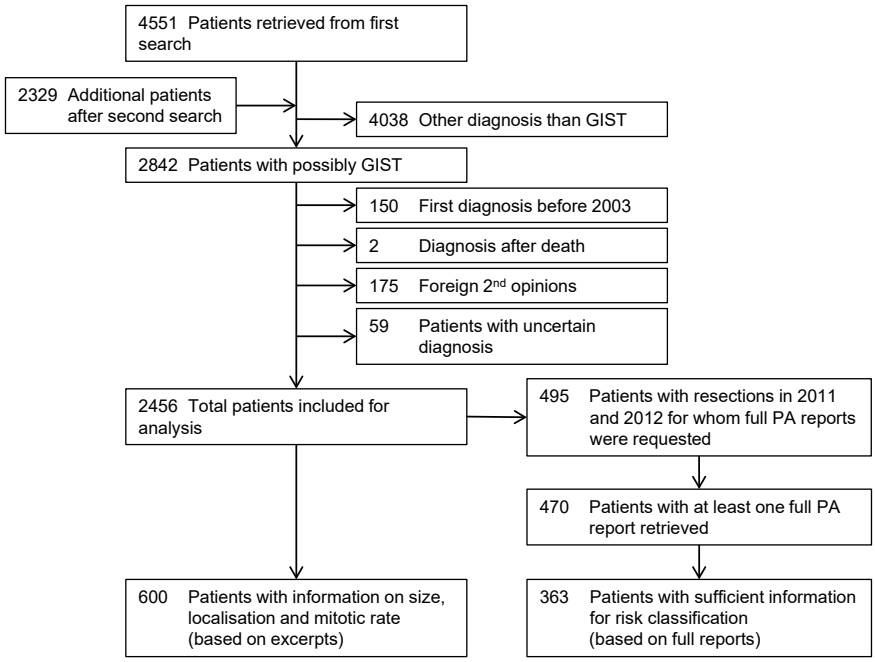

Figure 1 Diagram of inclusion and exclusion of patients

The mean age of patients was 65 years (SD 13), median 67 years (range 3-96) and 1307 (53.2%) patients were male. (See also supplementary figure 1) The localisation of the GISTs (patients with excerpts between 2003 and 2012) was the stomach in 59.8%, small intestine in 21.1%, rectum in 2.2%, colon in 1.6%, oesophagus in 0.6% and intra-abdominal not further specified in 11.0%. For the patients with full reports between 2011 and 2012 the localisation was stomach in 65.0%, small intestine in 26.8%, rectum in 3.1%, colon in 1.6%, oesophagus in 0.8% and intra-abdominal not further specified 1.8%. The group with a small intestine GIST was further subdivided in duodenum 6.1%, jejunum 5.1%, ileum 1.0%, and not specified in 14.5%. (supplementary table 1)

Of the 6 patients <21 years of age, 4 were female (3, 15, 18 and 20 years) and 2 were male (14 and 17 years). Localisations were the stomach (n=4), colon (n=1) and intra-abdominal not further specified (n=1).

Incidence rates (table 1 and figure 2A)

The standardized incidence rate increased from 12.2 per million in 2003 to 17.7 in 2012 ($p<0.05$). Age of peak incidence was 70-74 years with an incidence of 73.9 per million in 2012 for this age group. The incidence of GIST before the age of 21 was 0.13 per million per year.

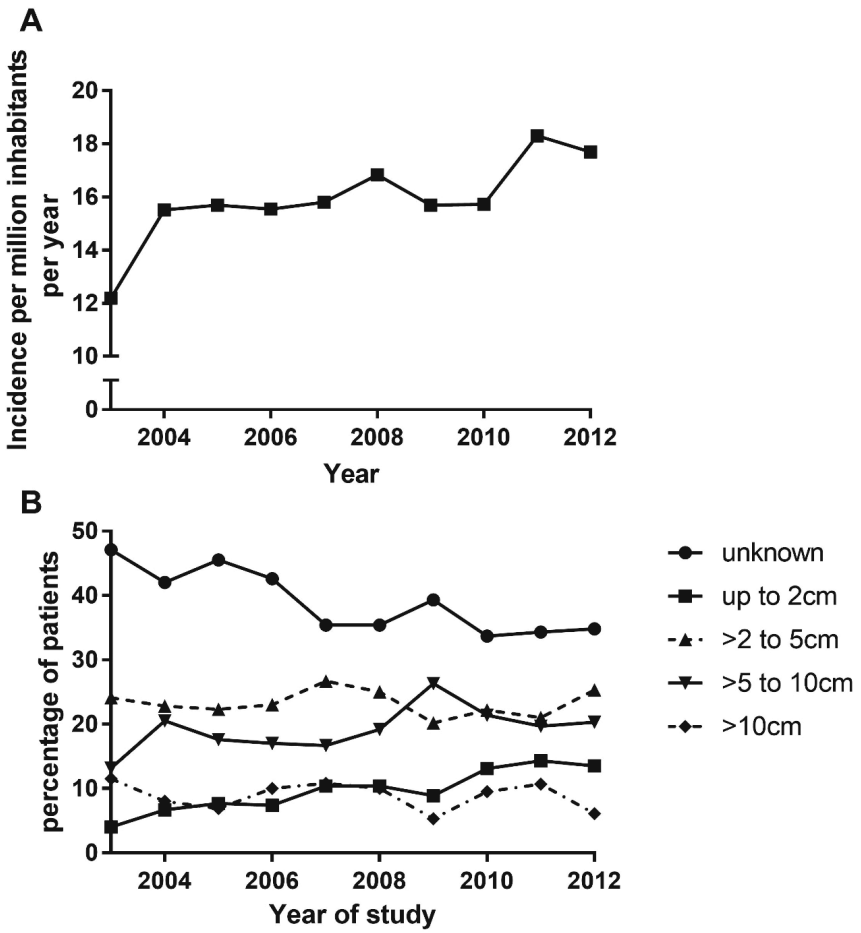

Figure 2A. Incidence of GIST standardized for the Dutch population of 2012
Figure 2B. Relative incidence of the four tumour diameter groups

Table 1: Incidence rates

Year	Absolute number of patients	Crude incidence rate, patients per million inhabitants	WHO age standardized incidence per million inhabitants	Standardized incidence (Dutch population 2012) per million inhabitants	European Standardized Rate per million inhabitants
2003	174	10.7	7.2	12.2	13.5
2004	224	13.8	9.3	15.5	17.2
2005	233	14.3	9.5	15.7	17.2
2006	230	14.1	8.9	15.5	17.2
2007	240	14.7	9.6	15.8	17.3
2008	260	15.8	10.1	16.8	18.5
2009	247	15.0	9.2	15.7	17.1
2010	252	15.2	9.6	15.7	17.1
2011	300	18.0	10.9	18.3	20.1
2012	296	17.7	10.8	17.7	19.4

During the 10-year study period, the proportion of tumours with a size < 2 cm significantly increased ($p<0.0001$) from 4.0 to 13.5% with at the same time a decrease in the proportion of patients for which tumour size is not reported from 47.1 to 34.8% (ns) with a stable absolute number. (Figure 2B)

Histology

Detailed histological findings were only evaluated for patients with a full pathology report. Of the 429 patients (87.7% of patients with a full report) with known morphology, 81.6% had spindle cell morphology, 9.3% epithelioid subtype and 9.1% mixed epithelioid/spindle cell subtype. No differences in morphology were found for the specified localisations. For GIST patients <21 years histologic subtype was mixed morphology in two, epithelioid subtype in two and unknown in two patients.

Immunohistochemistry results were analysed for patients with full pathology reports. CD117 was reported in 89.4% of patients and of these 93.6% tested positive. For DOG1 42.9% of patients were tested with a positive result in 98.6%. For additional results of immunohistochemistry see supplementary table 2. For 49 patients (10.0%) no positive immunohistochemistry was reported for CD117 and/or DOG-1 in the full pathology reports or excerpts of the patients with a full pathology report. Only one was actually reported as being negative for both CD117 and DOG-1, all others had at least one of both not reported.

Resection margins were reported in 404 of 489 patients (82.6%) with a R0 resection in 84.9%, R1 in 11.6% and R2 in 3.5%.

Risk classification (table 2 and supplementary table 3)

Full pathology reports were requested of all resections performed in 2011 and 2012. Of the 489 patients with at least one full pathology report, 414-444 patients had sufficient data for risk classification depending on the applied risk classification (because of different criteria not all classifications were able to classify the same patients). Although comparison of the incidence of risk categories is difficult because risk classifications differ in the number of patients eligible for risk stratification, both the Gold risk assessment and the Miettinen 2002 classification seem to allocate more patients to the highest risk group compared to the other risk classifications. All risk classifications had a significant and good to very good correlation ($p<0.001$) with each other, with an R ranging from 0.808 (Gold vs Joensuu) to 0.957 (Miettinen 2002 vs Miettinen/AFIP).

Table 2: Distribution of patients (with full reports) in the different risk classifications

Risk groups	**2011-2012 (Full reports)**	
	Absolute number of patients	**Percentage of patients that could be stratified (not possible: percentage of all patients)**
	Fletcher 2002	
Very low risk	74	16.7%
Low risk	137	30.9%
Intermediate risk	109	24.5%
High risk	124	27.9%
Not possible	45	9.2%
	Miettinen 2002	
Probably benign	159	38.5%
Uncertain or low malignant potential	97	23.5%
Probably malignant	157	38.0%
Not possible	76	15.5%
	Joensuu 2006	
Very low, if any malignant potential	66	16.2%
Low malignant potential	191	46.8%

Table 2: Continued.

Risk groups	2011-2012 (Full reports)	
	Absolute number of patients	**Percentage of patients that could be stratified (not possible: percentage of all patients)**
Intermediate malignant potential	70	17.2%
Probably malignant	81	19.9%
Not possible	81	16.6%
Miettinen 2006		
None	68	16.4%
Very low risk	93	22.5%
Low risk	101	24.4%
Moderate risk	67	16.2%
High risk	85	20.5%
Not possible	75	15.3%
Gold 2009 (chance of 5-year recurrence free survival)		
90-100% (low risk)	185	42.7%
75-90% (moderate risk)	102	23.6%
0-75% (high risk)	146	33.7%
Not possible	56	11.5%

Not all patients are present in every classification because they do not have all data essential for that classification.

Mutational status (table 3)

Mutational status was reported in 461 of the 2456 patients (18.8%) based on excerpts and in 166 of 489 patients (33.9%) based on patients with full pathology reports. The presence of PDGFRA mutations is relatively high with a frequency of 16.3%. Supplementary figure 2 shows the distribution of mutated genes compared to age. The number of patients with mutational analysis performed increased during the years of study from 5.2% in 2003 to 29.4% in 2012. (p=0.000)

The frequency of reported mutational analysis increased from low risk tumours (24.7%) to the high-risk group (67.1%) (p=0.000). (Supplementary table 4)

Table 3: Mutation frequencies

Gene mutated	All patients after analysis of the excerpts 2003-2012		All patients with full pathology reports 2011 and 2012	
	Number of patients	Percentage of total known mutations n=461)[1]	Number of patients	Percentage of total known mutations (n=166)[1]
KIT	322	69.8%	112	67.5%
Exon 9	30	9.3%	11	9.8%
Exon 11	261	81.1%	97	86.6%
Exon 13	8	2.5%	2	1.8%
Exon 17	1	0.3%	1	0.9%
Not reported	22	6.8%	1	0.9%
PDGFRA	64	13.9%	27	16.3%
Exon 12	5	7.8%	1	3.7%
Exon 14	3	4.7%	3	11.1%
Exon 18	46	71.9%	22	81.4%
Not reported	10	15.6%	1	3.7%
BRAF	1	0.2%	1	0.6%
SDHB deficiency	5	1.1%	3	1.8%
Neurofibromatosis	3	0.7%	4	2.4%
Wild-type, i.e. KIT and PDGFRA negative, in most patients no other mutation tested[2]	66	14.3%	19	11.4%

[1] For the exons: percentage of patients with a mutation in the specific gene.
[2] Patients with a wild-type GIST were at least tested for mutations in KIT exon 9 and 11 and PDGFRA exon 12 and 18. Most of these patients were not tested for SDH deficiency or BRAF mutations.

Centres of diagnosis, resection and revision

Fifty-two laboratories diagnosed GIST and 49 laboratories had at least one surgical resection specimen during the two years for which we requested full pathology reports. The pathology department of five GIST centres in the Netherlands diagnosed and revised more than 30 pathology resection specimens (>15/year) of GIST in 2011 and 2012 (15 laboratories ≤5 specimens, 25 laboratories 6-20 specimens, 4 laboratories 20-30 specimens in these 2 years and 3 no specimen). If this cut-off of >15 pathology

specimens of GIST/year is used as definition of a GIST reference centre and with inclusion of all the regional soft tissue pathology panels, then for 13.2% of patients the primary diagnosis was established in a GIST centre, surgery was done in 16.2% of the patients in a GIST centre and 35.9% of the patients were diagnosed or had a revision of their diagnosis within 3 months in a GIST reference centre. No significant increase was found in the number of pathology revisions over the years of study (2003 28.7%, 2012 41.2% of patients), although there seems to be an increasing trend in the number of reviews after the guidelines of 2010. (Supplementary table 5)

It was also assessed whether the pathology specimens revised by a reference centre or specialised soft tissue pathology panel were high risk classified patients according to the Miettinen/AFIP criteria. Only 30.9% of the patients with a full pathology report with no risk for recurrence had a revision of the pathology diagnosis compared to 67.1% of the patients with a high risk. (Supplementary table 4) Of all patients with a resection and a revision in a reference centre, 61.2% had mutational analysis performed compared to 10.4% of all the other patients.

Last we analysed whether high risk patients diagnosed in 2011 and 2012 had a mutation analysis. Of the patients diagnosed in a GIST reference centre, 92.3% had a mutation analysis, but only 16.7% of the patients diagnosed in one of the other centres.

Discussion

The current study shows an increase in incidence of pathology proven GIST from 12.2 to 17.7 per million inhabitants between 2003 and 2012. This increase in incidence is also found in several other studies, like the SEER study (SEER database study, standardized to the 2000 US standard population, 2001: 5.5/million, 2011 7.8/million)[5], a Taiwanese study (Taiwanese Cancer Registry, standardized to the 2000 US standard population, 1998: 11.3/million, 2008: 19.7/million)[6] and last a study from Shanghai (Shanghai Cancer Registry, WHO standardized, 2004: 10.1/million, 2008: 14.5/million).[7] None of these studies report a cause for this increase. Studies reporting incidences before 2000 report also an increase in incidence, however this is caused by the introduction of CD117 immunohistochemistry to identify GIST.[10]

We can only hypothesize about the cause of the increase in The Netherlands. First, it could be an increased use of diagnostic procedures such as CT scans, gastroscopy and endoscopic ultrasound, which is supported by the increase in number of patients with a small tumour size. Another possible reason is an increased awareness of the diagnosis after the introduction of imatinib as effective treatment. The last possibility could be a real increase in the incidence; although this is a possibility, until now no causal factors or risk factors for the development of GIST are known.

The difference in crude incidence for 2003 in the Goettsch paper[4] and our paper(our data 174 patients vs. Goettsch 206 patients) could be explained by the revision of historical pathology specimens after 2003 or by improvements in patient identification by PALGA, resulting in less double counted patients for incidence analysis.

The incidence of 17.7 per million inhabitants is to the upper limit of reported incidences, although comparison is hampered by a lack of standardized incidence rates.[5-10] This high incidence rate is probably caused by one of the strengths of our study: the way PALGA registers diagnoses. PALGA is a fully automated archive of pathology reports, with 100% coverage of all Dutch pathology reports and registers also small and incidental GISTs not appearing in cancer registries. With the addition of the extensive search, the long study period and the inclusion of small and incidentally found GISTs, this study gives the best possible estimate of GIST incidence. Most of the earlier studies used cancer registries that use a health care provider notification system, which is probably biased as small and incidentally found GISTs are clinically less relevant as was shown in a recent study.[11] A Dutch Cancer Registry (DCR) study on rare cancers reported an incidence of 9 per million inhabitants for 2004-2008 compared to an incidence of 13.8 to 15.8 per million in our study.[38] The DCR is probably not registering small GISTs, explaining the difference.

The ESMO guideline of 2010 recommends to perform mutation analysis in all GISTs, because mutational status is related both to prognosis and efficacy of treatment. However, only a minority of patients in 2011 and 2012 (33.9%) had mutational status reported.[16,17,28] When considering high risk patients, mutational analysis was performed in 67.1% of patients.[16,17] Because this study is based on pathology reports, exact reasons for not performing mutational analysis are not known. Almost all patients with a high risk GIST and a primary diagnosis or revision in a GIST centre had a mutational analysis (2011 and 2012 92.3%) compared to a much lower rate in the non-GIST centres (2011 and 2012 16.7%), explaining the rather low rate of mutational analysis performed in high risk patients and stressing the importance of referring patients to a GIST centre. The frequency of mutations was in line with that reported in a French study.[9] PDGFRa mutant GIST was slightly overrepresented, which may be explained by the imatinib resistance of PDGFRa mutated GIST and therefore due to progression leading to an indication for mutation analysis.[39] The relative high percentage of patients which were characterized as wild-type could have technical reasons because most patients were only sequenced for KIT and PDGFRa mutations in the most common hotspots.

In the past, risk classification was not incorporated in the guidelines, and so, mitotic rate and size often not reported in the conclusion. To get a better overview of the risk classifications, we requested full pathology reports for all patients with a resection in 2011 and 2012. Comparing the different risk classifications it seems that the Gold and Miettinen 2002 criteria allocate more patients to the highest risk category compared to the other known risk stratifications, but comparison is difficult because these

classifications do not include exactly the same patients in our analysis. E.g., both the Joensuu and the Miettinen 2002 criteria do only provide stratification rules for gastric and intestinal tumours. Also, the number of risk groups differs between classifications. These factors hamper comparison of the different stratifications.

Since 2008 the ESMO guideline recommends mutation analysis for all GISTs and the 2010 guidelines recommends revision of pathology by an expert pathologist, we here show that in 2012 only 41.2% of patients had a revision of pathology within 3 months and only 29.4% of patients had mutational analysis performed. This was much better for high risk patients (based on the Miettinen/AFIP classification) with 67.1% for both mutational analysis and pathology review.

In conclusion, this is the second nationwide GIST incidence study ever performed in the Netherlands and follows the previous study in the Netherlands in 2003.[4] It shows that the registered incidence of GIST has risen from 12.2 to 17.7 per million, which can be partly explained by an increase in the incidence of small GISTs. Both the Gold risk assessment and the Miettinen 2002 criteria seem to allocate more patients than the other commonly used risk classification systems to a high-risk category. We found that the majority of pathology reports currently do not contain the recommended data of the ESMO guideline. So, the incidence of GISTs apparently increases, mainly due to the increase of small GIST and for these small GISTs the guidelines are probably less well adhered to.

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Author contributions

AJV, HG, PCWH and JB designed the study. The PALGA group provided the data for this analysis. AJV collected the data and did the data analysis. AJV wrote the first manuscript. PCWH, HG, JB and LO carefully read the manuscript and commented on the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Research involving Human Participants
Not applicable

Informed consent
Because fully anonymized pathology reports were used, no informed consent was obtained.

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Conflict of interest statement
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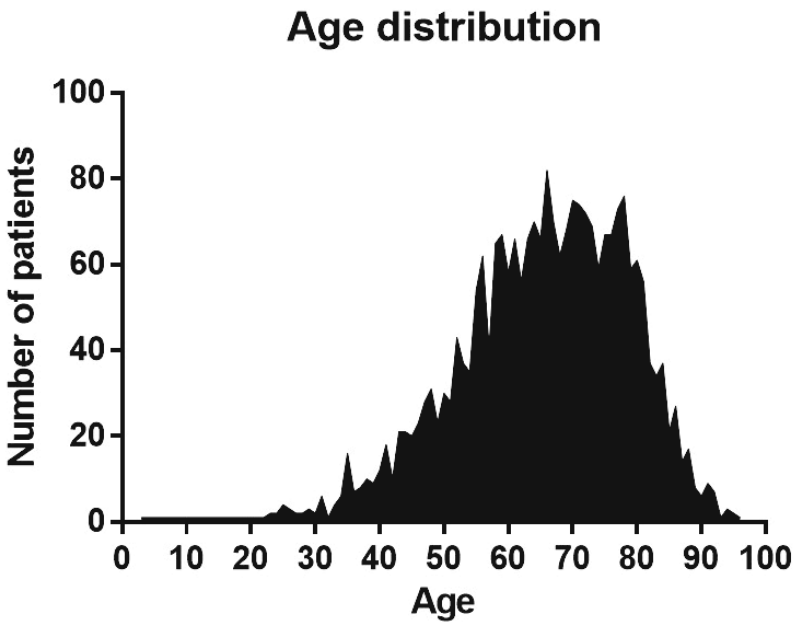
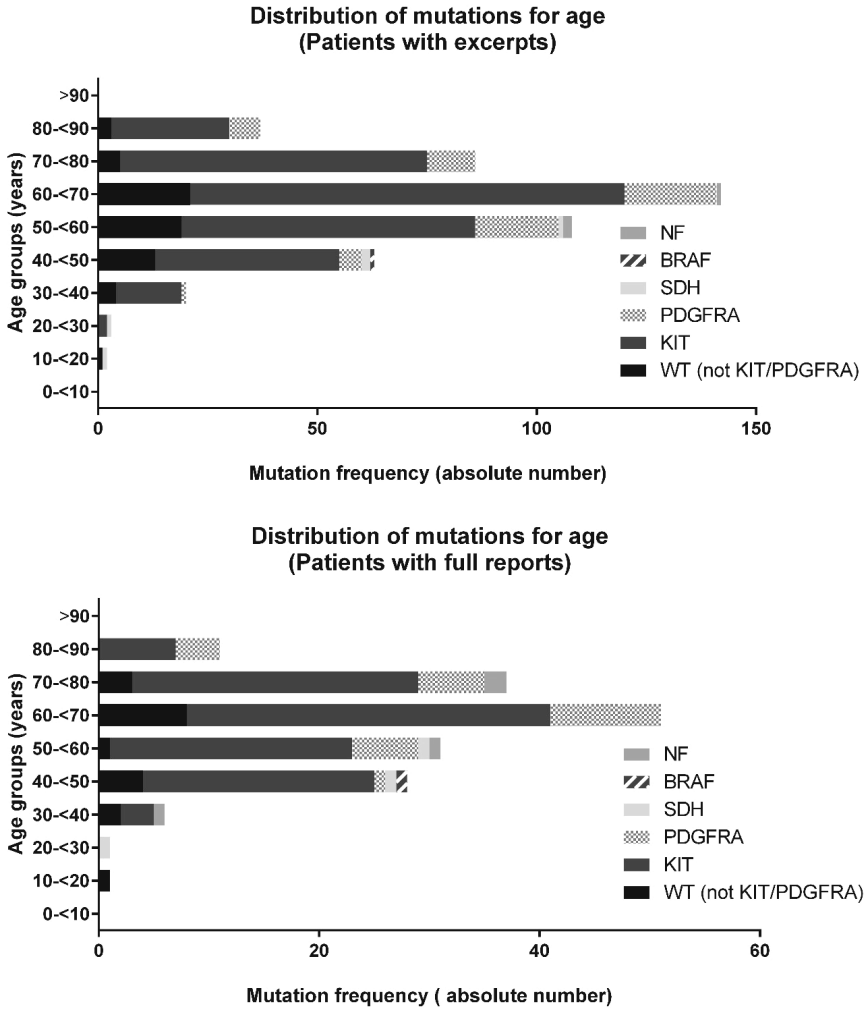
Additional data



Supplementary figure 1: Age distribution



Supplementary figure 2: Distribution of mutations for age

Wild-type GIST patients were tested for mutations at least in KIT exon 9, 11 and PDGFRA exon 12 and 18. Most of these patients were not tested for SDH deficiency or BRAF mutations.

Supplementary table 1: Localisation of GIST

	Patients with excerpts 2003-2012 (also containing the patients with a full pathology report 2011-2012)		Patients with full pathology reports 2011-2012	
Localisation	**Number**	**Percentage**	**Number**	**Percentage**
Stomach	1469	59.8 %	318	65.0%
Small intestine	521	21.1 %	131	26.8%
Duodenum	89	3.6 %	30	6.1%
Jejunum	94	3.8 %	25	5.1%
Ileum	33	1.3 %	5	1.0%
Not specified	305	12.4 %	71	14.5%
Rectum	53	2.2 %	15	3.1%
Colon	39	1.6 %	8	1.6%
Oesophagus	14	0.6 %	4	0.8%
Liver, most probably metastases	46	1.9 %	2	0.4%
Pancreas	11	0.4 %	1	0.2%
Intra-abdominal, not further specified	270	11.0 %	9	1.8%
Other	25	1.0 %	1	0.2%
Unknown	8	0.3 %	0	0.0%
Total	2456	100.0 %	489	100.0%

Supplementary table 2: Results of immunohistochemistry

	Full pathology reports	
Marker	**Percentage of patients in which it is reported**	**Patients with a positive result**
CD117	89.4%	93.6%
DOG1	42.9%	98.6%
SDHB deficiency[1]	1.8%	33.3% negative
CD34	72.4%	77.4%
Desmin	60.7%	0.7%
Smooth muscle actin	51.7%	19.4%

[1]Recently introduced and only of interest in KIT/PDGFRA wild-type GIST

Supplementary table 3: Distribution of patients in the different risk classifications (all excerpts)

	2003-2012 (Excerpts)	
Risk groups	**Absolute number of patients**	**Percentage of patients that could be stratified (not possible: percentage of all patients)**
Fletcher 2002		
Very low risk	89	9.9%
Low risk	241	26.8%
Intermediate risk	208	23.1%
High risk	362	40.2%
Not possible	1556	63.4%
Miettinen 2002		
Probably benign	252	30.4%
Uncertain or low malignant potential	182	21.9%
Probably malignant	396	47.7%
Not possible	1626	66.2%

Supplementary table 3: Continued.

Risk groups	2003-2012 (Excerpts)	
	Absolute number of patients	Percentage of patients that could be stratified (not possible: percentage of all patients)
Joensuu 2006		
Very low, if any malignant potential	79	10.1%
Low malignant potential	359	46.1%
Intermediate malignant potential	136	17.5%
Probably malignant	205	26.3%
Not possible	1677	68.3%
Miettinen 2006		
None	82	10.8%
Very low risk	173	22.9%
Low risk	185	24.4%
Moderate risk	133	17.6%
High risk	184	24.3%
Not possible	1699	69.2%
Gold 2009 (chance of 5-year recurrence free survival)		
90-100% (low risk)	285	35.6%
75-90% (moderate risk)	190	23.8%
0-75% (high risk)	325	40.6%
Not possible	1656	67.4%

Supplementary table 4: Reference centre review and mutation analysis compared to Miettinen/AFIP risk group

Miettinen/AFIP risk group (N=)		Percentage mutation analysis	Percentage reference centre review
None	(68)	8.8 %	30.9 %
Very low	(93)	24.7 %	32.3 %
Low	(101)	29.7 %	33.7 %
Moderate	(67)	43.3 %	38.8 %
High	(85)	67.1 %	67.1 %
Unknown	(75)	36.0 %	48.0 %

Supplementary table 5: reference centre review during years of study

Year of diagnosis	Reference centre review within 3 months after diagnosis
2003	28.7 %
2004	26.8 %
2005	36.1 %
2006	28.7 %
2007	40.4 %
2008	25.8 %
2009	32.8 %
2010	35.3 %
2011	38.7 %
2012	41.2 %

Imatinib-induced agranulocytosis in patients with gastrointestinal stromal tumours

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Abstract

Agranulocytosis is a rare but serious side-effect of imatinib in gastrointestinal stromal tumour (GIST) patients. Imatinib is an inhibitor of the proto-oncogene, tyrosine kinase c-kit and the first-line agent in patients with locally advanced and metastatic GIST. Little evidence is available on the management of this adverse event, and consensus-based guidelines are lacking. In this article, we describe 4 patients with agranulocytosis after starting imatinib. In addition, an overview of the available literature concerning the underlying mechanisms is given, and therapeutic strategies for overcoming this adverse event are discussed. In our experience it appears safe to restart imatinib after normalization of neutrophil count. In case of relapse of agranulocytosis, reintroduction combined with prednisolone, with treatment with granulocyte colony-stimulating factor (G-CSF) or dose reduction can be considered.

Introduction

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours originating from the gastrointestinal tract. Constitutive activation of *KIT* receptor tyrosine kinase plays a pivotal role in the pathogenesis of GIST. Imatinib (Glivec; Gleevec) is a selective tyrosine kinase inhibitor active against the proto-oncogene c-kit (CD117), BCR-ABL (or Philadelphia chromosome in chronic myeloid leukaemia) and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Currently, imatinib is the standard treatment in locally advanced and metastatic GIST patients. Furthermore, imatinib has been approved for patients with chronic myeloid leukaemia (CML).

Overall, imatinib therapy is well tolerated. Common side effects are periorbital oedema, nausea, diarrhoea, muscle cramps, fatigue and skin rash. Dose-dependent hematologic toxicity affecting all hematopoietic lineages to a variable degree is observed clinically, especially in imatinib-treated CML-patients.[1] In GIST patients treated with imatinib grade 3-4 neutropenia is reported in 4.8% of all cases.[2] Nevertheless, imatinib-induced complete agranulocytosis (a neutrophil count less than 0.1 $x10^3$ /µL) is thought to be a rare adverse event.[3] After a first episode of imatinib-induced agranulocytosis treating clinicians are often reluctant restarting this effective drug.

In this article we report 4 GIST patients with imatinib-induced agranulocytosis (Table 1). Additionally, we give an overview of available literature regarding the possible underlying mechanisms and the different therapeutic strategies for overcoming this adverse event. Finally, we give our recommendations for treating imatinib-induced agranulocytosis.

Case report

Patient A, an 87-year old man, presented with a large intra-abdominal tumour (7.0 x 6.5 cm) and pulmonary lesions. Biopsy of the abdominal mass showed a GIST (mitotic index 4/10 HPF, KIT exon 11 mutated). His medical history included restless legs syndrome, gastroesophageal reflux disease and locally advanced prostate cancer (T3bN0M0) 1 year earlier, for which he was treated with radiotherapy and hormonal therapy. His medications included gosereline implant, tolterodine, tamsulosin, hydroquinine, pantoprazole and acetaminophen. Baseline laboratory testing showed a decreased haemoglobin level (Hb 10.3 g/dL, range 14.0-17.5 g/dL), all other bone marrow and organ functions were normal. Treatment with imatinib at a dose of 400 mg daily was commenced. Five weeks later he was admitted to our hospital because of fever and hypotension (90/50 mmHg). Further physical examination was unremarkable. Laboratory testing showed an Hb of 9.2g/dL, white blood cell count (WBC) of 8.3 $x10^3$ /µL (range 4.0 – 10.5 $x10^3$ /µL) with a complete agranulocytosis (absolute neutrophil count; ANC <0.1 $x10^3$ /µL, range 1.8-7.2 $x10^3$ /µL) and a thrombocytopenia (119 $x10^3$/µL, range 150-400 $x10^3$/µL).

Table 1. Summary of Cases Described in This Article

Patient		Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of IM[a]	Recurrence[b]	Cancer-related Outcome
A	**First episode**	400 mg	5 weeks	Stopped until recovery	10 days	Yes	Yes	Progression-free after 8 months
	Second episode	400 mg	6 weeks	Reintroduction with prednisolone	2 weeks	Yes	No	
B	**First episode**	400 mg	1 month	G-CSF dose and reduction (300 mg)	10 days	Yes	Yes	IM stopped after 3 months due to hepatic toxicity.
	Second episode	300 mg	2 weeks	Stopped until recovery	1 week	Yes	No	Progression-free after 11 years
C		400 mg	1 month	G-CSF	2 days	No	N/A	Early resection due to progression
D		400 mg	1 month	Dose reduction (300 mg)	10 days	Yes	No	Resection after 6 months of therapy

G-CSF, Granulocyte colony-stimulating factor; IM, imatinib mesylate; N/A, not applicable. [a]Reintroduction was done after complete recovery of the agranulocytosis. [b]Recurrence of agranulocytosis.

Imatinib was discontinued and broad-spectrum antibiotics were initiated. As possible contributing factor to neutropenia hydroquinine was stopped. Further investigation including urine analysis and culture, chest X-ray and blood cultures did not reveal a source of infection. He was afebrile on the second day, and he was discharged from hospital on the sixth day. Full neutrophil recovery was reached 10 days after imatinib discontinuation. Three weeks after discharge, imatinib was restarted (400 mg/day) with weekly monitoring of blood levels. Six weeks afterward, the ANC dropped to 0.5 x 10^3 / µL. Imatinib was discontinued again and now ANC normalized within 2 weeks (2.2 x10^3 / µL). Within 1 month, 400mg imatinib once daily was restarted in combination with 10mg prednisolone. After 3 months of prednisolone, the dose was decreased to 10mg every

other day and stopped a week later. Eight months later, agranulocytosis did not recur, and the patient remained progression free.

Patient B, a 41-year old female, underwent incomplete surgical resection of a multinodular gastric GIST (7 cm, spindle cell type, c-kit positive, mitotic index 0/50 HPF). At the time of diagnosis, metastases in liver and intra-abdominal lymph nodes were present. Palliative imatinib treatment at a dose of 400 mg daily was commenced. Baseline laboratory testing revealed mild normocytic anaemia (Hb 11 g/dL; MCV 81 μm^3), WBC 8.9x10^3 /µL and ANC 7.1 x10^3 /µL. One month after initiation of systemic treatment, she was admitted because of fever. Laboratory testing showed a microcytic anaemia (Hb 10.3 g/dL; MCV 78 μm^3), WBC 1.9 x10^3/µL and ANC 0.17 x10^3/µL. Two days later ANC dropped below detection threshold (<0.05 x10^3/µL). Imatinib was discontinued, and broad-spectrum antibiotics were started. Because of ongoing neutropenia on the fifth inpatient day, bone marrow examination was performed revealing an impaired granulopoiesis. A maturation arrest of neutrophils in the myelocyte stadium was seen without any other abnormalities. In addition, "normal" bowel tissue and neutrophil granulocytes in blood were screened for *KIT* exon 11 mutations. No mutations could be demonstrated in these samples.

Granulocyte colony-stimulating factors (G-CSF; 300 µg daily) was given for 5 days, resulting in rapid normalization of ANC (18.5x10^3 /µL). Further investigation did not reveal a source of infection, and she was discharged with a good clinical condition. Repeated bone marrow examination 2 weeks after discharge was unremarkable. Imatinib was restarted at a dose of 300 mg daily. Two weeks later neutropenia recurred (ANC 1.2 x10^3 /µL), and imatinib was discontinued. Full neutrophil recovery was reached 1 week later, and imatinib was restarted (300 mg). Routine laboratory tests in the following 3 months were normal. Then imatinib was stopped because of imatinib-induced hepatitis. No alternative treatment was started. Follow-up CT scans showed no progression of the residual lesions in the last 11 years.

Patient C, a 45-year old woman, was diagnosed with an abdominal tumour (8.1 x 7.9 cm) originating from the small bowel. Ultrasound-guided biopsy showed a wild type GIST. Neo-adjuvant treatment with imatinib (400 mg daily) was started. The patient was taking no other medication. Baseline laboratory testing was unremarkable. One month after starting imatinib, she complained of fever, chills, and a sore throat. Laboratory testing showed a WBC of 3.1 x 10^3/µL and ANC of <0.1 x 10^3/µL. Imatinib was promptly discontinued, and she was admitted for the administration of broad-spectrum antibiotics and G-CSF (filgrastim 1x300 µg). Within 2 days she clinically improved, the fever resolved, and the ANC rose to 0.6 x 10^3/µL. Response evaluation after 1 month showed progressive disease, and an R0 resection of the tumour was performed. Adjuvant imatinib treatment was not given.

Patient D, a 53-year old man, was found to have a rectal mass during evaluation for rectal bleeding. Biopsy revealed a c-kit-positive spindle cell wild-type GIST. Laboratory testing showed an Hb of 7.1 g/dL. Neo-adjuvant treatment with imatinib (400 mg daily) was started because of the close relationship of the tumour with the anal sphincter. During routine laboratory testing 1 month after the start of imatinib, an ANC of 0.1 x 10^3/μL was detected, and imatinib was discontinued. Ten days later the ANC recovered to 3.7 x 10^3/μL, and imatinib was restarted at a dose of once daily 300 mg. Neo-adjuvant treatment with imatinib could be continued during 6 months in total without recurrence of agranulocytosis, CT scans after 3 and 6 months showed partial response and stable disease, respectively, after which the patient was planned for resection.

Discussion

Non-chemotherapy drug-induced agranulocytosis is a rare but potentially serious adverse event that is characterized by a decrease in peripheral neutrophil count to less than 0.5 x 10^3/ μL due to cytotoxic or immunogenic mechanisms. The most feared complication of severe neutropenia is the development of potentially life-threatening infection. In 1 GIST patient, pulmonary tuberculosis secondary to grade 3 imatinib-induced neutropenia was described in 2005 by Takashima et al.[4]

Imatinib is a selective tyrosine kinase inhibitor active against c-kit (CD117), BCR-ABL and PDGFR tyrosine kinases. Imatinib is approved for treatment of CML and GIST. Myelosuppression can occur at any time during imatinib therapy, but it usually begins within the first 2 to 4 weeks of treatment.[5] In our cases, neutropenia occurred within approximately 1 month after initiation of imatinib. The incidence of hematotoxicity in CML patients treated in the first months is previously described to be most predominant at the start of treatment and decreases after 18 months.[6] Hematologic side effects are mainly dose-dependent, include all 3 lineages, and are reversible on cessation of treatment. However, 1 study comparing imatinib 400 mg daily with 800 mg daily found no difference in the incidence of neutropenia.[7] Whether the development of imatinib-induced agranulocytosis is related to drug exposure (imatinib drug levels) is unknown. In none of our 4 cases imatinib drug levels were measured. In the future, measuring the imatinib drug level may provide further insight into the underlying mechanisms of imatinib-induced agranulocytosis.

For now, it remains unclear which patients are at risk for developing hematologic toxicity. A low ANC and low haemoglobin concentration at the initiation of imatinib are potential risk factors.[8] The development of myelosuppression is particularly common in CML patients treated with imatinib. In this specific group, grade 3-4 neutropenia (ANC 0.5-1.0 and <0.5 x 10^3/μL, respectively) was reported to occur in 35-45% of patients who were treated with 400 mg daily.[9] In CML patients, myelosuppression is expected due to suppression of the malignant clone by inhibiting the BCR-ABL.

Interestingly, myelosuppression is also seen in imatinib-treated GIST patients who are assumed to have an uncompromised bone marrow function. The fact that imatinib can affect the function of normal, non-malignant cells suggests that additional pathways are involved leading to myelosuppression.[6]

The c-kit proto-oncogene (CD117), which is targeted by imatinib, has been shown to be present in several cell types including normal hematopoietic stem cells.[10] However, in vitro studies showed that the inhibitory effect of imatinib on normal CD34+ progenitor cells is largely independent of c-kit signalling. This suggests that other mechanisms might be involved in the inhibitory effect.[11] The exact mechanism by which imatinib induces its anti-proliferative effect on normal CD34+ cells has yet to be clarified.

In addition to BCR-ABL and c-kit, imatinib also inhibits platelet-derived growth factor (PDGF) activity. PDGF has been demonstrated to be an effective cytokine for the ex vivo expansion of normal early stem and progenitor cells.[12] Inhibition of PDGF activity by imatinib can therefore also contribute to myelosuppression.

Significant myelosuppression results in treatment interruptions or dose reduction, which may compromise responses to imatinib. In the case of clear agranulocytosis, cessation of imatinib treatment remains crucial to avoid further hazardous exposure. In patient B, repeated bone marrow examination demonstrated impaired granulopoiesis with a maturation arrest of neutrophils in the myelocyte stadium, which was reversible on cessation of imatinib treatment. All our patients experienced full recovery of the neutrophil count only a few days after discontinuation of imatinib. This is in line with 1 case study on imatinib induced agranulocytosis in a GIST patient describing agranulocytosis and severe skin rash, which both spontaneously recovered after cessation of therapy.[13]

Limited data are available about the risk of recurrent neutropenia when imatinib is readministered when ANC >1.5 x 10^3/μL. Re-challenge with imatinib in a slightly reduced dose after agranulocytosis in patient D was uneventful with normal ANC. Patients A and B experienced recurrence of the neutropenia after imatinib rechallenge. Patient A was able to continue imatinib treatment in combination with prednisolone therapy. Patient B could restart imatinib after the second episode without further hematologic toxicity.

Administration of G-CSF in patients B and C might have accelerated neutrophil regeneration.[14] In patients with CML, G-CSF has been shown to be effective in overcoming imatinib-induced neutropenia.[4,15–17] In this way, recovery of neutrophil counts can even be achieved during uninterrupted imatinib therapy. Treatment with G-CSF in nonchemotherapy drug-induced agranulocytosis is associated with a lower median duration of neutropenia (8 days in treated patients vs. 9 days in untreated patients, P = .015). In this report no significant association between decreased case-fatality

rates and use of hematopoietic cell growth factors could be observed.[3] However, imatinib therapy was not included in this analysis, and to our best knowledge, G-CSF administration in imatinib-induced neutropenia in GIST patients has never been studied. It therefore remains questionable whether the use of expensive G-CSF results in a clinically significant benefit and is justified in the absence of severe infection.

Patient A was able to continue imatinib treatment in combination with prednisolone therapy. This strategy was not previously described in imatinib induced agranulocytosis. Considering the short period this treatment is given to the patient and its low cost, this option can be considered. However, one can argue that re-introduction without prednisolone might have been uneventful as well. Furthermore, no immunological response was seen in the patient's bone marrow. Therefore, any possible effect of corticosteroids is unclear. Patient B could restart imatinib after the second episode without further hematologic toxicity. In this case, imatinib was reintroduced in a decreased dose of 300 mg. This strategy was also used in a study describing 13 CML patients receiving G-CSF without discontinuation of imatinib. [5] Hwang et al described a dose reduction to 100 mg in one GIST patient, without relapse of agranulocytosis or skin toxicity observed.[13] Despite dose reductions all patients in both reports show response.

Table 2 A Literature Review on Different Treatment Strategies Described for Imatinib Induced Agranulocytosis

Article	No. of patients	Primary disease	Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of Imatinib	Outcome
Heim 2003[16]	6	CML	400 - 600 mg	12-41 days (median 28 days)	G-CSF with continuation of imatinib	1-7 days (median 6 days) with G-CSF 28-42 days (median 28 days) before G-CSF	Yes, all patients	1 death (blast crisis)
Heim 2003[16]	3	CML	600 mg	Unknown	Stop imatinib until recovery	Not reported	Yes, 1 patient	2 blast crises 1 CHR but no CCR
Quintas 2004[15]	13	CML	400 – 800 mg	4-174 days (median 67 days)	G-CSF with continuation of imatinib and dose reduction to 300 mg	Within 21 days (43-144 days) with G-CSF 4-49 days (median 20 days) before G-CSF	Yes, all patients	All alive, all response to imatinib
Takashima 2005[4]	1	GIST	400 mg	5 months	Stop imatinib	Not reported	No	Died 1 year later due to progressive disease
Zaucha 2006[18]	1	CML	600 mg	1 month	G-CSF with continuation of imatinib	No recovery	no	Died of septic shock
Khouri 2008[5]	1	CML	400 mg	1 month	Stop imatinib, start G-CSF	Not reported	Not reported	Alive

Table 2 A Continued.

Article	No. of patients	Primary disease	Imatinib Daily Dose	Time to Agranulocytosis	Intervention	Time to Recovery Agranulocytosis	Reintroduction of Imatinib	Outcome
Hwang 2009[17]	1	CML	400 mg	3 months	G-CSF 300ug/day, twice weekly	1 week	yes	Relapse agranulocytosis, bone marrow examination showed M. Kahler
Hwang 2010[13]	1	GIST	400 mg	3 months	Stop imatinib and wait for recovery	1 month	Yes, with reduced dose of 100 mg due to skin rash	Alive and partial response
Zhao 2011[19]	38	CML	400 mg	12 days in control group	Berbamine in combination with imatinib withdrawal	79 (29-132) days in control group	Yes	Control: Recurrence of agranulocytosis in 10/19 pts
				10 days in Berbamine group		42 (28-88) days in Berbamine group		CCR in 17/29
						(recovery to ANC >2.0 x 10^9/l)		Berbamine: Recurrence of agranulocytosis in 3/16 pts
								CCR in 23/34

CML: chronic lymphatic leukaemia; GIST: gastrointestinal stromal tumour; G-CSF: Granulocyte Colony Stimulating Factor; CHR: complete haematological response; CCR: complete cytogenic response

In Table 2 a summary of available studies on different treatment strategies for imatinib-induced agranulocytosis is given.

Based on the sparse literature and our, albeit limited, experience in these 4 cases, we propose recommendations for patients with GIST presented with imatinib-induced agranulocytosis (Figure 1). At the first episode of agranulocytosis, we recommend cessation of imatinib treatment until full neutrophil recovery. When neutrophils are recovered, imatinib can be restarted at the same dose. If there is a relapse of imatinib-induced agranulocytosis, we recommend a rechallenge with dose reduction, or the use of either G-CSF or low dose corticosteroids in combination with full-dose imatinib. In case of a second relapse or in case of life-threatening relapse, one can consider alternative therapy. This can consist of second-line tyrosine kinase, like sunitinib, or early planned surgery in case of neo-adjuvant therapy.

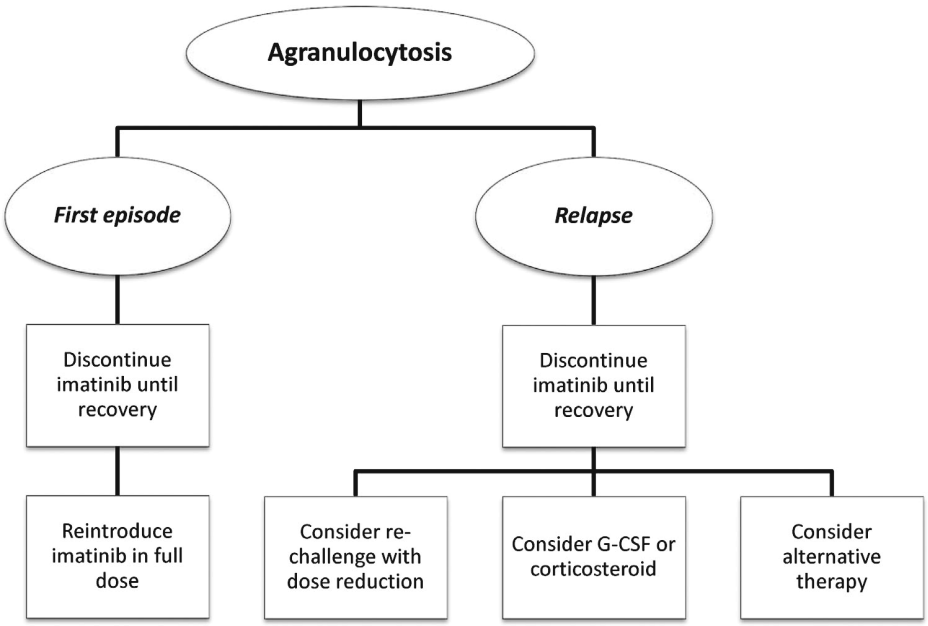

Figure 1. Recommendations for management of imatinib-induced agranulocytosis

When a patient presents with imatinib-induced agranulocytosis, we recommend stopping imatinib and waiting for full recovery. If the patient has a fever, broad-spectrum antibiotics should be administered. After full recovery, imatinib can be reintroduced at the same dose. In case of relapse of agranulocytosis, one should consider a rechallenge with imatinib in combination with dose reduction, granulocyte colony-stimulating factor (G-CSF), or low-dose corticosteroids, that is, prednisone 10 mg once daily. Prednisone dose can be slowly tapered with strict monitoring of the hemogram. One can also move to alternative therapy, for example, second-line therapy or surgery in the case of neoadjuvant therapy.

Conclusion

Imatinib-induced agranulocytosis is a rare but potentially serious adverse event with life-threatening infection as most feared complication. Imatinib is usually effective in locally advanced and metastatic GIST, and a rechallenge with imatinib should be considered after a first episode of agranulocytosis and full recovery of the neutrophil count. In our limited experience this appears a safe approach, with strict monitoring of the hemogram. The use of G-CSF or corticosteroids can be considered. Imatinib treatment should not routinely be withheld to GIST patients encountering a first episode of imatinib-induced agranulocytosis.

Declaration of Conflicting Interests

The first and second author equally contributed to the article. All authors listed sufficiently contributed to the article to be included as authors. There is no conflict of interest, financial or other.

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Prognostic relevance of distant metastases versus locally advanced disease in soft tissue sarcomas:

an EORTC-STBSG database study

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Abstract

Introduction

In patients with advanced soft tissue sarcoma treated with chemotherapy, WHO performance status, histologic subtype and histologic grade are known prognostic factors. Although the difference between the subgroups: locally advanced disease only, metastatic disease only and both local and metastatic disease is easily made, its prognostic relevance is thus far unknown. The aim of this EORTC database study was to study the difference in prognosis between these subgroups in patients receiving first line chemotherapy for advanced soft tissue sarcoma.

Methods

A retrospective database analysis was performed on 2473 patients receiving first line chemotherapy for advanced soft tissue sarcoma from 12 EORTC sarcoma trials in order to establish the difference in prognosis for the three subgroups. Endpoints were overall survival, progression-free survival and overall response rate. Factors studied were age, sex, histologic subtype, histologic grade, WHO performance status, treatment and time since initial diagnosis.

Results

Overall survival differed significantly between patients with locally advanced disease only, with metastatic disease only and with both locally advanced and metastatic disease with a median overall survival of 15.4, 12.9 and 10.6 months respectively. Similar differences were seen for progression-free survival (5.8, 4.3 and 3.2 months respectively).

Conclusion

This large retrospective database study shows that patients with advanced soft tissue sarcomas treated with first line chemotherapy with locally advanced disease, metastatic disease and both local and metastatic disease have different outcomes. This should be accounted for in future study design, interpretation and comparison of study results and daily practice.

Introduction

Soft tissue sarcomas (STS) are a rare group of tumours consisting of more than 70 histological different subtypes.[1] For the treatment of most subtypes, doxorubicin alone or in combination remains first line treatment with e.g. pazopanib and trabectedin as second line options.[2-5] For anthracycline and ifosfamide based treatments, prognostic and predictive factors were established.[6-9] These studies identified response to chemotherapy, WHO performance score, histological subtype and time since initial diagnosis to be prognostic for overall survival (OS) in STS.[6-9] One of these studies also identified a difference in OS between patients with locally advanced disease (LAD) and patients with distant metastases (DM), favouring the first subgroup when treated with first-line ifosfamide therapy.[6]

Although the difference between LAD and DM is easily made, no study investigated whether differences in outcome and response exist between these two subgroups, which could make them factors of prognostic relevance. The identification of prognostic factors is necessary for patient care and design of clinical trials. The aim of this study is to investigate whether important differences exist in OS, progression free survival (PFS) and response rate (ORR) between the different disease subgroups and is an exploratory analysis of the prognostic factors for OS, PFS and ORR in patients with STS and either LAD or DM at the moment of inclusion in a first line chemotherapy study of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG).

Methods

Patients

The EORTC-STBSG database contains data of 3708 patients from 15 EORTC advanced STS trials considering first line treatment.[4,5,10-22] Supplementary table 1 and 2 describe the different studies and the number of patients included in this study. From this database patients were excluded who had no documentation of lesions at trial entry, who had no survival data available, who were treated with a CYVADIC (cyclophosphamide/vincristine/doxorubicin/dacarbazine) regimen (EORTC-study 62761)[10] or docetaxel (1 arm of 62941)[17], who had prior (adjuvant or palliative) chemotherapy, for whom not enough information was available to distinguish primary from metastatic disease (62883 and 62901)[14,15], or who were diagnosed with gastrointestinal stromal tumour (GIST) or an ineligible tumour, being not STS.

Patients were grouped in a group with local disease only (LAD), a group with metastatic disease only (DM) and both locally advanced and metastatic disease. LAD was defined either as locally advanced disease not amenable to surgery or locally recurrent disease. DM only was defined as distant metastatic disease without evidence for local disease.

Patients in the group with both had local disease and distant metastatic disease at study inclusion.

Endpoints

Study endpoints were OS, PFS and ORR to therapy. OS was computed from the date of randomization or the date of prospective registration (nonrandomized trials) to date of death. Patients alive at last follow up were censored. PFS was defined as time interval between date of randomization or prospective registration and date of first documented progression or death, whichever comes first. ORR to chemotherapy was evaluated according to WHO or RECIST criteria depending on the study.[23-25] In this study it was analysed as binary variable, i.e. complete response and partial response are considered response and stable disease, progression or non-evaluable assessment were considered failures.

Statistical methods

Covariates

Demographic data included were age, sex and performance status before the start of chemotherapy. Performance status was measured on the WHO scale. Variables related to the history of the sarcoma were the site of the primary tumour, the use of prior radiotherapy and/or prior surgery, and time since first diagnosis of sarcoma. Because information on prior radiotherapy or prior surgery was not collected in the more recent trials it has not been included in the univariate and multivariate prognostic factor analysis to reduce the loss of data due to missing information. In most of the included studies patients had to have progression in the six months before study inclusion or had to have a histological grade of at least 2 or intermediate. Treatment was aggregated in 4 categories: anthracyclines alone (doxorubicin, epirubicin), ifosfamide alone, combination of anthracyclines and ifosfamide and other (brostallicin and trabectedin).

The way histological grade and histological subtype were used was earlier described in a study by our group.[6] Histological subtype was aggregated into the 4 most common groups: synovial sarcoma, leiomyosarcoma, liposarcoma and others. If both a local and central histological subtype were available, the central diagnosis was used. Twenty-five percent of patients had a discrepancy between the central and local diagnosis. If only a local diagnosis was available this diagnosis was used.

Statistics

Categorical data were summarized by frequencies and percentages, continuous covariates were summarized by median, interquartile range and overall range and were presented according to the three different groups. The characteristics were compared with a χ^2-test for categorical variables and a (non-parametric) Kruskal Wallis test for the continuous variables.

The potential prognostic value of all factors was investigated by univariate analysis, using univariate Cox or logistic regression models according to outcome. The prognostic value of the factors was subsequently assessed in a multivariate model, using stepwise selection. All models were stratified by treatment for heterogeneity that may be introduced by merging data from several clinical trials. Statistical significance was set at 0.05 for all analyses.

To reduce the loss of a considerable amount of information for the multivariate analysis due to a substantial amount of missing data for grade and site of primary tumour, the value "missing" was a separate category in all these models. Sensitivity analyses were performed to study the impact of this approach on the final interpretation of the models.

In addition, the analyses were repeated for only those patients included in studies after 1999 to account for the diagnosis of GIST, improved radiology techniques and improved treatment regimens, which is included in the supplementary materials.

Results

Patients

In total, 2473 patients from 12 trials were included in this study, which were separated in 3 subgroups: LAD (329 patients), DM (1202 patients) and patients with both LAD and DM (942 patients). (Supplementary figure 1) Table 1 shows the characteristics of the three subgroups. Median follow-up in years, as determined by the reverse Kaplan-Meier estimates, was 3.6 years (interquartile range 2.2-6.4) for LAD, 3.2 years (2.1-4.9) for DM, and 3.6 years (2.1-6.4) for patients with both.

Differences in survival and ORR

Compared to LAD, patients with DM had a worse prognosis (hazard ratio (HR) 1.25 (95% CI 1.08-1.45)) and patients with both LAD and DM had the worst (HR 1.59 (1.37-1.84)) (P<0.001). (Figure 1A) Median OS was 15.4 (95% CI 13.0-16.9), 12.9 (12.4-13.9) and 10.6 months (9.8-11.3) respectively. Of all patients 94.5% showed disease progression during follow-up. For PFS the same differences in survival were seen, with HR of 1.40 (1.23-1.59) for DM and 1.58 (1.38-1.81) for both LAD and DM (P<0.001). (Figure 1B) Median PFS was 5.8 (95% CI 4.4-6.5), 4.3 (3.9-4.7) and 3.2 months (2.9-3.5) respectively.

Table 1 Patient's characteristics

Patient's characteristics					
	Disease stage				
	Locally advanced (N=329)	Metastases only (N=1202)	Both (N=942)	Total (N=2473)	
	N (%)	N (%)	N (%)	N (%)	*P* -value
Gender					0.002
Male	143 (43.5)	565 (47.0)	500 (53.1)	1208 (48.8)	
Female	186 (56.5)	637 (53.0)	442 (46.9)	1265 (51.2)	
Performance status					<0.001
PS 0	132 (40.1)	635 (52.8)	390 (41.4)	1157 (46.8)	
PS 1	155 (47.1)	515 (42.8)	476 (50.5)	1146 (46.3)	
PS 2+	38 (11.6)	50 (4.2)	74 (7.9)	162 (6.6)	
Unknown	4 (1.2)	2 (0.2)	2 (0.2)	8 (0.3)	
Age (years)					0.387
< 40 yrs	78 (23.7)	257 (21.4)	216 (22.9)	551 (22.3)	
40-50 yrs	66 (20.1)	278 (23.1)	210 (22.3)	554 (22.4)	
50-60 yrs	85 (25.8)	360 (30.0)	274 (29.1)	719 (29.1)	
>=60 yrs	95 (28.9)	285 (23.7)	230 (24.4)	610 (24.7)	
Median	52	51	51	51	0.949[a]
Range	16 - 79	17 - 84	10 - 88	10 - 88	
Q1-Q3	40 - 61	42 – 60	41 - 60	41 - 60	
Unknown	5 (1.5)	22 (1.8)	12 (1.3)	39 (1.6)	
Prior radiotherapy					<0.001
No	274 (83.3)	590 (49.1)	690 (73.2)	1554 (62.8)	
Yes	33 (10.0)	464 (38.6)	170 (18.0)	667 (27.0)	
Unknown	22 (6.7)	148 (12.3)	82 (8.7)	252 (10.2)	
Prior Surgery					<0.001
No surgery	53 (16.1)	16 (1.3)	161 (17.1)	230 (9.3)	
Non-optimal surgery	91 (27.7)	106 (8.8)	184 (19.5)	381 (15.4)	
Complete surgery	68 (20.7)	487 (40.5)	178 (18.9)	733 (29.6)	
Unknown	117 (35.6)	593 (49.3)	419 (44.5)	1129 (45.7)	

Table 1 Continued.

Patient's characteristics					
	Disease stage				
	Locally advanced (N=329)	Metastases only (N=1202)	Both (N=942)	Total (N=2473)	
	N (%)	N (%)	N (%)	N (%)	*P* -value
Histology					<0.001
Leiomyosarcoma	85 (25.8)	412 (34.3)	281 (29.8)	778 (31.5)	
Synovial sarcoma	23 (7.0)	160 (13.3)	77 (8.2)	260 (10.5)	
Liposarcoma	48 (14.6)	114 (9.5)	87 (9.2)	249 (10.1)	
Other	173 (52.6)	516 (42.9)	497 (52.8)	1186 (48.0)	
Histopathological grade					0.259
Grade I	36 (10.9)	97 (8.1)	68 (7.2)	201 (8.1)	
Grade II	86 (26.1)	345 (28.7)	261 (27.7)	692 (28.0)	
Grade III	104 (31.6)	436 (36.3)	315 (33.4)	855 (34.6)	
Unknown	103 (31.3)	324 (27.0)	298 (31.6)	725 (29.3)	
Site of primary tumour					<0.001
Other	222 (67.5)	501 (41.7)	540 (57.3)	1263 (51.1)	
Extremity	37 (11.2)	457 (38.0)	233 (24.7)	727 (29.4)	
Unknown	70 (21.3)	244 (20.3)	169 (17.9)	483 (19.5)	
Time between the initial diagnosis of sarcoma and registration					<0.001
<6 months	233 (70.8)	416 (34.6)	650 (69.0)	1299 (52.5)	
6-12 months	32 (9.7)	190 (15.8)	80 (8.5)	302 (12.2)	
1-2 yrs	22 (6.7)	238 (19.8)	82 (8.7)	342 (13.8)	
>=2 yrs	40 (12.2)	352 (29.3)	118 (12.5)	510 (20.6)	
Median (months)	1.9	11.8	2.3	6.3	<0.001[a]
Range (months)	0.0 - 222.8	0.0 - 346.5	0.0 - 198.7	0.0 - 346.5	
Q1-Q3 (months)	0.8 - 9.2	4.3 - 28.5	0.9 - 9.5	1.4 - 19.1	
Unknown	2 (0.6)	6 (0.5)	12 (1.3)	20 (0.8)	

Table 1 Continued.

Patient's characteristics					
	Disease stage				
	Locally advanced (N=329)	Metastases only (N=1202)	Both (N=942)	Total (N=2473)	
	N (%)	N (%)	N (%)	N (%)	*P* -value
Treatment					
Anthracyclines	137 (41.6)	461 (38.4)	369 (39.2)	967 (39.1)	
DOX+IFO	129 (39.2)	432 (35.9)	394 (41.8)	955 (38.6)	
IFO ALONE	53 (16.1)	206 (17.1)	125 (13.3)	384 (15.5)	
Other	10 (3.0)	103 (8.6)	54 (5.7)	167 (6.8)	
Primary site involved					
No	0 (0.0)	1202 (100.0)	0 (0.0)	1202 (48.6)	
Yes	329 (100.0)	0 (0.0)	942 (100.0)	1271 (51.4)	
Lung metastases					
No	329 (100.0)	316 (26.3)	361 (38.3)	1006 (40.7)	
Yes	0 (0.0)	886 (73.7)	581 (61.7)	1467 (59.3)	
Bone metastases					
No	329 (100.0)	1071 (89.1)	810 (86.0)	2210 (89.4)	
Yes	0 (0.0)	131 (10.9)	132 (14.0)	263 (10.6)	
Liver metastases					
No	329 (100.0)	979 (81.4)	745 (79.1)	2053 (83.0)	
Yes	0 (0.0)	223 (18.6)	197 (20.9)	420 (17.0)	
Other metastases					
No	329 (100.0)	709 (59.0)	532 (56.5)	1570 (63.5)	
Yes	0 (0.0)	493 (41.0)	410 (43.5)	903 (36.5)	

[a]Kruskal-Wallis test

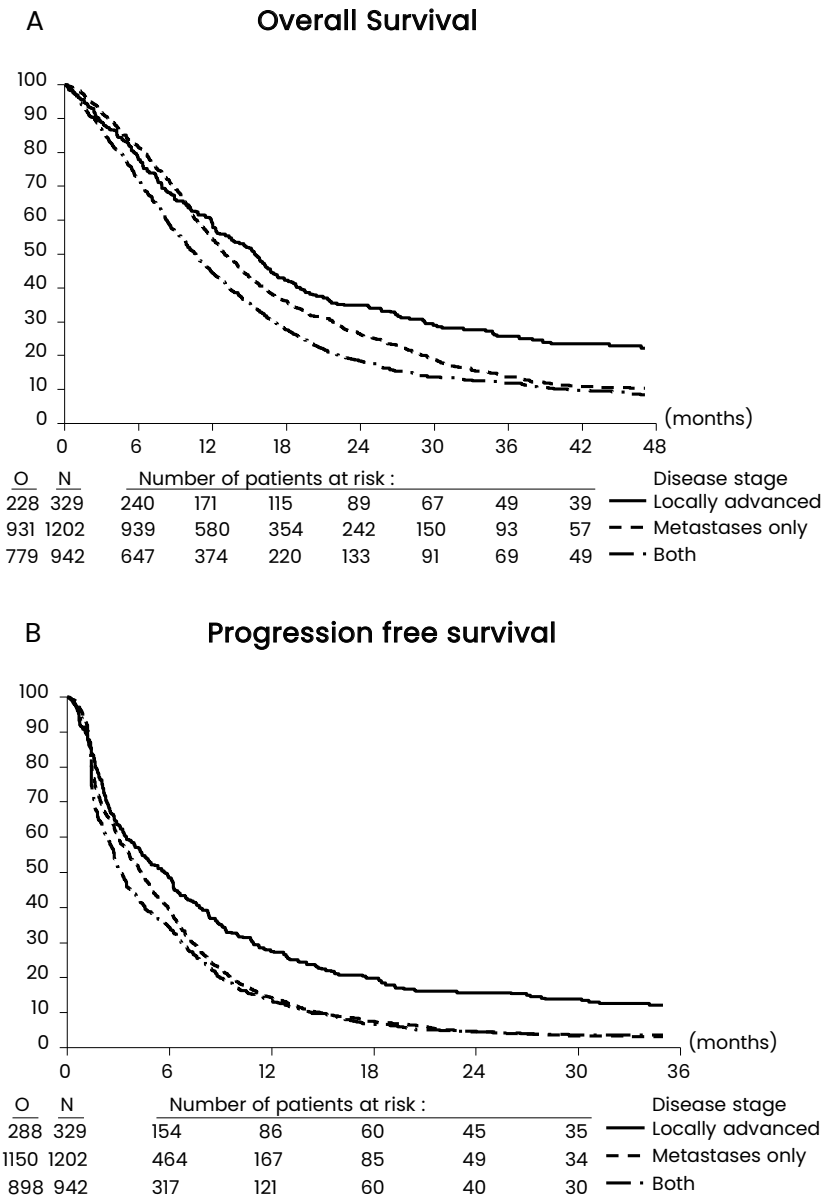

Figure 1 Overall survival (A) and progression free survival (B) according to disease stage

ORR differed among the three groups with the lowest ORR in patients with both LAD and DM (p=0.003). (Table 2)

Table 2 Overall response rate

	Disease stage			
	Locally advanced (N=329)	**Metastases only (N=1202)**	**Both (N=942)**	**Total (N=2473)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Best overall response				
Complete Response (CR)	16 (4.9)	34 (2.8)	16 (1.7)	66 (2.7)
Partial Response (PR)	47 (14.3)	226 (18.8)	133 (14.1)	406 (16.4)
Stable Disease (SD)	145 (44.1)	482 (40.1)	362 (38.4)	989 (40.0)
Progressive Disease (PD)	77 (23.4)	385 (32.0)	347 (36.8)	809 (32.7)
Not Evaluable	44 (13.4)	75 (6.2)	84 (8.9)	203 (8.2)
Responders				
Failure	266 (80.9)	942 (78.4)	793 (84.2)	2001 (80.9)
Responders (CR+PR)	63 (19.1)	260 (21.6)	149 (15.8)	472 (19.1)

Prognostic factors for OS

Table 3 shows the results of the univariate analysis. Multivariate analyses for LAD identified good performance status, histological subtype (synovial and liposarcoma), time since initial diagnosis (being not 6-12 months) and extremity site of tumour as favourable prognostic factors (table 4). For DM, the favourable prognostic factors were good performance status, histological subtype (synovial and liposarcoma) and long interval since initial diagnosis (table 4). Favourable prognostic factors for OS for patients with both LAD and DM were good performance status, female gender, younger age, lower grade, extremity site of primary tumour and long interval since initial diagnosis (table 4).

Table 3 results of univariate analysis for prognostic factors for overall survival

		Overall Survival – stratified by treatment					
		Locally advanced tumour		Metastases only		Both	
		Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)
Performance status	**PS 0**	1.00	<0.001 (df=2)	1.00	<0.001 (df=2)	1.00	<0.001 (df=2)
	PS 1	1.62 (1.21, 2.17)		1.60 (1.39, 1.83)		1.49 (1.28, 1.74)	
	PS 2+	2.38 (1.55, 3.65)		3.37 (2.46, 4.61)		1.91 (1.45, 2.50)	
Gender	**Male**	1.00	0.712	1.00	0.387	1.00	0.125
	Female	1.05 (0.80, 1.38)		0.94 (0.83, 1.08)		0.89 (0.77, 1.03)	
Age	**< 40 yrs**	1.00	0.030 (df=3)	1.00	0.206 (df=3)	1.00	0.028 (df=3)
	40-50 yrs	1.36 (0.90, 2.04)		1.13 (0.93, 1.37)		1.04 (0.84, 1.28)	
	50-60 yrs	1.40 (0.94, 2.06)		1.19 (0.99, 1.42)		1.31 (1.08, 1.60)	
	>=60 yrs	1.77 (1.21, 2.59)		1.22 (1.00, 1.49)		1.15 (0.93, 1.42)	
Histological cell type	**Leiomyosarcoma**	1.00	0.005 (df=3)	1.00	0.004 (df=3)	1.00	0.043 (df=3)
	Synovial	0.55 (0.30, 1.00)		0.82 (0.66, 1.00)		0.83 (0.63, 1.11)	
	Liposarcoma	0.51 (0.31, 0.84)		0.66 (0.52, 0.85)		0.66 (0.49, 0.89)	
	Other	1.03 (0.76, 1.41)		0.96 (0.83, 1.12)		0.91 (0.78, 1.07)	

Table 3 Continued.

		Overall Survival – stratified by treatment					
		Locally advanced tumour		Metastases only		Both	
		Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)
Grade	**Grade I**	1.00	0.071 (df=3)	1.00	0.004 (df=3)	1.00	<0.001 (df=3)
	Grade II	1.25 (0.77, 2.02)		1.33 (1.02, 1.73)		1.34 (0.99, 1.82)	
	Grade III	1.71 (1.08, 2.70)		1.55 (1.19, 2.00)		1.87 (1.38, 2.53)	
	Unknown	1.61 (1.00, 2.57)		1.52 (1.16, 2.00)		1.59 (1.17, 2.16)	
Site of primary tumour	**Other**	1.00	0.001 (df=2)	1.00	0.131 (df=2)	1.00	0.085 (df=2)
	Extremity	0.41 (0.25, 0.67)		0.87 (0.75, 1.01)		0.82 (0.69, 0.98)	
	Unknown	1.05 (0.75, 1.48)		0.87 (0.73, 1.05)		0.95 (0.78, 1.16)	
Time since initial diagnosis	**<6 months**	1.00	0.002 (df=3)	1.00	<0.001 (df=3)	1.00	0.002 (df=3)
	6-12 months	2.05 (1.34, 3.16)		1.05 (0.86, 1.27)		1.05 (0.81, 1.36)	
	1-2 yrs	1.21 (0.71, 2.08)		0.84 (0.70, 1.01)		1.02 (0.79, 1.31)	
	>=2 yrs	0.74 (0.47, 1.15)		0.63 (0.53, 0.74)		0.65 (0.52, 0.82)	

Table 4 Multivariate analysis for prognostic factors for overall survival

Parameter	Levels	Locally advanced disease Hazard ratio (95% CI)	Distant metastatic disease Hazard ratio (95% CI)	Both Hazard ratio (95% CI)
Performance status	**PS 0**	1.00	1.00	1.00
	PS 1	1.71 (1.27, 2.31)	1.62 (1.41, 1.86)	1.44 (1.24, 1.69)
	PS 2+	2.40 (1.51, 3.81)	3.52 (2.56, 4.84)	1.77 (1.33, 2.34)
		***P*<0.001 (df=2)**	***P* <0.001 (df=2)**	***P* <0.001 (df=2)**
Histology	**Leiomyosarcoma**	1.00	1.00	
	Liposarcoma	0.62 (0.37, 1.04)	0.64 (0.50, 0.83)	
	Other	1.17 (0.85, 1.62)	0.95 (0.81, 1.10)	
	Synovial sarcoma	0.76 (0.41, 1.42)	0.82 (0.66, 1.00)	
		***P* =0.047 (df=3)**	***P* =0.003 (df=3)**	
Site of primary tumour	**Other**	1.00		1.00
	Extremity	0.40 (0.24, 0.66)		0.77 (0.65, 0.92)
	Unknown	*0.78 (0.54, 1.12)*		*0.90 (0.73, 1.10)*
		***P* =0.001 (df=2)**		***P* =0.016 (df=2)**
Time since initial diagnosis	**<6 months**	1.00	1.00	1.00
	6-12 months	2.03 (1.31, 3.14)	1.16 (0.95, 1.41)	1.09 (0.84, 1.42)
	1-2 yrs	1.56 (0.89, 2.74)	0.91 (0.76, 1.10)	0.95 (0.74, 1.23)
	>=2 yrs	0.90 (0.57, 1.42)	0.69 (0.58, 0.82)	0.67 (0.53, 0.85)
		***P* =0.006 (df=3)**	***P* <0.001 (df=3)**	***P* =0.008 (df=3)**
Gender	**Male**			1.00
	Female			0.84 (0.72, 0.97)
				***P* =0.019 (df=1)**
Age	**< 40 yrs**			1.00
	40-50 yrs			1.05 (0.85, 1.31)
	50-60 yrs			1.44 (1.18, 1.77)
	>=60 yrs			1.17 (0.94, 1.46)
				***P* =0.002 (df=3)**
Histologic grade	**Grade I**			1.00
	Grade II			1.32 (0.97, 1.80)
	Grade III			1.76 (1.30, 2.39)
	Unknown			*1.45 (1.06, 1.98)*
				***P* <.001 (df=3)**

Prognostic factors for PFS

Table 5 shows the results of the univariate analysis. Multivariate analyses for LAD identified good performance status and time since initial diagnosis (being not 6-12 months) as favourable prognostic factors (table 6). For DM, the favourable prognostic factors were good performance status, histological subtype (synovial and liposarcoma) and long time since initial diagnosis (table 6). Favourable prognostic factors for PFS for patients with both LAD and DM were good performance status, histological subtype (synovial and liposarcoma) and lower grade (table 6).

Table 5 Univariate analysis for prognostic factors for progression free survival

		Progression free survival – stratified by treatment					
		Locally advanced tumour		Metastases only		Both	
		Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)
Performance status	**PS 0**	1.00	<0.001 (df=2)	1.00	<0.001 (df=2)	1.00	0.006 (df=2)
	PS 1	1.39 (1.07, 1.80)		1.26 (1.12, 1.43)		1.23 (1.07, 1.42)	
	PS 2+	2.14 (1.44, 3.17)		1.83 (1.35, 2.48)		1.34 (1.03, 1.74)	
Gender	**Male**	1.00	0.510	1.00	0.999	1.00	0.471
	Female	0.92 (0.72, 1.18)		1.00 (0.89, 1.12)		0.95 (0.83, 1.09)	
Age	**< 40 yrs**	1.00	0.197 (df=3)	1.00	0.273 (df=3)	1.00	0.045 (df=3)
	40-50 yrs	1.26 (0.87, 1.82)		1.12 (0.94, 1.33)		1.06 (0.87, 1.29)	
	50-60 yrs	1.39 (0.98, 1.96)		1.11 (0.94, 1.32)		1.28 (1.06, 1.55)	
	>=60 yrs	1.40 (1.00, 1.97)		1.20 (1.00, 1.43)		1.19 (0.97, 1.46)	
Histological cell type	**Leiomyosarcoma**	1.00	0.047 (df=3)	1.00	0.001 (df=3)	1.00	0.013 (df=3)
	Synovial sarcoma	0.60 (0.35, 1.01)		0.75 (0.63, 0.91)		0.70 (0.54, 0.91)	
	Liposarcoma	0.99 (0.66, 1.49)		0.68 (0.55, 0.84)		0.73 (0.57, 0.94)	
	Other	1.18 (0.88, 1.59)		0.86 (0.75, 0.99)		0.87 (0.75, 1.01)	

Table 5 Continued.

		Progression free survival – stratified by treatment					
		Locally advanced tumour		Metastases only		Both	
		Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)	Hazard Ratio (95% CI)	P-Value (Score test)
Histologic grade	**Grade I**	1.00	0.798 (df=3)	1.00	0.165 (df=3)	1.00	0.014 (df=3)
	Grade II	1.10 (0.72, 1.68)		1.17 (0.93, 1.48)		1.31 (0.99, 1.72)	
	Grade III	1.20 (0.79, 1.81)		1.27 (1.01, 1.60)		1.53 (1.16, 2.01)	
	Unknown	1.20 (0.79, 1.83)		1.26 (0.99, 1.59)		1.43 (1.08, 1.89)	
Site of primary tumour	**Other**	1.00	0.076 (df=2)	1.00	0.006	1.00	0.642 (df=2)
	Extremity	0.66 (0.44, 0.99)		0.81 (0.71, 0.92)		0.93 (0.79, 1.09)	
	Unknown	1.10 (0.81, 1.50)		0.91 (0.77, 1.07)		0.99 (0.82, 1.19)	
Time since initial diagnosis	**<6 months**	1.00	0.001 (df=3)	1.00	<0.001 (df=3)	1.00	0.153 (df=3)
	6-12 months	2.10 (1.41, 3.14)		1.05 (0.88, 1.25)		1.08 (0.85, 1.37)	
	1-2 yrs	1.78 (1.09, 2.89)		0.96 (0.81, 1.13)		1.23 (0.97, 1.55)	
	>=2 yrs	1.08 (0.74, 1.58)		0.70 (0.61, 0.82)		0.88 (0.72, 1.08)	

Table 6 Multivariate analysis for prognostic factors for progression free survival

		Locally advanced disease	Distant metastatic disease	Both
Parameter	**Levels**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Performance status	**PS 0**	1.00	1.00	1.00
	PS 1	1.43 (1.10, 1.87)	1.28 (1.13, 1.45)	1.20 (1.04, 1.39)
	PS 2+	2.11 (1.41, 3.17)	1.90 (1.40, 2.57)	1.24 (0.95, 1.62)
		***P* <.001 (df=2)**	***P* <.001 (df=2)**	***P* =0.031 (df=2)**
Histology	**Leiomyosarcoma**		1.00	1.00
	Liposarcoma		0.69 (0.55, 0.85)	0.77 (0.60, 1.00)
	Other		0.86 (0.75, 0.99)	0.85 (0.73, 0.99)
	Synovial sarcoma		0.77 (0.64, 0.93)	0.70 (0.54, 0.92)
			***P* =0.002 (df=3)**	***P* =0.024 (df=3)**
Time since initial diagnosis	**<6 months**	1.00	1.00	
	6-12 months	1.92 (1.28, 2.88)	1.11 (0.93, 1.33)	
	1-2 yrs	2.07 (1.26, 3.39)	1.01 (0.85, 1.19)	
	>=2 yrs	1.08 (0.74, 1.58)	0.74 (0.64, 0.87)	
		***P* =0.001 (df=3)**	***P* <.001 (df=3)**	
Histologic grade	**Grade I**			1.00
	Grade II			1.31 (0.99, 1.73)
	Grade III			1.50 (1.14, 1.98)
	Unknown			*1.41 (1.07, 1.87)*
				***P* =0.029 (df=3)**

Prognostic factors for overall response

Results of the univariate analysis and multivariate analysis for prognostic factors for ORR are shown in table 7 and 8.

Table 7 Univariate analysis for prognostic factors for overall response rate (a lower odds ratio indicates a higher change for good response)

		Response rate – stratified by treatment					
		Locally advanced tumour		Metastases only		Both	
		Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Performance Status	**PS 0**	1.00	0.161 (df=2)	1.00	0.801 (df=2)	1.00	0.572 (df=2)
	PS 1	0.73 (0.40, 1.32)		1.07 (0.79, 1.43)		0.83 (0.57, 1.21)	
	PS 2+	2.02 (0.65, 6.29)		1.24 (0.60, 2.56)		0.79 (0.40, 1.55)	
Gender	**Male**	1.00	0.856 (df=1)	1.00	0.053 (df=1)	1.00	0.225 (df=1)
	Female	1.05 (0.60, 1.86)		1.32 (1.00, 1.76)		0.80 (0.56, 1.15)	
Age	**< 40 yrs**	1.00	0.445 (df=3)	1.00	0.137 (df=3)	1.00	0.043 (df=3)
	40-50 yrs	1.33 (0.60, 2.95)		1.44 (0.96, 2.16)		0.79 (0.49, 1.27)	
	50-60 yrs	1.79 (0.81, 3.92)		1.39 (0.95, 2.04)		1.58 (0.95, 2.62)	
	>=60 yrs	1.66 (0.78, 3.54)		1.59 (1.04, 2.43)		1.26 (0.74, 2.16)	
Histological cell type	**Leiomyosarcoma**	1.00	0.289 (df=3)	1.00	<0.001 (df=3)	1.00	0.772 (df=3)
	Synovial	0.41 (0.14, 1.14)		0.42 (0.27, 0.66)		0.78 (0.39, 1.56)	
	Liposarcoma	1.20 (0.42, 3.40)		0.32 (0.20, 0.53)		0.77 (0.39, 1.51)	
	Other	0.84 (0.42, 1.67)		0.67 (0.47, 0.96)		0.83 (0.54, 1.25)	

Table 7 Continued.

		Response rate – stratified by treatment					
		Locally advanced tumour		Metastases only		Both	
		Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Grade	**Grade I**	1.00	0.418 (df=3)	1.00	0.180 (df=3)	1.00	0.022 (df=3)
	Grade II	1.30 (0.43, 3.90)		1.27 (0.71, 2.24)		1.93 (0.90, 4.12)	
	Grade III	0.67 (0.25, 1.81)		0.87 (0.50, 1.50)		0.87 (0.44, 1.75)	
	Unknown	0.85 (0.31, 2.37)		1.14 (0.64, 2.04)		1.10 (0.54, 2.23)	
Site of primary tumour	**Other**	1.00	0.597 (df=2)	1.00	<0.001 (df=2)	1.00	0.742 (df=2)
	Extremity	0.84 (0.36, 2.00)		0.44 (0.31, 0.60)		0.98 (0.63, 1.51)	
	Unknown	0.71 (0.36, 1.40)		0.78 (0.52, 1.18)		0.83 (0.52, 1.33)	
Time since initial diagnosis	**<6 mon**	1.00	0.180 (df=3)	1.00	0.447 (df=3)	1.00	0.510 (df=3)
	6-12 mon	1.90 (0.63, 5.70)		1.42 (0.91, 2.22)		0.88 (0.47, 1.63)	
	1-2 yrs	1.67 (0.47, 5.98)		1.21 (0.81, 1.80)		0.76 (0.42, 1.37)	
	>=2 yrs	3.23 (0.95, 10.96)		1.12 (0.79, 1.60)		1.40 (0.73, 2.66)	

Table 8a Multivariate analysis for overall response rate for metastatic disease only (a lower odds ratio indicates a higher change for good response)

Parameter	Levels	Odds Ratio (95% CI)	P-value
Histology	**Leiomyosarcoma**	1.00	0.002 (df=3)
	Liposarcoma	0.40 (0.24, 0.66)	
	Other	0.80 (0.56, 1.16)	
	Synovial sarcoma	0.58 (0.36, 0.93)	
Site of primary tumour	**Other**	1.00	0.001 (df=2)
	Extremity	0.51 (0.36, 0.73)	
	Unknown	0.80 (0.53, 1.22)	

Table 8b Multivariate analysis for overall response rate for patients with both locally advanced and metastatic disease (a lower odds ratio indicates a higher change for good response)

Parameter	Levels	Odds Ratio (95% CI)	P-value
Grade	**Grade I**	1.00	0.022 (df=3)
	Grade II	1.93 (0.90, 4.12)	
	Grade III	0.87 (0.44, 1.75)	
	Unknown	1.10 (0.54, 2.23)	

Discussion

This study is the first showing that for all frontline treatments in locally advanced and/or metastatic soft tissue sarcomas OS, PFS and ORR outcomes differ according to disease subgroup. This difference should be accounted for in daily practice and when designing and interpreting clinical trials. We also established prognostic factors for OS, PFS and ORR in these different disease subgroups and important differences in prognostic factors between these disease subgroups were identified, which underlines the importance of accounting for the different disease subgroups. Patients with LAD had a better prognosis compared to both other groups. This difference may be explained by additional treatment with either surgery or radiotherapy in the locally advanced setting. No data on post-chemotherapy treatment was available in the study database used for this project and so we cannot provide evidence for this statement. The difference in survival between the different disease subgroups stresses the importance of stratification for disease subgroup in future trials.

In line with this observation, locally advanced tumours of the extremity had a better OS than other tumour sites, because these are more accessible to surgery and radiotherapy with relatively low morbidity. This was also found recently in an Indian study which showed that patients with extremity tumours and patients with multimodality treatment had a favourable prognosis, suggesting that the possibility of aggressive treatment of the primary tumour localization may result in a better survival.[26] Tumour site is also a known prognostic factor in surgically treated non-metastatic sarcoma patients.[27] Time since initial diagnosis behaves differently as prognostic factor between patients with LAD (both a very short time and a very long time from initial diagnosis were associated with a favourable prognosis) and both the other groups (only a long time interval from initial diagnosis having a favourable diagnosis). This could be because aggressive tumours tend to respond fast to chemotherapy and so become amenable to surgical therapy as a local treatment, which could prolong the OS. This was already shown in a previous database study of our group.[7] In the metastatic setting surgery usually is not an option and aggressive tumours will progress early. The fact that high histological grade is a favourable prognostic factor for ORR in patients with both LAD and DM supports this hypothesis. On the other hand, very early relapse, i.e. recurrence within 6 months after resection, could be caused by incomplete surgery, which would result in a group with mixed biology, and early relapse, i.e. recurrence between 6 and 12 months after resection, is caused mainly by bad biology. Because bad biology will lead to more rapidly progression compared to the mixed biology of the very early relapse group. This could also explain the difference in prognosis.

As in earlier studies for STS and other tumours performance status, histologic subtype and time since initial diagnosis were prognostic factors for OS.[8,9,28–30] Remarkably, in the multivariate analyses histologic subtype was no longer prognostic for patients with both LAD and DM. As was already mentioned in the methods section, histopathologic diagnosis was in approximately 25% of the patients different between local and central review. This difficulty with correctly classifying sarcomas could result in the differences in outcome between the various studies when studying histological subtype as prognostic factor. Histologic grade, also a known prognostic factor, was not identified as prognostic factor for OS in patients with LAD and dropped out in the multivariate model of metastatic disease, however this could be due to an underpowered comparison due to the lower number of patients in this group.[8] In general, synovial and liposarcoma are known to be sarcomas with a relatively good prognosis.[31] For both patients with LAD and patients with both LAD and DM, age and gender were both prognostic factors for patients with both local and metastatic disease compared to the two other groups. The difference in prognosis between sexes was found previously in other studies and it was hypothesized that it was caused by differences in pharmacokinetics of cytostatic drugs of amongst other cyclophosphamide and doxorubicin, with a decreased metabolism in women and so a higher drug exposure.[32] On the other hand the difference could be explained by the high grade undifferentiated uterine sarcomas, which of course only occur in women

and have a very poor prognosis.[33] However, whether these two explanations are the full explanation is questionable because it was not a prognostic factor for OS in patients with LAD or DM and it was not a prognostic factor for PFS and ORR. For PFS the known risk factors performance status, histological subtype, time since initial diagnosis and grade were identified as prognostic factors. No new prognostic factors were identified. The same difference for time since initial diagnosis was found as for OS. Grade was only prognostic for patients with both LAD and DM and such that a higher grade was associated with a worse PFS.[8] For LAD no prognostic factors for ORR were identified in contrast to patients with DM and patients with both LAD and DM. For patients with DM histology and site of primary tumour were identified. The role of primary tumour site may relate to later diagnosis and bulkier disease at presentation for non-extremity disease. As earlier mentioned low grade and high grade had a favourable prognosis compared to intermediate grade tumours for ORR in patients with both LAD and DM. High histologic grade was previously found to be prognostic, but the finding that low histologic grade was associated with a better overall response rate is surprising.[7] As grading of sarcomas is difficult and it was an inclusion criterion for the studies to be progressive within 6 months before study inclusion, it could be that the included grade I sarcomas had a more aggressive behaviour like grade III tumours.

The results of this retrospective study should be interpreted with care. First, the database contains studies over 32 years. In this time, treatment has changed and supportive measurements have improved. These could influence the prognostic factors. Also, the histologic subtypes of STS have changed over the years. High incident subtypes like malignant fibrous histiocytoma no longer exist in the current WHO classification.[1] Also new subtypes were identified during these years, like GIST often diagnosed as leiomyosarcoma before 2000.[34-36] An additional subgroup analysis with only those patients included in studies after 1999 was done to account for these changes. Although this subgroup analysis was hampered by the reduced number of patients, it resulted in comparable outcomes. (Supplementary data: additional subgroup analysis)

In the future, treatment will be more and more histological subtype and molecular driver specific. Furthermore, some studies included regimens which are currently no longer in use, such as ifosfamide 5 g/m2 as a 24-hour infusion and doxorubicin/ifosfamide combinations with lower doses than currently used. Ideally the results of this study should be validated in a prospective observational study, comparing the overall survival in these three subgroups under the current treatments available.

The results of this study are important for daily practice, because current treatment regimens are based on phase III studies currently not accounting for these differences and thereby introducing bias, as these studies suggest that included LAD patients are comparable to patients with both locally advanced and distant metastatic disease. Second, the prognosis is essential information for patients when considering palliative

treatment and the differences in prognosis between patients with LAD, DM and both should be used in this decision.

In conclusion, this study shows a difference in prognosis between patients with LAD, DM and patients with both LAD and DM. This study does indicate that there are a number of differences in prognostic factors between patients with LAD, DM and with both LAD and DM. Thus, in future trials the randomization should be stratified for disease stage.

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Conflicts of interest

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Supplementary data

Supplementary table 1 Included studies and study treatments

Study	Phase & design	Trt Arm A (N)	Trt arm B (N)	Trt Arm C (N)	N contributing to this substudy Total = 2473
1. EORTC 62761	**R. Ph II**	CYVADIC FU (191) #	CYVADIC Cy (121) #		-
2. EORTC 62801	**R. Ph II/III**	DOX 75 (106)	EPI 75 (104)		184
3. EORTC 62842	**Ph II**	DOX 50 + IFO 5000 (203)			189
4. EORTC 62851	**R. Ph III**	DOX 75 (295)	DOX 50 + IFO 5000 (297)	CYVADIC FU (157) #	512
5. EORTC 62883	**Ph II**	DOX 75 + IFO 5000 (111)#			-
6. EORTC 62901	**R. Ph II/III**	DOX 75 (112) #	EPI 3*50 (111) #	EPI 1*150 (111) #	-
7. EORTC 62903	**R. Ph III**	DOX 50 + IFO 5000 (157)	DOX 75 + IFO 5000 (157)		293
8. EORTC 62912	**R. ph II**	IFO 5000 (93)	IFO 3*3000 (89)		100
9. EORTC 62941	**R. Ph II**	DOX 75 (42)	DOCETAXEL (44)#		40
10. EORTC 62953	**Ph II**	IFO 12 (124)			91
11. EORTC 62962	**R. Ph II**	DOX 75 (45)	Caelyx (50)		88
12. EORTC 62971	**R. Ph III**	DOX 75 (110)	IFO 3*3000 (109)	IFO 5000 (107)	292
13. EORTC 62012	**R. Ph III**	DOX 75 (228)	DOX 75 + IFO 10 (227)		435
14. EORTC 62061	**R. Ph II**	DOX 75 (39)	Brostallicin (N=79)		116
15. EORTC 62091	**R. Ph II**	DOX 75 (43)	Trabectedin 3hrs (N=47)	Trabectedin 24hrs (N=43)	133

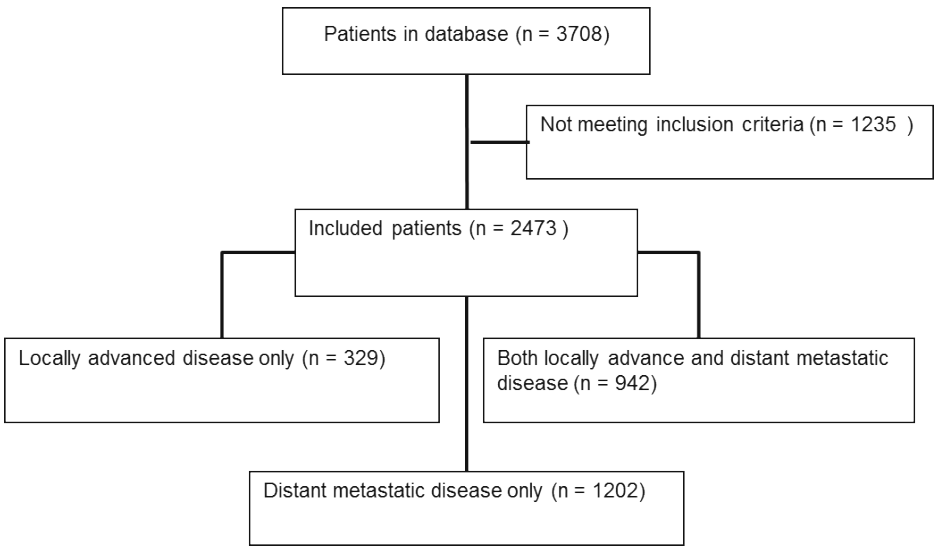
R. randomized, Ph phase, CYVADIC cyclophosphamide, vincristine, doxorubicin, dacarbazin, DOX doxorubicin, EPI epirubicin, IFO ifosfamide, given dose is in mg/m^2
Treatment arms that were excluded

Supplementary table 2 Inclusion per year

YEAR	Protocol												
Frequency	62012	62061	62091	62801	62842	62851	62903	62912	62941	62953	62962	62971	Total
1980	0	0	0	4	0	0	0	0	0	0	0	0	4
1981	0	0	0	84	0	0	0	0	0	0	0	0	84
1982	0	0	0	72	0	0	0	0	0	0	0	0	72
1983	0	0	0	24	0	0	0	0	0	0	0	0	24
1984	0	0	0	0	74	0	0	0	0	0	0	0	74
1985	0	0	0	0	114	11	0	0	0	0	0	0	125
1986	0	0	0	0	1	123	0	0	0	0	0	0	124
1987	0	0	0	0	0	122	0	0	0	0	0	0	122
1988	0	0	0	0	0	146	0	0	0	0	0	0	146
1989	0	0	0	0	0	95	0	0	0	0	0	0	95
1990	0	0	0	0	0	15	0	0	0	0	0	0	15
1992	0	0	0	0	0	0	48	0	0	0	0	0	48
1993	0	0	0	0	0	0	123	0	0	0	0	0	123
1994	0	0	0	0	0	0	105	13	0	0	0	0	118
1995	0	0	0	0	0	0	17	66	24	0	0	0	107
1996	0	0	0	0	0	0	0	21	16	28	0	0	65
1997	0	0	0	0	0	0	0	0	0	63	40	0	103
1998	0	0	0	0	0	0	0	0	0	0	48	49	97
1999	0	0	0	0	0	0	0	0	0	0	0	106	106
2000	0	0	0	0	0	0	0	0	0	0	0	86	86
2001	0	0	0	0	0	0	0	0	0	0	0	51	51
2003	10	0	0	0	0	0	0	0	0	0	0	0	10
2004	55	0	0	0	0	0	0	0	0	0	0	0	55
2005	68	0	0	0	0	0	0	0	0	0	0	0	68
2006	63	3	0	0	0	0	0	0	0	0	0	0	66
2007	59	71	0	0	0	0	0	0	0	0	0	0	130
2008	63	42	0	0	0	0	0	0	0	0	0	0	105
2009	86	0	0	0	0	0	0	0	0	0	0	0	86
2010	31	0	0	0	0	0	0	0	0	0	0	0	31
2011	0	0	27	0	0	0	0	0	0	0	0	0	27
2012	0	0	106	0	0	0	0	0	0	0	0	0	106
Total	435	116	133	184	189	512	293	100	40	91	88	292	2473

Supplementary table 3 Histologic subtypes included

	Disease stage			
	Locally advanced (N=173)	**Metastases only (N=516)**	**Both (N=497)**	**Total (N=1186)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Histological cell type for other				
Malignant fibrous histiocytoma	41 (23.7)	124 (24.0)	90 (18.1)	255 (21.5)
Fibrosarcoma	12 (6.9)	37 (7.2)	40 (8.0)	89 (7.5)
Rhabdomyosarcoma	10 (5.8)	17 (3.3)	29 (5.8)	56 (4.7)
Angiosarcoma	12 (6.9)	28 (5.4)	45 (9.1)	85 (7.2)
Neurogenic sarcomas	25 (14.5)	50 (9.7)	34 (6.8)	109 (9.2)
Miscellaneous	47 (27.2)	210 (40.7)	180 (36.2)	437 (36.8)
Unclassified	26 (15.0)	50 (9.7)	79 (15.9)	155 (13.1)



Supplementary figure 1 Consort diagram

Subgroup analysis of patients treated after 1999

Post 1999 subgroup analysis: protocols 62012, 62061, 62091

Limited subgroup (N =684) of which the majority belongs to 62012 (435) – phase 3 and two smaller phase 2 studies

Supplementary analysis: patients included in studies after 1999

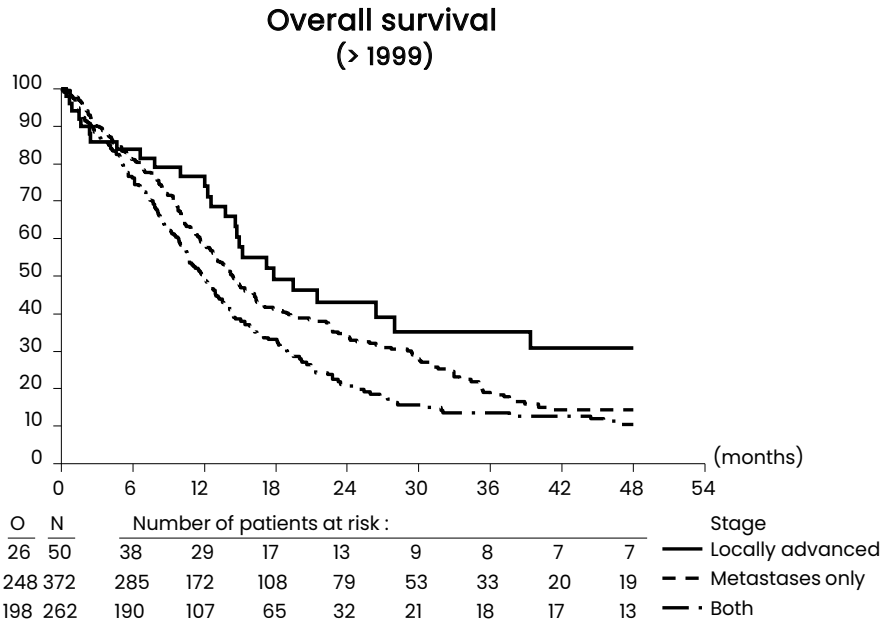
Patient's characteristics				
	Disease stage			
	Locally advanced (N=50)	**Metastases only (N=372)**	**Both (N=262)**	**Total (N=684)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Gender				
Male	22 (44.0)	172 (46.2)	129 (49.2)	323 (47.2)
Female	28 (56.0)	200 (53.8)	133 (50.8)	361 (52.8)
Performance status				
PS 0	28 (56.0)	225 (60.5)	119 (45.4)	372 (54.4)
PS 1	22 (44.0)	145 (39.0)	143 (54.6)	310 (45.3)
PS 2+	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)
Age (years)				
< 40 yrs	13 (26.0)	54 (14.5)	49 (18.7)	116 (17.0)
40-50 yrs	4 (8.0)	88 (23.7)	68 (26.0)	160 (23.4)
50-60 yrs	19 (38.0)	131 (35.2)	85 (32.4)	235 (34.4)
>=60 yrs	14 (28.0)	99 (26.6)	60 (22.9)	173 (25.3)
Median	54	54	51	53
Range	21 - 78	18 - 84	19 - 88	18 - 88
Q1-Q3	36 - 60	44 - 60	43 - 59	44 - 60
Prior radiotherapy				
No	26 (52.0)	110 (29.6)	143 (54.6)	279 (40.8)
Yes	2 (4.0)	116 (31.2)	38 (14.5)	156 (22.8)
Missing	22 (44.0)	146 (39.2)	81 (30.9)	249 (36.4)

Supplementary analysis continued

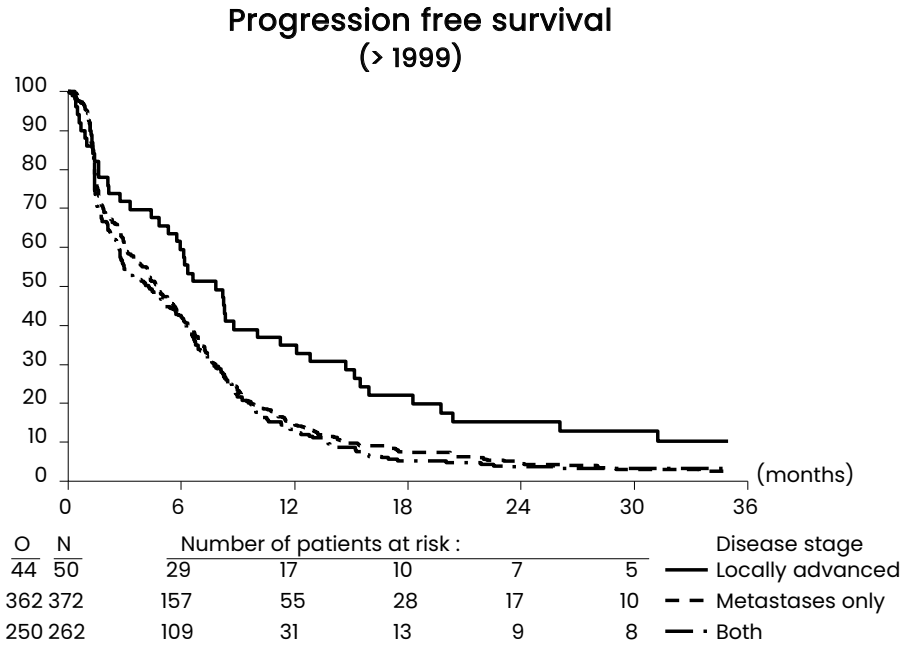
Patient's characteristics				
	Disease stage			
	Locally advanced (N=50)	Metastases only (N=372)	Both (N=262)	Total (N=684)
	N (%)	N (%)	N (%)	N (%)
Prior Surgery				
Unknown	50 (100.0)	372 (100.0)	262 (100.0)	684 (100.0)
histology				
Leiomyosarcoma	10 (20.0)	107 (28.8)	69 (26.3)	186 (27.2)
Synovial sarcoma	3 (6.0)	53 (14.2)	23 (8.8)	79 (11.5)
Liposarcoma	16 (32.0)	44 (11.8)	37 (14.1)	97 (14.2)
Other	21 (42.0)	168 (45.2)	133 (50.8)	322 (47.1)
Histopathological grade				
Grade I	4 (8.0)	15 (4.0)	12 (4.6)	31 (4.5)
Grade II	19 (38.0)	123 (33.1)	98 (37.4)	240 (35.1)
Grade III	16 (32.0)	170 (45.7)	113 (43.1)	299 (43.7)
Missing	11 (22.0)	64 (17.2)	39 (14.9)	114 (16.7)
Site of primary tumour				
Other	40 (80.0)	183 (49.2)	183 (69.8)	406 (59.4)
Extremity	10 (20.0)	176 (47.3)	76 (29.0)	262 (38.3)
Missing	0 (0.0)	13 (3.5)	3 (1.1)	16 (2.3)
Time between the initial diagnosis of sarcoma and registration				
<6 mon	31 (62.0)	121 (32.5)	175 (66.8)	327 (47.8)
6-12 mon	7 (14.0)	60 (16.1)	21 (8.0)	88 (12.9)
1-2 yrs	6 (12.0)	64 (17.2)	26 (9.9)	96 (14.0)
>=2 yrs	6 (12.0)	127 (34.1)	40 (15.3)	173 (25.3)
Median	2.3	12.3	2.6	8.1
Range	0.0 - 117.7	0.2 - 249.8	0.0 - 198.7	0.0 - 249.8
Q1-Q3	1.1 - 11.9	5.2 - 33.5	1.2 - 12.2	1.9 - 24.6

Supplementary analysis continued

Patient's characteristics				
	Disease stage			
	Locally advanced (N=50)	Metastases only (N=372)	Both (N=262)	Total (N=684)
	N (%)	N (%)	N (%)	N (%)
Treatment				
Anthracyclines	25 (50.0)	159 (42.7)	115 (43.9)	299 (43.7)
DOX+IFO	15 (30.0)	110 (29.6)	93 (35.5)	218 (31.9)
Other	10 (20.0)	103 (27.7)	54 (20.6)	167 (24.4)
Primary site involved				
No	0 (0.0)	372 (100.0)	0 (0.0)	372 (54.4)
Yes	50 (100.0)	0 (0.0)	262 (100.0)	312 (45.6)
Lung metastases				
No	50 (100.0)	86 (23.1)	80 (30.5)	216 (31.6)
Yes	0 (0.0)	286 (76.9)	182 (69.5)	468 (68.4)
Bone metastases				
No	50 (100.0)	323 (86.8)	213 (81.3)	586 (85.7)
Yes	0 (0.0)	49 (13.2)	49 (18.7)	98 (14.3)
Liver metastases				
No	50 (100.0)	300 (80.6)	211 (80.5)	561 (82.0)
Yes	0 (0.0)	72 (19.4)	51 (19.5)	123 (18.0)
Other metastases				
No	50 (100.0)	148 (39.8)	89 (34.0)	287 (42.0)
Yes	0 (0.0)	224 (60.2)	173 (66.0)	397 (58.0)



Disease stage	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 2 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Locally advanced	50	26	17.84 (13.80, 39.39)	43.0 (27.0, 58.1)	1.00	<0.001 (df=2)
Metastases only	372	248	14.36 (12.81, 16.26)	33.8 (28.3, 39.3)	1.51 (1.01, 2.27)	
Both	262	198	11.93 (10.51, 13.47)	20.6 (15.3, 26.5)	1.99 (1.32, 3.01)	



Disease stage	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	% at 1 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Locally advanced	50	44	7.85 (5.29, 11.24)	34.9 (22.0, 48.1)	1.00	0.002 (df=2)
Metastases only	372	362	4.78 (3.91, 5.59)	14.8 (11.4, 18.6)	1.65 (1.20, 2.28)	
Both	262	250	4.27 (2.89, 5.52)	12.4 (8.7, 16.8)	1.79 (1.29, 2.48)	

	Disease stage		
	Locally advanced (N=50)	**Metastases only (N=372)**	**Both (N=262)**
	N (%)	**N (%)**	**N (%)**
Best overall response			
Complete Response (CR)	0 (0.0)	6 (1.6)	1 (0.4)
Partial Response (PR)	4 (8.0)	77 (20.7)	30 (11.5)
Stable Disease (SD)	31 (62.0)	159 (42.7)	125 (47.7)
Progressive Disease (PD)	11 (22.0)	116 (31.2)	84 (32.1)
Not Evaluable	4 (8.0)	14 (3.8)	22 (8.4)
Responders			
Failure	46 (92.0)	289 (77.7)	231 (88.2)
Responders (CR+PR)	4 (8.0)	83 (22.3)	31 (11.8)

Multivariate analysis

Very low power in locally advanced subgroup with only N=50

Overall survival – metastases only

Parameter	**Levels**	**Hazard Ratio (95% CI)**	**P-value**
Performance status	**PS 0**	1.00	<.001 (df=2)
	PS 1	1.84 (1.42, 2.39)	
	PS 2+	9.52 (2.24, 40.47)	
Time since initial diagnosis	**<6 months**	1.00	<.001 (df=3)
	6-12 months	0.58 (0.40, 0.86)	
	1-2 yrs	0.59 (0.40, 0.86)	
	>=2 yrs	0.44 (0.32, 0.61)	
Gender	**Male**	1.00	0.034 (df=1)
	Female	0.76 (0.59, 0.98)	

Overall survival – both

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Performance status	**PS 0**	1.00	0.002 (df=1)
	PS 1	1.57 (1.18, 2.09)	

Progression free survival – metastases only

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Performance status	**PS 0**	1.00	<.001 (df=2)
	PS 1	1.51 (1.21, 1.87)	
	PS 2+	3.22 (0.78, 13.19)	
Time since initial diagnosis	**<6 months**	1.00	<.001 (df=3)
	6-12 months	0.73 (0.53, 1.00)	
	1-2 yrs	0.66 (0.48, 0.90)	
	>=2 yrs	0.51 (0.39, 0.66)	

Progression free survival – both

Parameter	Levels	Hazard Ratio (95% CI)	P-value
Grade	**Grade I**	1.00	0.050 (df=3)
	Grade II	1.21 (0.66, 2.22)	
	Grade III	1.72 (0.94, 3.15)	
	Unknown	1.68 (0.83, 3.39)	

Response rate – metastases only

Parameter	Levels	Odds Ratio (95% CI)	P-value
Histology	**Leiomyosarcoma**	1.00	0.001 (df=3)
	Liposarcoma	0.26 (0.11, 0.62)	
	Other	1.36 (0.66, 2.81)	
	Synovial sarcoma	1.03 (0.40, 2.62)	
Site of primary tumour	**Other**	1.00	0.001 (df=2)
	Extremity	0.31 (0.16, 0.59)	
	Unknown	0.21 (0.05, 0.87)	
Grade	**Grade I**	1.00	0.013 (df=3)
	Grade II	3.35 (0.90, 12.51)	
	Grade III	2.20 (0.60, 8.07)	
	Unknown	0.66 (0.15, 2.80)	
SEX	**Male**	1.00	0.045 (df=1)
	Female	0.56 (0.32, 0.99)	

Response rate – both:

None significant

Survival of soft tissue sarcoma patients after completing six cycles of first-line anthracycline containing treatment:

an EORTC-STBSG database study

Clin Sarcoma Res 2020; 10:18

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Abstract

Introduction

Doxorubicin based chemotherapy is standard first line treatment for patients with soft tissue sarcoma. Currently several options to improve survival after doxorubicin-based chemotherapy are being studied. This study reports on survival after completing 6 cycles of doxorubicin containing first line treatment, which is important when designing studies trying to improve outcomes of first line treatment.

Methods

A retrospective database analysis was performed on 2045 patients from 12 EORTC sarcoma trials receiving first line doxorubicin-based chemotherapy for advanced soft tissue sarcoma in order to establish progression free survival and overall survival after completing 6 cycles of first line doxorubicin-based chemotherapy. Endpoints were overall survival and progression free survival. Factors studied were histologic subtype and type of doxorubicin chemotherapy.

Results

748 of 2045 patients (36.6%) received at least 6 cycles and did not progress during or at the end of chemotherapy. 475 of 2045 (23.2%) patients received exactly 6 cycles and did not progress during or at the end of chemotherapy. Median progression free survival after 6 cycles of doxorubicin-based chemotherapy was 4.2 months (95% confidence interval 3.7-4.8) and median overall survival 15.7 months (14.0-17.8). Significant differences in progression free survival were found between chemotherapy regimens, but not for overall survival.

These data are also reported for patients receiving 7 or more cycles of chemotherapy and for patients with 3 or more cycles of chemotherapy.

Conclusion

This large retrospective study is the first to report progression free survival and overall survival after completion of 6 cycles of first line doxorubicin containing chemotherapy. These results are important when designing new studies exploring for example maintenance therapy after doxorubicin-based chemotherapy. Approximately one third of all patients may qualify for maintenance therapy.

Introduction

Soft tissue sarcomas (STS) are a rare group of tumours comprising approximately 1% of all cancers and containing approximately 70 different histological entities.[1] Clinical behaviour differs between the various histological entities.[1] Surgery is the primary treatment for localized disease when resection is possible with the option of adding neo-adjuvant or adjuvant radiotherapy.[2] For patients with locally advanced and/or distant metastatic disease the goal of treatment is to prolong survival and treatment mainly consists of systemic treatment, e.g. cytotoxic drugs and tyrosine kinase inhibitors.[2]

The current first line chemotherapy consists of anthracycline based chemotherapy either as monotherapy or combination therapy.[3] Survival remains poor for patients presenting with incurable disease. Overall survival (OS) with doxorubicin monotherapy is approximately 12.8 months and with doxorubicin/ifosfamide combination therapy approximately 14.3 months.[3] More recent trials report slightly better median OS for doxorubicin monotherapy with 17.6 months (GeDDiS), 16.9 months (PICASSO III) and 19.0 months (SARC021).[4-6] In 2016, Tap *et al.* reported the results of a phase Ib/II trial adding olaratumab, a PDGFRα blocking monoclonal antibody, to doxorubicin.[7] The results of this study were promising with an increase in progression free survival (PFS) of 2.5 months and an impressive increase in median OS from 14.7 months to 26.5 months with the addition of olaratumab.[7] This improvement in OS resulted in an accelerated approval by the U.S. Food and Drug Administration and a conditional approval by the European Medical Agency. However, recently the results of the phase III study with olaratumab, ANNOUNCE (NCT02451943), were presented during the annual meeting of the ASCO 2019 and did not show a difference between doxorubicin/placebo and doxorubicin/olaratumab. Based on these results olaratumab was withdrawn from the market.[8]

Now, other treatment strategies have to be studied to increase the PFS and OS of STS patients including the addition of maintenance therapy after completing six cycles of doxorubicin. In order to assist in the design of maintenance studies it is important to have survival data of patients after completing six cycles of doxorubicin containing treatment and to understand the extent of the attrition in the number of patients available for study, indeed the percentage who could possibly benefit from maintenance therapy by not having progressed before completing 6 cycles of treatment. This study reports the OS data of study patients completing six cycles of anthracycline or anthracycline combination therapy in the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trial database.

Methods

Patients

The European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group study database contains data from 12 trials studying doxorubicin alone or in combination with ifosfamide.[3,9–19] All but one study, included patients with locally advanced or metastatic STS. The study by Steward *et al.* only included patients with metastatic STS.[12] Patients with at least 1 cycle of treatment were considered for this study. Reasons for exclusion were previous treatment with chemotherapy either as adjuvant or palliative treatment, patients without data on progression and death and patients diagnosed with Gastrointestinal Stromal Tumour (GIST). Among these patients, we focused on patients who did not progress before the end of treatment. End of treatment was considered to be 21 days after the date of administration of the last treatment. (Supplementary figure 1) Analysis was done in three different subgroups: patients who received exactly 6 cycles of doxorubicin containing chemotherapy, patients with 7 or more cycles and patients with less than 6 cycles who stopped treatment for reasons other than progression.

The EORTC studies 62012, 62061, 62091, 62962 and 62971 had treatment regimens including a maximum number of 6 cycles of doxorubicin, 62941 7 cycles and the other studies aimed for a cumulative dose of 550 mg/m^2 of doxorubicin allowing for more if the ejection fraction remained within certain limits.

Endpoints

Endpoints were PFS and OS after completing treatment, because the aim of the study was to determine PFS and OS after completion of 6 cycles of doxorubicin containing treatment in patients who did not have progressive disease at that time point. PFS was defined as the time between end of treatment and progression or death. OS was defined as the time between end of treatment and death. Also calculated were PFS from date of randomisation to date of progression or death and OS from date of randomisation to date of death. Patients progressing between start of treatment and 21 days after the last administration date were not considered for the PFS and OS after treatment analysis, because only those patients who do not have progression before the start of maintenance treatment will qualify for maintenance treatment. Time on treatment was calculated from date of randomisation or registration and the end of treatment.

Covariates

Patients were grouped according to treatment *i.e.* doxorubicin 75mg/m^2 monotherapy, doxorubicin 50mg/m^2 combined with ifosfamide 5g/m^2, doxorubicin 75mg/m^2 combined with ifosfamide 5g/m^2 and doxorubicin 75mg/m^2 combined with ifosfamide 10g/m^2. The other covariate considered in this study was histologic subtype. If central pathology review was available the central pathology diagnosis was used, if it was not present the

local pathology diagnosis was used. Only histologic subtypes comprising more than ten percent of patients were considered for separate analysis.

Statistics

PFS and OS were calculated using the Kaplan Meier method. PFS and OS were compared using a cox proportional hazard model. Significance was set at p=0.05.

Results

In total, 2045 patients were included in this study. Almost 50% of patients were treated with doxorubicin 75 mg/m^2 as monotherapy; the other patients were treated with one of the combination regimens. (Supplementary Table 1 shows the distribution of patients according to study and treatment regimen. Supplementary Table 2 shows the number of treatment cycles by study.) Median time on treatment was 15 weeks, corresponding to a median number of 5 cycles. Of all patients, 43.7% of patients (894) were treated with 6 or more cycles of chemotherapy, 70.2% of patients were treated with 3 or more cycles. Five hundred fifty-five patients (27.1%) received exactly 6 cycles of chemotherapy. Median follow-up for all patients was 4.1 years (Inter quartile range (IQR) 2.5-6.5 years). Most of the patients receiving more than 6 cycles, were included in studies studying the doxorubicin 50 mg/m^2/ifosfamide 5 gram/m^2 regimen. (Supplementary table 1)

Of these patients with at least 6 cycles of treatment 748 patients (83.7% of all patients treated with 6 or more cycles) did not progress before or at the end of treatment. For exactly 6 cycles, 475 patients (85.6% of patients treated with exactly 6 cycles) did not progress before the end of treatment. Table 1 shows the percentage of patients considered for this study per treatment strategy.

Baseline characteristics

Table 2a/b and 3a/b and supplementary table 1a-d show the characteristics of the included patients. No important differences exist between the different groups. The most common histologic subtype was leiomyosarcoma (31%), followed by the no longer existing histologic entity malignant fibrous histiocytoma (MFH) (13%) and synovial sarcoma (10%). (Supplementary Table 3) As none of the other subtypes did comprise ten percent of the patients as an entity, these were considered together when histologic subtype was studied (also MFH was added to the miscellaneous group as this entity no longer exists; smaller subgroups would reduce the statistical power).

Table 1 Distribution of patients per treatment strategy and number of cycles

	Treatment				
	DOX 75 (N= 948)	**DOX 50 - IFO 5 (N=614)**	**DOX 75 – IFO 5 (N=266)**	**DOX 75 - IFO 10 (N=217)**	**Total (N=2045)**
Number of patients with <u>at least</u> 6 cycles	403 (42.5)	270 (44.0)	103 (38.7)	118 (54.4)	895 (43.7)
Progression before / at end of treatment	67 (16.6)	55 (20.4)	15 (14.6)	9 (7.6	146 (16.3)
No progression before / at end of treatment	336 (83.4)	215 (79.6)	88 (85.4)	109 (92.4)	748 (83.6)
Number of patients with <u>less than</u> 6 cycles	545 (57.4)	344 (56.0)	163 (61.3)	99 (45.6)	1151 (56.3)
Progression before / at end of treatment	312 (57.2)	175 (50.9)	52 (31.9)	28 (28.3)	567 (49.3)
No progression before / at end of treatment	233 (42.8)	168 (49.1)	111 (68.1)	71 (71.7)	584 (50.7)

Table 2a Baseline characteristics

	Less than 6 cycles			**Exactly 6 cycles**			**More than 6 cycles**		
	PD before end of treatment (N=567)	**No PD before end of treatment (N=584)**	**Total (N=1151)**	**PD before end of treatment (N=80)**	**No PD before end of treatment (N=475)**	**Total (N=555)**	**PD before end of treatment (N=66)**	**No PD before end of treatment (N=273)**	**Total (N=339)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Gender									
Male	273 (48.1)	284 (48.6)	557 (48.4)	45 (56.3)	226 (47.6)	271 (48.8)	26 (39.4)	139 (50.9)	165 (48.7)
Female	294 (51.9)	299 (51.2)	593 (51.5)	35 (43.8)	248 (52.2)	283 (51.0)	40 (60.6)	134 (49.1)	174 (51.3)

Table 2a Continued.

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Age									
< 40 rs	122 (21.5)	124 (21.2)	246 (21.4)	26 (32.5)	125 (26.3)	151 (27.2)	18 (27.3)	80 (29.3)	98 (28.9)
40-50 yrs	137 (24.2)	122 (20.9)	259 (22.5)	20 (25.0)	115 (24.2)	135 (24.3)	11 (16.7)	64 (23.4)	75 (22.1)
50-60 yrs	164 (28.9)	170 (29.1)	334 (29.0)	19 (23.8)	148 (31.2)	167 (30.1)	13 (19.7)	73 (26.7)	86 (25.4)
>=60 yrs	134 (23.6)	156 (26.7)	290 (25.2)	13 (16.3)	85 (17.9)	98 (17.7)	16 (24.2)	49 (17.9)	65 (19.2)
Missing	10 (1.8)	12 (2.1)	22 (1.9)	2 (2.5)	2 (0.4)	4 (0.7)	8 (12.1)	7 (2.6)	15 (4.4)
Performance status									
PS 0	223 (39.3)	265 (45.4)	488 (42.4)	38 (47.5)	274 (57.7)	312 (56.2)	25 (37.9)	127 (46.5)	152 (44.8)
PS 1	275 (48.5)	265 (45.4)	540 (46.9)	34 (42.5)	189 (39.8)	223 (40.2)	32 (48.5)	120 (44.0)	152 (44.8)
PS 2+	67 (11.8)	51 (8.7)	118 (10.3)	8 (10.0)	11 (2.3)	19 (3.4)	9 (13.6)	24 (8.8)	33 (9.7)
Missing	2 (0.4)	3 (0.5)	5 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.7)	2 (0.6)

Table 2b Baseline characteristics

	Exactly 6 cycles - no PD				
	Treatment				
	DOX 75 (N=223)	DOX 50-IFO 5 (N=80)	DOX 75-IFO 5 (N=63)	DOX 75-IFO 10 (N=109)	Total (N=475)
	N (%)	N (%)	N (%)	N (%)	N (%)
Gender					
Male	102 (45.7)	34 (42.5)	30 (47.6)	60 (55.0)	226 (47.6)
Female	121 (54.3)	45 (56.3)	33 (52.4)	49 (45.0)	248 (52.2)
Missing	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)
Age					
< 40 yrs	45 (20.2)	23 (28.8)	26 (41.3)	31 (28.4)	125 (26.3)
40-50 yrs	54 (24.2)	15 (18.8)	9 (14.3)	37 (33.9)	115 (24.2)
50-60 yrs	77 (34.5)	19 (23.8)	14 (22.2)	38 (34.9)	148 (31.2)
>=60 yrs	47 (21.1)	21 (26.3)	14 (22.2)	3 (2.8)	85 (17.9)
Missing	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	2 (0.4)
Performance status					
PS 0	132 (59.2)	39 (48.8)	38 (60.3)	65 (59.6)	274 (57.7)
PS 1	84 (37.7)	37 (46.3)	24 (38.1)	44 (40.4)	189 (39.8)
PS 2+	7 (3.1)	3 (3.8)	1 (1.6)	0 (0.0)	11 (2.3)
Missing	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)

Table 3a Tumour and treatment characteristics

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Histopathological grading									
Grade I and II	38 (6.7)	30 (5.1)	68 (5.9)	6 (7.5)	52 (10.9)	58 (10.5)	8 (12.1)	24 (8.8)	32 (9.4)
Grade III	331 (58.4)	366 (62.7)	697 (60.6)	46 (57.5)	331 (69.7)	377 (67.9)	33 (50.0)	152 (55.7)	185 (54.6)
Missing	198 (34.9)	188 (32.2)	386 (33.5)	28 (35.0)	92 (19.4)	120 (21.6)	25 (37.9)	97 (35.5)	122 (36.0)
Site of primary tumour									
Other	284 (50.1)	257 (44.0)	541 (47.0)	32 (40.0)	245 (51.6)	277 (49.9)	26 (39.4)	106 (38.8)	132 (38.9)
Extremities	129 (22.8)	143 (24.5)	272 (23.6)	27 (33.8)	152 (32.0)	179 (32.3)	17 (25.8)	73 (26.7)	90 (26.5)
Missing	154 (27.2)	184 (31.5)	338 (29.4)	21 (26.3)	78 (16.4)	99 (17.8)	23 (34.8)	94 (34.4)	117 (34.5)
Histology									
Leiomyosarcoma	192 (33.9)	180 (30.8)	372 (32.3)	23 (28.8)	128 (26.9)	151 (27.2)	25 (37.9)	79 (28.9)	104 (30.7)
Synovial sarcoma	32 (5.6)	59 (10.1)	91 (7.9)	10 (12.5)	71 (14.9)	81 (14.6)	6 (9.1)	29 (10.6)	35 (10.3)
Other	315 (55.6)	317 (54.3)	632 (54.9)	44 (55.0)	266 (56.0)	310 (55.9)	35 (53.0)	151 (55.3)	186 (54.9)

Table 3a Continued.

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	28 (4.9)	28 (4.8)	56 (4.9)	3 (3.8)	10 (2.1)	13 (2.3)	0 (0.0)	14 (5.1)	14 (4.1)
Prior Surgery									
No surgery	60 (10.6)	57 (9.8)	117 (10.2)	10 (12.5)	19 (4.0)	29 (5.2)	3 (4.5)	25 (9.2)	28 (8.3)
Non optimal surgery	104 (18.3)	77 (13.2)	181 (15.7)	18 (22.5)	23 (4.8)	41 (7.4)	10 (15.2)	64 (23.4)	74 (21.8)
Complete surgery	155 (27.3)	128 (21.9)	283 (24.6)	13 (16.3)	66 (13.9)	79 (14.2)	35 (53.0)	106 (38.8)	141 (41.6)
Unknown	248 (43.7)	322 (55.1)	570 (49.5)	39 (48.8)	367 (77.3)	406 (73.2)	18 (27.3)	78 (28.6)	96 (28.3)
Prior radiotherapy									
No	435 (76.7)	390 (66.8)	825 (71.7)	58 (72.5)	279 (58.7)	337 (60.7)	43 (65.2)	191 (70.0)	234 (69.0)
Yes	119 (21.0)	171 (29.3)	290 (25.2)	19 (23.8)	153 (32.2)	172 (31.0)	23 (34.8)	82 (30.0)	105 (31.0)
Missing	13 (2.3)	23 (3.9)	36 (3.1)	3 (3.8)	43 (9.1)	46 (8.3)	0 (0)	0 (0)	0 (0)

Table 3a Continued.

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Primary site involved									
No	195 (34.4)	219 (37.5)	414 (36.0)	35 (43.8)	244 (51.4)	279 (50.3)	36 (54.5)	112 (41.0)	148 (43.7)
Yes	310 (54.7)	288 (49.3)	598 (52.0)	37 (46.3)	192 (40.4)	229 (41.3)	25 (37.9)	133 (48.7)	158 (46.6)
Missing	62 (10.9)	77 (13.2)	139 (12.1)	8 (10.0)	39 (8.2)	47 (8.5)	5 (7.6)	28 (10.3)	33 (9.7)
Metastatic Site involved									
No	79 (13.9)	99 (17.0)	178 (15.5)	10 (12.5)	49 (10.3)	59 (10.6)	10 (15.2)	45 (16.5)	55 (16.2)
Yes	426 (75.1)	408 (69.9)	834 (72.5)	62 (77.5)	387 (81.5)	449 (80.9)	51 (77.3)	200 (73.3)	251 (74.0)
Missing	62 (10.9)	77 (13.2)	139 (12.1)	8 (10.0)	39 (8.2)	47 (8.5)	5 (7.6)	28 (10.3)	33 (9.7)

Table 3b Tumour and treatment characteristics

Exactly 6 cycles - no PD					
	Treatment				
	DOX 75 (N=223)	DOX 50-IFO 5 (N=80)	DOX 75-IFO 5 (N=63)	DOX 75-IFO 10 (N=109)	Total (N=475)
	N (%)	N (%)	N (%)	N (%)	N (%)
Histopathological grading					
Grade I and II	26 (11.7)	12 (15.0)	8 (12.7)	6 (5.5)	52 (10.9)
Grade III	158 (70.9)	38 (47.5)	33 (52.4)	102 (93.6)	331 (69.7)
Unknown	39 (17.5)	30 (37.5)	22 (34.9)	1 (0.9)	92 (19.4)
Site of primary tumour					
Other	130 (58.3)	40 (50.0)	17 (27.0)	58 (53.2)	245 (51.6)
Extremities	76 (34.1)	15 (18.8)	12 (19.0)	49 (45.0)	152 (32.0)
Missing	17 (7.6)	25 (31.3)	34 (54.0)	2 (1.8)	78 (16.4)
Histology					
Leiomyosarcoma	66 (29.6)	25 (31.3)	13 (20.6)	24 (22.0)	128 (26.9)
Synovial sarcoma	37 (16.6)	8 (10.0)	7 (11.1)	19 (17.4)	71 (14.9)
Other	119 (53.4)	42 (52.5)	40 (63.5)	65 (59.6)	266 (56.0)
Missing	1 (0.4)	5 (6.3)	3 (4.8)	1 (0.9)	10 (2.1)
Prior Surgery					
No surgery	8 (3.6)	11 (13.8)	0 (0.0)	0 (0.0)	19 (4.0)
Non optimal surgery	11 (4.9)	12 (15.0)	0 (0.0)	0 (0.0)	23 (4.8)
Complete surgery	42 (18.8)	24 (30.0)	0 (0.0)	0 (0.0)	66 (13.9)
Unknown	162 (72.6)	33 (41.3)	63 (100.0)	109 (100.0)	367 (77.3)
Prior radiotherapy					
No	115 (51.6)	57 (71.3)	41 (65.1)	66 (60.6)	279 (58.7)
Yes	66 (29.6)	22 (27.5)	22 (34.9)	43 (39.4)	153 (32.2)
Missing	42 (18.8)	1 (1.3)	0 (0.0)	0 (0.0)	43 (9.1)
Primary site involved					
No	122 (54.7)	42 (52.5)	22 (34.9)	58 (53.2)	244 (51.4)
Yes	86 (38.6)	38 (47.5)	17 (27.0)	51 (46.8)	192 (40.4)
Missing	15 (6.7)	0 (0.0)	24 (38.1)	0 (0.0)	39 (8.2)

Table 3b Continued.

	Exactly 6 cycles - no PD				
	Treatment				
	DOX 75 (N=223)	DOX 50-IFO 5 (N=80)	DOX 75-IFO 5 (N=63)	DOX 75-IFO 10 (N=109)	Total (N=475)
	N (%)	N (%)	N (%)	N (%)	N (%)
Metastatic Site involved					
No	22 (9.9)	14 (17.5)	5 (7.9)	8 (7.3)	49 (10.3)
Yes	186 (83.4)	66 (82.5)	34 (54.0)	101 (92.7)	387 (81.5)
Missing	15 (6.7)	0 (0.0)	24 (38.1)	0 (0.0)	39 (8.2)

Patients treated with at least 6 cycles of treatment

Considering the 748 patients with at least 6 cycles of treatment and without progression before or at the end of treatment, the median PFS from randomisation was 9.4 months (95% confidence interval: 8.9-9.9) and median PFS from end of treatment was 4.3 months (95% confidence interval: 3.8-4.7). (Supplementary table S4 shows the PFS per treatment regimen) PFS for the different histologies was comparable and is provided in supplementary table 5.

Median OS from randomisation was 19.5 months (95% confidence interval: 18.2-21.3) and median OS from end of treatment was 14.5 months (95% confidence interval: 12.8-16.1). (Supplementary table 6) The median OS according to histology were approximately the same and are provided in supplementary table 7.

Patients treated with exactly 6 cycles of treatment

Because longer treatment duration could lead to bias, we also did the analysis for patients treated with exactly 6 cycles. For this analysis, 475 patients were included (85.6% of the total receiving 6 cycles). The median PFS from randomisation was 8.7 months (95% confidence interval: 8.2-9.1) and the median PFS from end of treatment was 4.2 months (95% confidence interval: 3.7-4.8). (Supplementary table 8) A significant effect of treatment on PFS was found, patients receiving doxorubicin monotherapy had a worse PFS compared to patients receiving doxorubicin 75mg/m^2 combined with ifosfamide 10 g/m^2 combination therapy (p=0.021 and p=0.036 respectively, as already reported by Judson *et al.* [3]). In this analysis, no significant effect of histology on PFS was found. (Supplementary table 9)

Median OS from randomisation for these patients was 20.1 months (95% confidence interval: 18.3-22.3 months) and median OS from end of treatment was 15.7 months (95% confidence interval: 14.0-17.8). There was no statistically significant effect of treatment regimen or histology on OS. (Supplementary table 10 and 11)

Patients treated with less than 6 cycles and no progressive disease

The progression-free survival for patients treated with less than 6 cycles of doxorubicin-containing treatment regimens was 3.8 months (95% confidence interval 3.5-4.3 months) from randomisation. (Supplementary table 12) OS was 10.0 months (95% confidence interval 9.1-10.8 months). (Supplementary table 14) As there can be a bias due to the number of cycles given, no formal statistical comparisons were done. The median progression-free survival and OS for the different treatment regimens are shown in supplementary tables 13 and 15 respectively, but did not differ.

Discussion

In this study, we report the progression-free and OS of patients completing 6 cycles of doxorubicin-based chemotherapy who did not progress before completion of this treatment. Knowledge of the PFS and OS of patients completing 6 cycles of doxorubicin without progressive disease is essential for planning maintenance studies with cytotoxic chemotherapy or tyrosine kinase inhibitors. It is also important to know what percentage of the total number of patients receiving systemic therapy is likely to be available for such trials.

The prognosis of patients with metastatic STS remains poor, with a median OS of 12.8 to 14.3 months respectively in a recently reported study of first-line doxorubicin versus doxorubicin/ifosfamide.[3] More recent studies show a median OS around 18 months.[4-6] As already mentioned in the introduction, since 2016 olaratumab has been introduced in some countries in addition to doxorubicin following the demonstration of a major increase in OS in a phase II trial.[7] However, the results of the phase III ANNOUNCE study did not show an improved OS of the addition of olaratumab to doxorubicin, as was recently presented during the annual meeting of ASCO 2019, leading to the withdrawal from the market.[8] Now, one of the other strategies that could be explored to improve the OS of STS patients is the addition of maintenance therapy after first-line chemotherapy. This is a well-established concept in colorectal cancer, non-small cell lung cancer and ovarian cancer.[20-22] Progression after first-line treatment can result in a deterioration in performance status making it difficult or impossible to administer second-line treatment. Maintenance treatment is intended to improve OS by prolonging the progression-free survival after first-line treatment by direct continuation of chemotherapy. In STS, this is even more a problem, because doxorubicin is first-line treatment and has a maximum safe cumulative dose of 450mg/m^2 (6 cycles), although even at this dose there is evidence of cardiac damage in a significant percentage of patients. Administration of

higher cumulative doses, e.g. 600mg/m^2 (8 cycles) as in the olaratumab study, is only possible with the co-administration of the cardioprotective agent cardioxane since the risk of cardiotoxicity at this dose without cardioprotection is in the region of 50%. An alternative to doxorubicin would be the use of liposomal doxorubicin, which does not have the cardiotoxic potential of doxorubicin.[16] When considering maintenance treatment, one needs to take into account the risks of this therapy and the loss in quality of life caused by the maintenance treatment. Drugs that have some proven utility against sarcomas and could be used in maintenance treatment include pazopanib and trabectedin, which are both well-tolerated.[23-25] Although the concept of maintenance treatment after doxorubicin is attractive, maintenance studies had trouble recruiting due to the temporary registration and availability of olaratumab in most of the western world. Probably, these trials will now recruit more easily, because olaratumab failed in the phase III trial. For designing future studies of maintenance therapy in STS, data on PFS and OS in this setting are essential.

It is important to realise that of all patients included in the database, only 43.7% received 6 cycles or more and only 83.7% of these did not progress before the end of treatment (36.6% of all patients). Patients treated with more than 6 cycles have a similar OS as patients receiving exactly 6 cycles of doxorubicin, but patients receiving less than 6 cycles without progressive disease at the end of treatment have a worse survival. Based on this database study we roughly estimate that only one third of all patients (all patients receiving 6 or more cycles and no progressive disease at end of treatment) will qualify for maintenance treatment.

The PFS of 8.7 months and the OS of 20.1 months from randomisation is much longer than the mean OS of patients included in first line studies. Of course, this is an expected difference because responding patients will have a better prognosis compared to patients not responding to chemotherapy. On the other hand, this improved survival should be accounted for when planning maintenance studies and single arm phase II studies.

One of the major limitations of this study is the long interval between the first included patient and the last included patient. Ifosfamide was already available in the early years of this study, but trabectedin, pazopanib and gemcitabine/docetaxel are new second or later line treatments prolonging PFS and/or OS.[19,23,26] These new second line treatments will cause bias when comparing older regimens like doxorubicin 50mg/m^2 combined with ifosfamide 5g/m^2 to newer regimens like doxorubicin 75mg/m^2 combined with ifosfamide 10g/m^2. The improved supportive care over the years will increase this bias somewhat further.

In this study, treatment regimen had only a significant effect on PFS, with doxorubicin 75mg/m^2 combined with ifosfamide 10g/m^2 having the best PFS. No significant effect

on OS was found, but a trend towards an increase in OS was found for patients with doxorubicin/ifosfamide combination therapy, which is more or less comparable with our study on this regimen, showing only a very little improvement in OS compared with doxorubicin 75mg/m^2 monotherapy.[3] The increase in PFS without an increase in OS in this study could be the effect of sequentially using these agents compared to using them concurrently. For other tumours like colorectal cancer it has been shown that sequential treatment is comparable to concurrent treatment.[27] Second, as the study design selects for responding patients, the difference in OS between this study and the EORTC 62012 study could be caused by the increased response rate with doxorubicin/ifosfamide.

Importantly, this study shows no effect of histology on the outcome of patients, although the number of separately studied subtypes was small. This is in contrast to earlier studies, showing a better survival in for example synovial sarcoma.[28] These differences could be caused by the low number of included patients in this study, or by the exclusion of patients with progression during treatment, thereby selecting for responding patients.

Conclusions

This is the first study reporting the progression-free survival and OS of patients completing 6 cycles of doxorubicin containing treatment without progressive disease before completion of treatment. These data are important for future study design and daily patient care as one of the ways forwards to improve survival in advanced STS could be maintenance treatment for the minority of patients whose disease is sensitive to chemotherapy. Future trials on maintenance treatment after first-line doxorubicin should only include patients receiving at least 6 (or more) cycles of doxorubicin or, when also including patients with less than 6 cycles of doxorubicin, should stratify for the number of cycles doxorubicin given.

Declarations

Ethics approval and consent to participate

All patients consented to participate in the different trials. For all studies, ethical approval was provided by the medical ethical committees of the different participating hospitals. Information about the ethics approval is provided in the manuscripts of the individual studies.

Consent for publication

Not applicable

Data availability

The data used in this manuscript is available on request. The data is stored at EORTC. For conditions and procedures to assess the data: https://www.eortc.org/data-sharing/

Conflicts of interest

AJV, SL, SM, IJ, MT and HG have nothing to disclose. ALC reports personal fees from Pharmamar, Lilly, Novartis and Amgen, all outside the submitted work. EW reports personal fees from Novartis, Lilly, Nanobiotix, Bayer, PharmaMar, Milestone, Menarini and New Oncology, all outside the submitted work.

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Author contributions

Study design: A.J.V., S.L., H.G.; Data acquisition: S.M., M.T., I.J., E.W., H.G., A.L.C.; Statistical analysis and interpretation: A.J.V., S.L., H.G.; Manuscript preparation: A.J.V., H.G.; Manuscript editing and review: All authors.; All authors read and approved the final manuscript.

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Supplementary data

It contains additional tables (also referred to in the manuscript) providing additional data about: the included number of patients per study and regimen and number of cycles and the distribution of histological subtype and grade in the different subgroups.

Also, additional data on overall and progression free survival according to number of cycles is presented.

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Supplementary data

Supplementary table 1 Included patients per study and regimen

	Protocol												
	62012 (N=433)	**62061 (N=38)**	**62091 (N=41)**	**62801 (N=94)**	**62842 (N=194)**	**62851 (N=538)**	**62883 (N=111)**	**62901 (N=107)**	**62903 (N=309)**	**62941 (N=39)**	**62962 (N=41)**	**62971 (N=100)**	**Total (N=2045)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Treatment													
DOX 75	216 (49.9)	38 (100.0)	41 (100.0)	94 (100.0)	0 (0.0)	272 (50.6)	0 (0.0)	107 (100.0)	0 (0.0)	39 (100.0)	41 (100.0)	100 (100.0)	948 (46.4)
DOX 50-IFO 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	194 (100.0)	266 (49.4)	0 (0.0)	0 (0.0)	154 (49.8)	0 (0.0)	0 (0.0)	0 (0.0)	614 (30.0)
DOX 75-IFO 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	111 (100.0)	0 (0.0)	155 (50.2)	0 (0.0)	0 (0.0)	0 (0.0)	266 (13.0)
DOX 75-IFO 10	217 (50.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	217 (10.6)

Supplementary table 2 Distribution of number of cycles by study

	Study												
Number of cycles	**62012**	**62061**	**62091**	**62801**	**62842**	**62851**	**62883**	**62901**	**62903**	**62941**	**62962**	**62971**	**Total**
1	34	6	5	6	10	59	10	12	26	3	4	4	179
2	94	7	9	20	33	107	18	22	62	6	10	28	416
3	30	0	1	15	20	56	15	13	36	5	4	13	208
4	32	2	3	7	23	63	18	12	28	4	6	15	213
5	17	1	0	14	17	40	13	5	21	2	0	5	135
6	225	22	23	8	25	70	31	16	81	6	14	34	555
7	1	0	0	10	12	48	5	21	26	13	2	1	139
8	0	0	0	7	29	46	1	6	14	0	1	0	104
9	0	0	0	2	4	23	0	0	5	0	0	0	34
10	0	0	0	3	13	14	0	0	8	0	0	0	38
11	0	0	0	1	0	5	0	0	2	0	0	0	8
12	0	0	0	0	4	1	0	0	0	0	0	0	5
13	0	0	0	1	1	1	0	0	0	0	0	0	3
14	0	0	0	0	0	3	0	0	0	0	0	0	3
15	0	0	0	0	2	1	0	0	0	0	0	0	3
16	0	0	0	0	0	1	0	0	0	0	0	0	1
17	0	0	0	0	1	0	0	0	0	0	0	0	1

Supplementary table 3a distribution of histological subtype and grade in patients treated with more than 6 cycles

	More than 6 cycles		
	Pts who progress before or at the end of treatment (N=66)	**Pts who did not progress before or at the end of treatment (N=273)**	**Total (N=339)**
	N (%)	**N (%)**	**N (%)**
Histological cell type			
MFH	5 (7.6)	39 (14.3)	44 (13.0)
Fibrosarcoma	5 (7.6)	13 (4.8)	18 (5.3)
Liposarcoma	6 (9.1)	25 (9.2)	31 (9.1)
Leiomyosarcoma	25 (37.9)	79 (28.9)	104 (30.7)
Rhabdomyosarcoma	2 (3.0)	4 (1.5)	6 (1.8)
Angiosarcoma	2 (3.0)	10 (3.7)	12 (3.5)
Synovial sarcoma	6 (9.1)	29 (10.6)	35 (10.3)
Neurogenic sarcoma	5 (7.6)	19 (7.0)	24 (7.1)
Miscellaneous	6 (9.1)	27 (9.9)	33 (9.7)
Unclassified	4 (6.1)	14 (5.1)	18 (5.3)
Missing	0 (0.0)	14 (5.1)	14 (4.1)
Histopathological grade			
I	8 (12.1)	24 (8.8)	32 (9.4)
II	15 (22.7)	59 (21.6)	74 (21.8)
III	18 (27.3)	93 (34.1)	111 (32.7)
Missing	25 (37.9)	97 (35.5)	122 (36.0)

Supplementary table 3b distribution of histological subtype and grade in patients treated with exactly 6 cycles

	Exactly 6 cycles		
	Pts who progress before or at the end of treatment (N=80)	**Pts who did not progress before or at the end of treatment (N=475)**	**Total (N=555)**
	N (%)	**N (%)**	**N (%)**
Histological cell type			
MFH	5 (6.3)	35 (7.4)	40 (7.2)
Fibrosarcoma	4 (5.0)	8 (1.7)	12 (2.2)
Liposarcoma	4 (5.0)	65 (13.7)	69 (12.4)
Leiomyosarcoma	23 (28.8)	128 (26.9)	151 (27.2)
Rhabdomyosarcoma	0 (0.0)	10 (2.1)	10 (1.8)
Angiosarcoma	3 (3.8)	22 (4.6)	25 (4.5)
Synovial sarcoma	10 (12.5)	71 (14.9)	81 (14.6)
Neurogenic sarcoma	10 (12.5)	13 (2.7)	23 (4.1)
Miscellaneous	13 (16.3)	92 (19.4)	105 (18.9)
Unclassified	5 (6.3)	21 (4.4)	26 (4.7)
Missing	3 (3.8)	10 (2.1)	13 (2.3)
Histopathological grade			
I	6 (7.5)	52 (10.9)	58 (10.5)
II	16 (20.0)	162 (34.1)	178 (32.1)
III	30 (37.5)	169 (35.6)	199 (35.9)
Missing	28 (35.0)	92 (19.4)	120 (21.6)

Supplementary table 3c distribution of histological subtype and grade in patients treated with less than 6 cycles and stopped for other reasons then progression

	Less than 6 cycles		
	Pts who progress before or at the end of treatment (N=567)	**Pts who did not progress before or at the end of treatment (N=584)**	**Total (N=1151)**
	N (%)	**N (%)**	**N (%)**
Histological cell type			
MFH	58 (10.2)	79 (13.5)	137 (11.9)
Fibrosarcoma	11 (1.9)	22 (3.8)	33 (2.9)
Liposarcoma	47 (8.3)	47 (8.0)	94 (8.2)
Leiomyosarcoma	192 (33.9)	180 (30.8)	372 (32.3)
Rhabdomyosarcoma	16 (2.8)	16 (2.7)	32 (2.8)
Angiosarcoma	23 (4.1)	14 (2.4)	37 (3.2)
Synovial sarcoma	32 (5.6)	59 (10.1)	91 (7.9)
Neurogenic sarcoma	18 (3.2)	29 (5.0)	47 (4.1)
Miscellaneous	93 (16.4)	80 (13.7)	173 (15.0)
Unclassified	49 (8.6)	30 (5.1)	79 (6.9)
Missing	28 (4.9)	28 (4.8)	56 (4.9)
Histopathological grade			
I	38 (6.7)	30 (5.1)	68 (5.9)
II	140 (24.7)	162 (27.7)	302 (26.2)
III	191 (33.7)	204 (34.9)	395 (34.3)
Missing	198 (34.9)	188 (32.2)	386 (33.5)

Supplementary table 3d distribution of histological subtype and grade in patients treated with exactly 6 cycles according to treatment protocol

	Exactly 6 cycles - no PD				
	DOX 75 (N=223)	**DOX 50-IFO 5 (N=80)**	**DOX 75-IFO 5 (N=63)**	**DOX 75-IFO 10 (N=109)**	**Total (N=475)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Histological cell type					
MFH	9 (4.0)	12 (15.0)	7 (11.1)	7 (6.4)	35 (7.4)
Fibrosarcoma	2 (0.9)	1 (1.3)	3 (4.8)	2 (1.8)	8 (1.7)
Liposarcoma	36 (16.1)	7 (8.8)	6 (9.5)	16 (14.7)	65 (13.7)
Leiomyosarcoma	66 (29.6)	25 (31.3)	13 (20.6)	24 (22.0)	128 (26.9)
Rhabdomyosarcoma	6 (2.7)	1 (1.3)	2 (3.2)	1 (0.9)	10 (2.1)
Angiosarcoma	12 (5.4)	2 (2.5)	2 (3.2)	6 (5.5)	22 (4.6)
Synovial sarcoma	37 (16.6)	8 (10.0)	7 (11.1)	19 (17.4)	71 (14.9)
Neurogenic sarcoma	4 (1.8)	4 (5.0)	5 (7.9)	0 (0.0)	13 (2.7)
Miscellaneous	40 (17.9)	11 (13.8)	8 (12.7)	33 (30.3)	92 (19.4)
Unclassified	10 (4.5)	4 (5.0)	7 (11.1)	0 (0.0)	21 (4.4)
Missing	1 (0.4)	5 (6.3)	3 (4.8)	1 (0.9)	10 (2.1)
Histopathological grade					
I	26 (11.7)	12 (15.0)	8 (12.7)	6 (5.5)	52 (10.9)
II	78 (35.0)	12 (15.0)	19 (30.2)	53 (48.6)	162 (34.1)
III	80 (35.9)	26 (32.5)	14 (22.2)	49 (45.0)	169 (35.6)
Missing	39 (17.5)	30 (37.5)	22 (34.9)	1 (0.9)	92 (19.4)

Supplementary table 4 Progression free survival of patients treated with ≥6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
PFS from Randomisation			
DOX 75	336	308	8.48 (7.92, 9.10)
DOX 50-IFO 5	215	188	10.61 (9.82, 11.70)
DOX 75-IFO 5	88	81	9.31 (8.25, 11.60)
DOX 75-IFO 10	109	98	9.66 (8.77, 11.37)
Total	748	675	9.40 (8.94, 9.89)
PFS from End of treatment			
DOX 75	336	308	3.42 (3.12, 4.07)
DOX 50-IFO 5	215	188	4.70 (3.68, 5.68)
DOX 75-IFO 5	88	81	4.93 (3.61, 6.97)
DOX 75-IFO 10	109	98	4.99 (4.37, 6.67)
Total	748	675	4.27 (3.84, 4.73)

Supplementary table 5 Progression free survival from End of treatment by histology for patients treated with ≥6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
		DOX 75	
Leiomyosarcoma	103	97	3.42 (2.92, 4.44)
Synovial sarcoma	44	41	3.42 (2.07, 4.34)
Other	183	166	3.42 (2.76, 4.44)
		DOX 50-IFO 5	
Leiomyosarcoma	58	52	3.25 (2.10, 4.53)
Synovial sarcoma	26	25	3.81 (2.14, 5.62)
Other	120	101	6.93 (5.03, 8.44)
		DOX 75-IFO 5	
Leiomyosarcoma	22	21	3.99 (2.60, 7.36)
Synovial sarcoma	11	10	3.19 (0.92, 11.93)
Other	50	45	6.34 (3.15, 10.09)
		DOX 75-IFO 10	
Leiomyosarcoma	24	22	4.90 (2.92, 8.51)
Synovial sarcoma	19	19	4.24 (2.96, 8.28)
Other	65	56	5.13 (4.37, 7.43)

Supplementary table 6 Overall survival of patients treated with ≥6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
OS from Randomisation			
DOX 75	336	237	18.73 (16.99, 21.88)
DOX 50-IFO 5	215	162	18.92 (16.66, 21.49)
DOX 75-IFO 5	88	77	19.19 (15.01, 23.75)
DOX 75-IFO 10	109	83	23.59 (19.32, 28.19)
Total	748	559	19.48 (18.20, 21.29)
OS from End of treatment			
DOX 75	336	237	13.96 (11.99, 16.76)
DOX 50-IFO 5	215	162	12.81 (10.94, 16.10)
DOX 75-IFO 5	88	77	15.05 (10.58, 18.89)
DOX 75-IFO 10	109	83	18.89 (14.95, 23.79)
Total	748	559	14.52 (12.78, 16.10)

Supplementary table 7 Overall survival from End of treatment by histology for patients treated with ≥6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)
DOX 75				
Leiomyosarcoma	103	70	16.59 (11.17, 22.11)	1.00
Synovial sarcoma	44	36	14.23 (9.30, 18.43)	1.18 (0.79, 1.76)
Other	183	127	12.94 (11.27, 16.76)	1.08 (0.80, 1.44)
DOX 50-IFO 5				
Leiomyosarcoma	58	49	10.68 (8.08, 13.08)	1.00
Synovial sarcoma	26	22	12.29 (7.56, 16.10)	1.10 (0.66, 1.83)
Other	119	80	18.63 (13.96, 22.34)	0.56 (0.39, 0.80)

Supplementary table 7 Continued.

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)
DOX 75-IFO 5				
Leiomyosarcoma	22	21	15.97 (9.20, 22.37)	1.00
Synovial sarcoma	11	10	14.78 (4.73, 26.71)	1.27 (0.60, 2.71)
Other	50	42	11.53 (7.75, 20.47)	0.93 (0.55, 1.58)
DOX 75-IFO 10				
Leiomyosarcoma	24	20	17.35 (9.99, 26.71)	1.00
Synovial sarcoma	19	17	18.89 (8.15, 25.10)	1.37 (0.71, 2.63)
Other	65	46	18.04 (11.37, 27.17)	0.85 (0.50, 1.44)

Supplementary table 8 Progression free survival of patients treated with exactly 6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)	P-Value (Score test)
PFS from Randomisation					
DOX 75	223	209	7.59 (7.23, 8.38)	1.00	0.021 (df=3)
DOX 50-IFO 5	80	74	8.85 (7.33, 10.81)	0.84 (0.65, 1.10)	
DOX 75-IFO 5	63	59	9.10 (7.36, 11.40)	0.74 (0.55, 0.99)	
DOX 75-IFO 10	109	98	9.66 (8.77, 11.37)	0.71 (0.56, 0.90)	
Total	475	440	8.67 (8.18, 9.13)		
PFS from End of treatment					
DOX 75	223	209	3.38 (2.73, 4.07)	1.00	0.036 (df=3)
DOX 50-IFO 5	80	74	4.47 (3.06, 5.88)	0.86 (0.66, 1.12)	
DOX 75-IFO 5	63	59	4.73 (3.12, 6.97)	0.75 (0.56, 1.00)	
DOX 75-IFO 10	109	98	4.99 (4.37, 6.67)	0.73 (0.57, 0.92)	
Total	475	440	4.24 (3.71, 4.80)		

Supplementary table 9 PFS from End of treatment by histology for patients treated with exactly 6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
		DOX 75	
Leiomyosarcoma	66	64	3.19 (2.60, 4.73)
Synovial sarcoma	37	35	2.89 (1.94, 4.07)
Other	119	110	3.71 (2.27, 5.09)
		DOX 50-IFO 5	
Leiomyosarcoma	25	23	3.29 (2.04, 5.88)
Synovial sarcoma	8	8	4.09 (0.03, 14.23)
Other	42	38	7.43 (3.48, 9.63)
		DOX 75-IFO 5	
Leiomyosarcoma	13	12	3.68 (2.37, 6.51)
Synovial sarcoma	7	6	3.19 (0.92, 14.78)
Other	40	38	5.80 (3.09, 10.09)
		DOX 75-IFO 10	
Leiomyosarcoma	24	22	4.90 (2.92, 8.51)
Synovial sarcoma	19	19	4.24 (2.96, 8.28)
Other	65	56	5.13 (4.37, 7.43)

Supplementary table 10 Overall survival of patients treated with exactly 6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)	P-Value (Score test)
			OS from Randomisation		
DOX 75	223	148	18.96 (17.08, 22.34)	1.00	0.340 (df=3)
DOX 50-IFO 5	80	63	20.11 (15.67, 24.61)	1.08 (0.81, 1.46)	
DOX 75-IFO 5	63	56	19.19 (15.01, 24.87)	1.15 (0.84, 1.56)	
DOX 75-IFO 10	109	83	23.59 (19.32, 28.19)	0.86 (0.66, 1.12)	
Total	475	350	20.14 (18.30, 22.34)		

Supplementary table 10 Continued.

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)	P-Value (Score test)
OS from End of treatment					
DOX 75	223	148	14.59 (12.55, 17.81)	1.00	0.356 (df=3)
DOX 50-IFO 5	80	63	14.52 (11.53, 20.30)	1.09 (0.81, 1.47)	
DOX 75-IFO 5	63	56	15.05 (10.58, 20.47)	1.15 (0.85, 1.57)	
DOX 75-IFO 10	109	83	18.89 (14.95, 23.79)	0.87 (0.66, 1.14)	
Total	475	350	15.74 (14.00, 17.81)		

Supplementary table 11 Overall survival from End of treatment by histology for patients treated with exactly 6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
DOX 75			
Leiomyosarcoma	66	38	17.31 (12.55, 28.88)
Synovial sarcoma	37	30	14.23 (9.30, 18.43)
Other	119	80	14.00 (11.63, 18.27)
DOX 50-IFO 5			
Leiomyosarcoma	25	22	13.08 (8.64, 23.59)
Synovial sarcoma	8	7	12.52 (7.56, 16.95)
Other	42	29	20.76 (13.70, 30.62)
DOX 75-IFO 5			
Leiomyosarcoma	13	12	15.05 (11.33, 27.10)
Synovial sarcoma	7	6	13.37 (2.50, 26.71)
Other	40	35	15.31 (7.06, 21.85)
DOX 75-IFO 10			
Leiomyosarcoma	24	20	17.35 (9.99, 26.71)
Liposarcoma	19	17	18.89 (8.15, 25.10)
Other	65	46	18.04 (11.37, 27.17)

Supplementary table 12 Progression free survival of patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
PFS from Randomisation			
DOX 75	233	222	2.76 (2.27, 3.09)
DOX 50-IFO 5	169	155	3.88 (3.32, 4.90)
DOX 75-IFO 5	111	107	6.93 (5.85, 8.11)
DOX 75-IFO 10	71	65	5.09 (3.84, 7.29)
Total	584	549	3.81 (3.45, 4.30)

Supplementary table 13 PFS from End of treatment by histology for patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

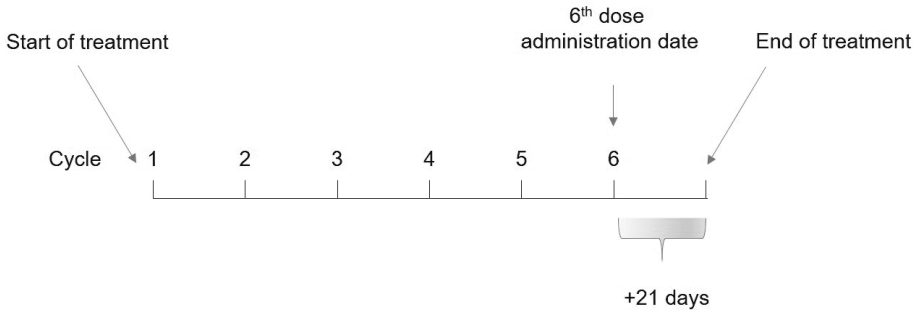
Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
DOX 75			
Leiomyosarcoma	53	52	3.12 (1.71, 3.88)
Synovial sarcoma	23	21	2.79 (1.68, 14.92)
Other	147	140	2.56 (2.23, 2.96)
DOX 50-IFO 5			
Leiomyosarcoma	58	55	3.48 (2.79, 4.90)
Synovial sarcoma	23	23	4.57 (3.09, 9.07)
Other	78	70	3.75 (2.76, 5.19)
DOX 75-IFO 5			
Leiomyosarcoma	43	43	7.13 (3.84, 8.51)
Synovial sarcoma	7	7	8.57 (6.14, 12.75)
Other	54	50	6.21 (5.16, 9.07)
DOX 75-IFO 10			
Leiomyosarcoma	26	26	5.06 (2.66, 7.23)
Synovial sarcoma	6	6	9.53 (2.79, 37.49)
Other	38	32	4.63 (3.22, 8.18)

Supplementary table 14 Overall survival of patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
OS from Randomisation			
DOX 75	233	194	8.15 (7.29, 9.76)
DOX 50-IFO 5	169	136	10.02 (8.21, 12.06)
DOX 75-IFO 5	111	103	12.12 (9.92, 13.93)
DOX 75-IFO 10	71	55	11.70 (9.95, 14.78)
Total	584	488	10.02 (9.07, 10.81)

Supplementary table 15 Overall survival from End of treatment by histology for patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
DOX 75			
Leiomyosarcoma	53	47	5.85 (3.38, 9.43)
Synovial sarcoma	23	13	17.05 (10.55, 32.10)
Other	147	125	5.26 (4.04, 6.80)
DOX 50-IFO 5			
Leiomyosarcoma	58	50	6.31 (4.47, 8.77)
Synovial sarcoma	23	19	9.00 (4.73, 21.65)
Other	78	61	6.60 (4.76, 10.28)
DOX 75-IFO 5			
Leiomyosarcoma	43	41	8.31 (5.98, 11.70)
Synovial sarcoma	7	7	11.89 (7.92, 19.12)
Other	54	48	9.99 (5.03, 13.90)
DOX 75-IFO 10			
Leiomyosarcoma	26	24	9.48 (7.56, 12.98)
Liposarcoma	6	4	15.28 (6.31, N)
Other	38	26	8.61 (5.68, 17.02)



Supplementary figure 1 Definition of end of treatment

A remarkable response to pazopanib, despite recurrent liver toxicity, in a patient with a high grade endometrial stromal sarcoma,

a case report

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Abstract

Background

Pazopanib is an oral tyrosine kinase inhibitor registered for metastatic renal cell carcinoma and soft tissue sarcoma. Liver toxicity is a common side effect for this class of agents. The current opinion is that in case of severe liver toxicity pazopanib should be interrupted and restarted at a lower dose after returning to Common Terminology Criteria for Adverse Events (CTCAE) grade 1. After recurrence of liver toxicity at the lower dose it is advised to permanently stop pazopanib. We describe a patient with an YWHAE-FAM22 translocated endometrial stromal sarcoma with a remarkable response to pazopanib despite recurrent liver toxicity.

Case

A 40-year-old woman was diagnosed with metastatic YWHAE-FAM22 translocated endometrial stromal sarcoma. She was treated successively with doxorubicin, megestrol acetate and anastrozole, before pazopanib was initiated. Several dose interruptions and reductions were necessary due to liver toxicity, but nevertheless she had a good partial response. Seven months after the start, pazopanib was permanently stopped because of a bilateral pneumothorax. Nine months later it was reinitiated because of progression and was continued for another 8 months until final disease progression.

Conclusion

In contrast to the current summary of product characteristics of pazopanib, the drug was successfully continued despite recurrent liver toxicity, and no further liver function deterioration was found. This case suggests that further dose reductions are good practice when liver toxicity limits treatment in responding patients.

Secondly, this patient with rare YWHAE-FAM22 translocated endometrial stromal sarcoma showed a remarkable response to VEGFR/KIT inhibitor pazopanib. Recently, it was reported that this specific subtype of endometrial stromal sarcoma overexpresses CD117, but has no KIT mutations.

This case illustrates that (a) pazopanib can be continued in patients with recurrent liver toxicity after dose reductions under strict surveillance and that (b) pazopanib shows good efficacy in YWHAE-FAM22 translocated endometrial stromal sarcoma.

Background

The oral anti-angiogenic tyrosine kinase inhibitor (TKI) pazopanib is a multi-target TKI.[1] Its main activity is against vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, platelet derived growth factor receptors (PDGFR) and KIT.[1] The phase III PALETTE study showed an increase in the progression free survival (PFS) from 1.6 months with placebo to 4.6 months with pazopanib (Votrient®, GlaxoSmithKline) in patients with metastatic soft tissue sarcoma.[2,3] Pazopanib is also effective in renal-cell carcinoma (RCC), with an increase in PFS from 4.2 months with placebo to 9.2 months with pazopanib.[4] Overall survival (OS) was also significantly increased with pazopanib despite cross-over from placebo treatment to pazopanib treatment.[5]

Liver toxicity is a well-known side effect of pazopanib, with an incidence in the PALETTE study of a grade $\geq$ 2 elevated alanine aminotransferase (ALAT) of 10% (placebo 3%) and aspartate aminotransferase (ASAT) of 8% (placebo 2%).[2] An increase in total bilirubin was not seen in this study. In the RCC study, a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade $\geq$3 increase in ALAT was found in 12% (placebo 1%), ASAT 7% (<1%) and total bilirubin 3% (1%).[4] Two patients in this RCC study were assessed as having died due to abnormal hepatic function. The current opinion is that physicians should be careful prescribing pazopanib in patients with abnormal ASAT, ALAT and total bilirubin levels and that treatment should be discontinued at least temporarily when grade 3 or more elevations occur during treatment. In case of recurrence of liver function abnormalities after restarting treatment pazopanib should be stopped permanently.[6]

Endometrial stromal neoplasms of the uterus are divided into four categories based on the 2014 WHO classification, i.e. endometrial stromal nodule, low-grade endometrial stromal sarcoma (ESS), high grade ESS and undifferentiated uterine sarcoma.[7,8] ESS is very rare, representing 0.2% of all genital tract malignancies and the patients are generally younger than in other uterine malignancies. Low grade ESS is usually CD10 positive and Cyclin D1 negative.[9] Fifty to sixty percent of the ESS harbour translocations involving JAZF1. Recently, it was found that high grade ESS (negative for CD10, positive for Cyclin D1) are characterised by a t(10;17)(q22;p13) translocation resulting in a YWHAE-FAM22 (also known as YWHAE-NUTM2A/B) gene fusion.[10,11] It is suggested that these tumours have a poor response to therapy compared to the lower grade ESS, which has a 5 year disease specific survival rate for FIGO stage III-IV of 50.3%.[12] Current treatment for metastatic or locally advanced disease consists of hormonal therapy and chemotherapy, *i.e.* doxorubicin or ifosfamide monotherapy or gemcitabine/docetaxel combination therapy.[9] Pazopanib is also registered for this soft tissue sarcoma subtype, but specific studies are not available and will not be run because of the rarity of this histologic subtype.

This case report describes a patient successfully treated with pazopanib for an ESS developing abnormal liver chemistry, which continued treatment with adapted dosing of pazopanib under careful surveillance of liver function. She had a remarkable response on pazopanib.

Case

A 40-year-old female presented with a 4 months history of recurrent right sided lower thoracic pain during sports. Medical history consisted of a hysterectomy for symptomatic uterine myomatosis four years previously, after giving birth to her second child. This was a non-radical non-oncological resection. The original pathology report revealed a 15 cm low grade ESS. Now, four years after the hysterectomy, a CT scan showed a large mediastinal mass with expansion in the upper abdomen and compression of the left atrium and multiple lesions in both lungs. A bronchoscopic biopsy showed cells similar to the earlier diagnosed ESS. Treatment with six courses of doxorubicin resulted in a very good partial response. Maintenance therapy with megestrol acetate 160 mg was started hoping to prolong the time to progression. Two years later, an increase in size and number of the lung metastases was observed, so megestrol acetate was stopped and anastrozole 1 mg started. Further disease progression was noticed 4 months later (figure 1A). Pazopanib 800 mg orally once daily was started in the named patient program in collaboration with the Leiden University Medical Centre, one of the Dutch sarcoma reference centres. At the same time, pathology review was performed, confirming the diagnosis of low grade ESS, but also noticing a CyclinD1 positive and CD10 negative higher grade component suggesting a YWHAE-FAM22 translocated ESS. (Figure 2 A-D) Fluorescent in situ hybridisation confirmed the diagnosis. The tumour showed high expression of KIT in the high-grade component of the tumour.

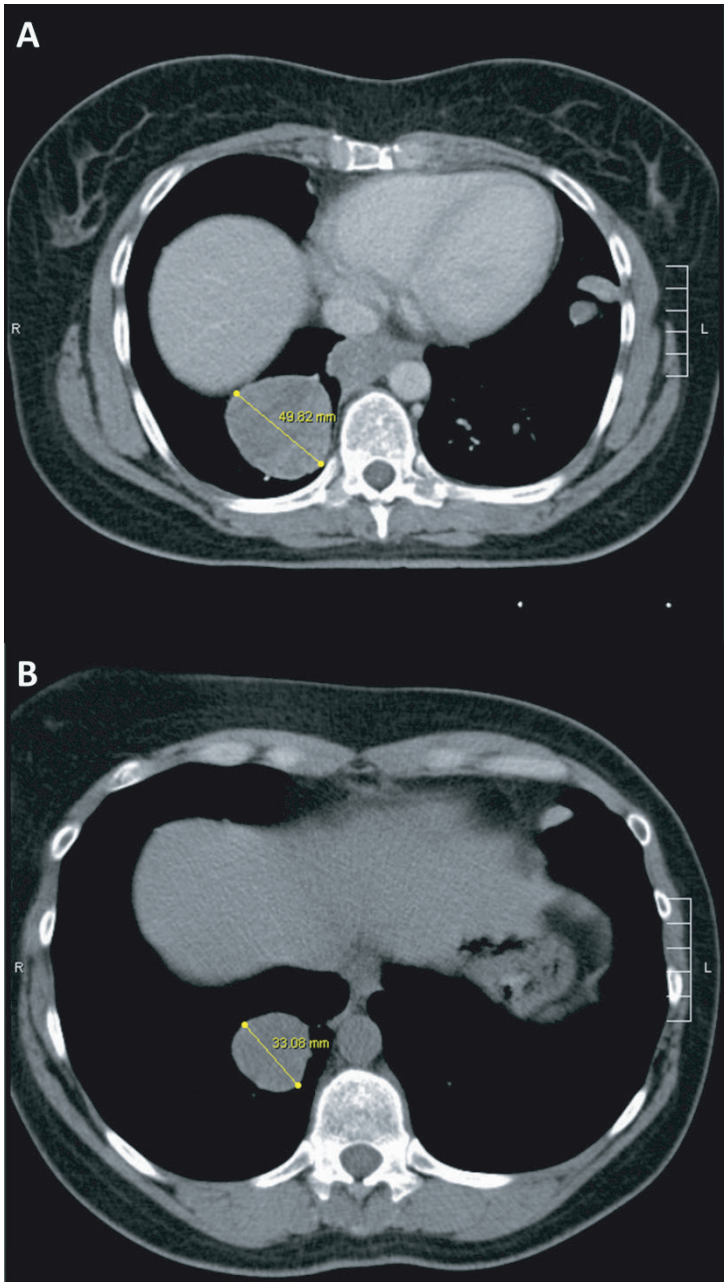

Figure 1 CT scans

Evaluation CT scans before start of pazopanib (A) and 12 weeks after start of pazopanib (so 6 weeks on pazopanib and 6 weeks off because of liver toxicity) (B) showing a shrinking pulmonary metastasis measured by largest diameter at both times.

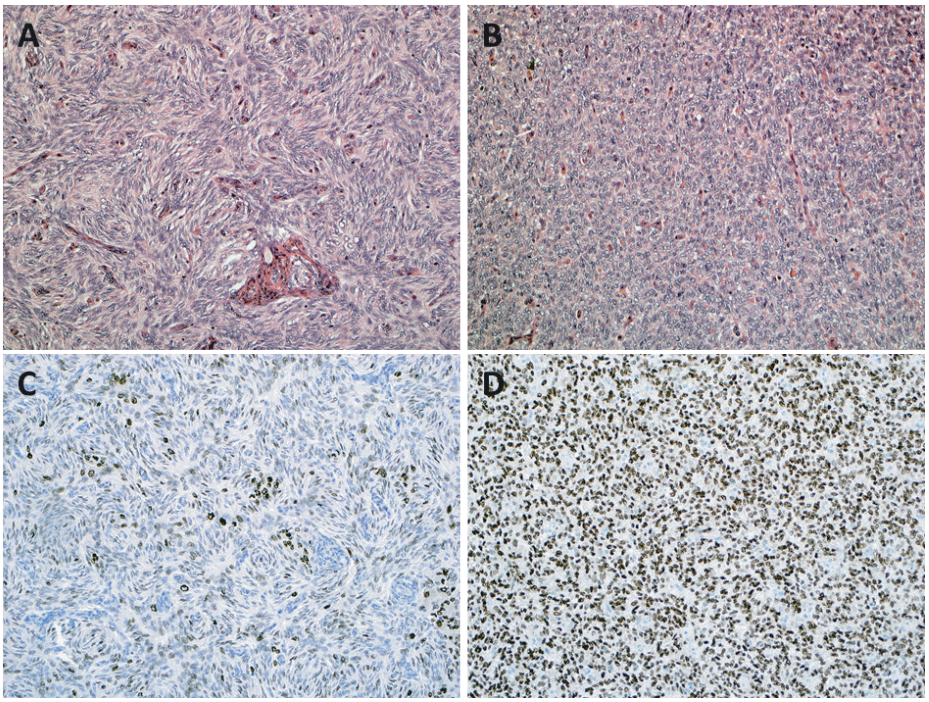

Figure 2 Histology

A: Normal HE slides of the lower grade component of ESS, showing spindled cells in a storiform pattern. B: HE slides of the high-grade component of ESS, showing round cells and open nuclei. C: Cyclin D1 expression of the lower grade component is weak and more heterogeneous. D: Diffuse and strong Cyclin D1 expression in the high-grade areas.

Six weeks after start of pazopanib 800 mg once daily an increase in ALAT to >10 times the upper limit of normal (ULN) was observed. (Figure 3) Hepatitis serology, liver ultrasound and liver biopsy were not performed because of the clear relationship of the increased liver enzymes with the start of pazopanib. She had no history of liver disease, no liver metastases and no liver function abnormalities before start of pazopanib. During the previous treatment with doxorubicin, y-glutamyl transferase increased to 20x ULN and ALAT to 6x ULN, no other liver function abnormalities occurred. The CT scan showed a decrease in the sum of the largest diameters of the target lesions of 23%. Pazopanib was put on hold immediately until the liver enzymes returned to normal. (Figure 3)

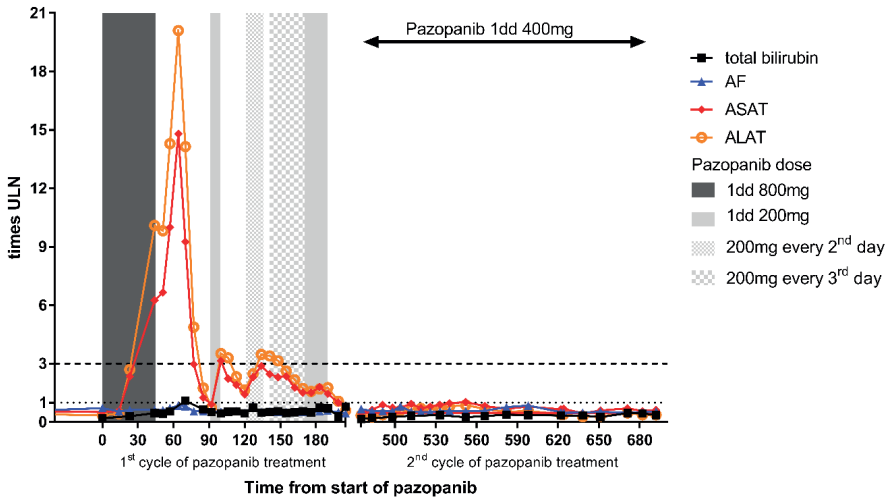

Figure 3 Course of pazopanib dose and laboratory parameters in time
ULN: upper limit of normal

After six weeks without pazopanib the CT scan showed a further decrease of the target lesions of 38% compared to baseline (19% compared to the previous CT scan) indicating a partial response. (Figure 1B) At the time the liver toxicity had almost recovered, a re-challenge with pazopanib 200 mg once daily was performed, but after one-week liver function abnormalities recurred and pazopanib was stopped again. After liver function recoverage, pazopanib 200 mg once every other day was initiated, but again after 2 weeks liver enzymes increased to >3x ULN. Another week later pazopanib 200mg every third day was given for 2 weeks, until a CT scan showed progression (six months after the start of pazopanib). She was still in very good clinical condition and besides the remarkable inclination of liver enzymes at the beginning of treatment and lesser rises thereafter she had had little other toxicity with pazopanib. She consented to another challenge with pazopanib 200 mg every day under further strict surveillance of liver enzymes. The liver enzymes remained < 3 times ULN, but 3 weeks later she was admitted with a bilateral pneumothorax and pazopanib was stopped. On the right side a pleurodesis was performed and on the left side it was drained. Anastrozole and leuprorelin were prescribed, hoping to slow down progression. Two months later, a CT scan again showed progressive disease, and ifosfamide chemotherapy (5 gram/m2 in a 24-hour continuous infusion every 3 weeks) was initiated. CT scans after 3 and 6 cycles showed stable disease. During ifosfamide treatment only a slight increase in γ-glutamyl transferase was noticed (increase to <2x ULN). Two months after the last ifosfamide administration, radiological progression was observed again and pazopanib 400 mg daily was prescribed again under strict weekly surveillance of the liver enzymes. This dose was chosen because patient had a pleural effusion due to the progression and

thereby a lot of complaints. To be sure of a therapeutic dose of pazopanib we started with 400mg daily. Two weeks after reinitiating pazopanib the pneumothorax on the left side recurred and persisted. Pazopanib was held for two weeks, but was then reinitiated after discussion of the risks with the patient. CT scans 6 weeks and 3.5 months after the restart of pazopanib showed stable disease. Pazopanib was stopped permanently 6 months after the restart because of progressive disease, and she died 2 weeks later. In the second period of pazopanib treatment, no liver toxicity occurred. No differences between co-medication were found between the first period of pazopanib treatment and the second. A summary of the patients' history is given in figure 4.

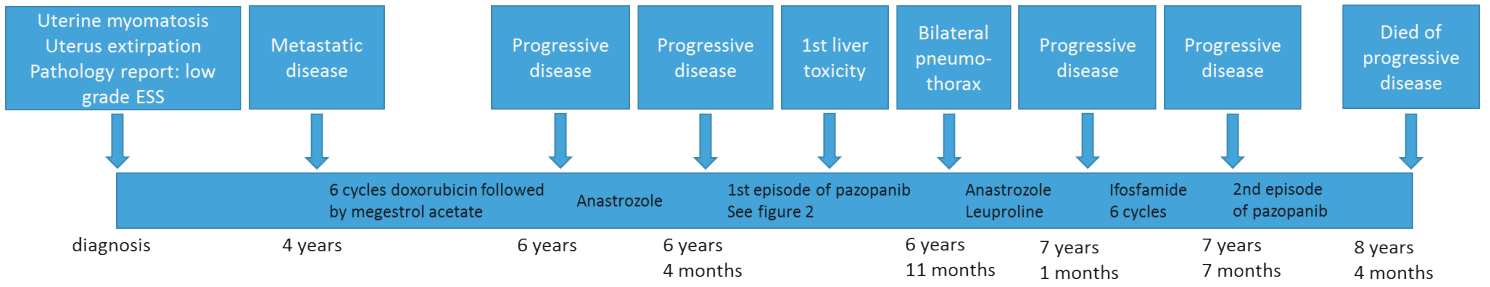

Figure 4 Timeline

Description of treatment in time.

The DNA of the patient was analyzed for single nucleotide polymorphisms (SNPs) in enzymes known to be involved in the absorption, distribution, metabolism and elimination of pazopanib.[13] The genes analyzed were *CYP3A4, CYP1A2, CYP2C8, ABCB1* and *SLCO1B1.* The main metabolizing enzyme for pazopanib, *CYP3A4* did not have SNPs associated with a decreased metabolic function. Two SNP variants in *CYP1A2* (rs762551 and rs2470890) and one in *SLCO1B1* (rs4149057) were detected, but no evidence exists that these polymorphisms cause elevated levels of pazopanib. So, this analysis did not result in the elucidation of a cause for the liver toxicity in this patient.

Discussion and Conclusion

This case report has 2 new learning messages: we present a patient with an ESS with a remarkable response on pazopanib and we describe clinical management of pazopanib induced recurrent liver toxicity.

Liver function test abnormalities, mainly elevations in ASAT and ALAT, are a common side effect of pazopanib and more in general of TKIs.[14] The exact pathophysiologic mechanism is unknown. A distinctive class effect seems to be unlikely, because pharmacologically different TKIs are known to be hepatotoxic and the substances are also very different chemical compounds. In a case series of two patients with liver toxicity of pazopanib liver histology showed mild active cholestatic hepatitis with inflammation that predominantly involved portal tracts.[15] Recently, it was reported that treatment with pazopanib in combination with prednisolone in case of liver function abnormalities prevented recurrence of liver function abnormalities in two patients.[16] UDP-glucuronosyltransferase isoform 1A1 has been related to bilirubin elevations during pazopanib treatment. These are probably patients with latent Gilbert syndrome becoming evident due to the inhibitory effect of pazopanib.[14] More recently, an association between HLA-B*57:01 and pazopanib induced liver toxicity was found.[17] Whether other germline genetic causes of pazopanib induced liver toxicity exist is unclear. The summary of product characteristics (SmPC) of pazopanib contains guidelines on handling liver toxicity.[6] If the elevation of ASAT and ALAT between 3 and 8x ULN it is safe to continue pazopanib with strict control of ASAT and ALAT until grade 1 toxicity. If ASAT and/or ALAT is more than 8x ULN then pazopanib should be stopped until recovery till grade I or less and if reinitiated restart with pazopanib once daily 400mg. It should be stopped permanently if ASAT and/or ALAT rise again to >3x ULN. Pazopanib should also be stopped if ASAT and/or ALAT are elevated >3x ULN concurrently with a bilirubin elevated >2x ULN. In our case, despite these recommendations, pazopanib was reintroduced at further reduced dose and no progressive liver insufficiency developed. Ultimately this strategy seemed to be effective until a dose reduction to 200mg once every second day. Another possible solution for toxicity management would be therapeutic drug monitoring, which is possible for pazopanib with a dried blood spot assay.[18] However, because the intrapatient variability of pazopanib levels is high, a recent study could not show an effect of therapeutic drug

monitoring on the interpatient variation.[19] A SNP analysis of genes for enzymes known to be involved in the metabolism of pazopanib did not provide an explanation for elevated pazopanib levels or liver toxicity in our patient. In case of further dose reductions after reduction to once daily 400mg, we suggest that patients should be monitored closely with once weekly liver function testing.

The second message of this case report regards the pazopanib response related to the tumour type. When feasible ESS is treated with radical surgery. Treatment of metastatic or locally progressive ESS consists of endocrine therapy as first line and when progressive on endocrine therapy chemotherapy. No specific data on the use of pazopanib in ESS is available, but this case report shows that pazopanib induced a partial response and prolonged PFS of 9 months which is more than the median PFS in the PALETTE study. Although in general ESS does not overexpress KIT, it was recently shown that ESS harbouring the YWHAE-FAM22 fusion gene frequently overexpress KIT (without a mutation in the KIT oncogene) in the high grade component of the tumour, as was the case in our patient.[11,20] This could explain the good response, in this rare histologic subtype, to pazopanib, which is an inhibitor of VEGFRs, PDGFRs and KIT. Based on these findings there may also be a potential role for imatinib, which was already reported in two cases.[21,22] Most probably the evidence for treatments in ESS will be not better than small case series due to the rarity of this disease.

The 3rd teaching point of this case report regarding the occurrence and clinical development of a pneumothorax during pazopanib treatment in (responding) patients with pleurally located metastatic lesions was addressed in a previous case series. [23]

In conclusion this case illustrates two important new points:

- First, reversible severe liver toxicity with pazopanib treatment is a known rare side effect of pazopanib and low dose personalized rechallenge in responding patients is a therapeutic option in experienced hands. This low dose personalized rechallenge is in conflict with the current SmPC of pazopanib and patients should be closely monitored for liver function abnormalities with for example weekly testing of the liver functions.

- Second, pazopanib was found to result in a good response in this patient with a YWHAE-FAM22A/B translocated ESS which may be related to the KIT overexpression in these tumours.

Declarations

Ethics approval, consent to participate and consent to publish

Because no experimental treatment was used ethics approval is not necessary. Patient consented to be part of the pazopanib compassionate use program and thereby consented for use of medical data for scientific purposes. Consent to publish was given by her family, because the patient has passed away. A copy of the written informed consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The patients information used for this study is not publicly available due to privacy regulations.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this case report.

Author contributions

AV and HG did the conception and design of the case report, did a review of the literature and wrote the case report. FW provided the patient information. JB and TB reviewed the histopathological specimens. FW, JB and TB revised the manuscript. All authors read and approved the final manuscript.

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Pneumothorax as adverse event in patients with lung metastases of soft tissue sarcoma treated with pazopanib:

a single reference centre case series

Clin Sarcoma Res 2014;4:14

A.J. Verschoor, H. Gelderblom

Abstract

Background

Recently, the phase III PALETTE study introduced pazopanib (Votrient®) as treatment for adult patients with locally advanced or metastatic non-liposarcoma soft tissue sarcoma after prior treatment with doxorubicin and/or ifosfamide. Pneumothorax was reported as adverse event in 8 of 246 treated patients (3.3%) in that study. This case series presents the incidence and clinic of this complication in the Leiden University Medical Centre.

Cases

Forty-three patients were treated with pazopanib of which six patients (14.0%) developed a pneumothorax. These six patients were treated for malignant peripheral nerve sheath tumour, angiosarcoma, synovial sarcoma, fibromyxomatoid sarcoma, pleomorphic sarcoma and endometrial stromal sarcoma. All six patients had subpleural pulmonary or pleural metastases at the start of pazopanib and the pneumothorax developed during or shortly after treatment with pazopanib and was difficult to treat.

Discussion

The incidence reported by us is higher than the incidence in the PALETTE study. Trials with pazopanib in renal cell carcinoma, urothelial carcinoma and cervix carcinoma did not report pneumothorax as an adverse event, suggesting pneumothorax as a specific adverse event in soft tissue sarcoma patients treated with pazopanib. This may be related to the fact that there is often pleural metastatic involvement and cystic degeneration due to pazopanib treatment may add to the risk.

Conclusion

The risk of an, often difficult to treat, pneumothorax during pazopanib therapy should be discussed with the patient before initiation of treatment for a pulmonary metastasized sarcoma and physicians should be alert to the occurrence of such an event.

Background

Soft tissue sarcomas (STS) are rare mesenchymal tumours originating from visceral and connective tissue. This group of tumours accounts for approximately one percent of all malignancies and consists of more than 50 histological subtypes.[1] The only curative treatment is surgical resection with large margins with or without adjuvant radiotherapy.[1] Treatment for locally advanced and metastatic disease is usually palliative and was until recently mostly confined to anthracycline or ifosfamide based chemotherapy, apart from specific chemotherapy regimens used for specific subgroups.[1] Reported response rates vary between 16-27% and median survival is reported to be 12 months.[2] Trabectedin was introduced recently for STS, mainly for patients with (myxoid) lipo- and leiomyosarcomas.[3,4]

More recently, the phase III PALETTE study[5] introduced pazopanib (Votrient®) as treatment for adult patients with non-lipomatous advanced STS who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy. This was based on a progression free survival of 4.6 months for pazopanib versus 1.6 months in the placebo arm. Pazopanib is an oral anti-angiogenic multi-targeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, platelet derived growth factor receptors and KIT. In the PALETTE study, treatment with pazopanib was complicated by the occurrence of a pneumothorax in 8 of the 246 patients. This case series reports on the incidence and clinic of this complication in all consecutive patients treated at the Leiden University Medical Centre.

Cases

In our institution, 43 STS patients were treated with pazopanib, of which 39 had pulmonary metastases and 36 of these patients had pleural or subpleural pulmonary metastases. Treatment was complicated by a pneumothorax in six (14.0%) patients.

The first patient is a 24-year old male, with a malignant peripheral nerve sheath tumour of the left brachial plexus, diagnosed three years before. Initial treatment consisted of local resection and irradiation, repeated one year later because of local recurrence. Pulmonary metastases, some localised pleural, were found seven months later for which six cycles of 3-weekly doxorubicin 75 mg/m2 was initiated. Progressive disease was diagnosed six months after the first doxorubicin cycle and treatment with pazopanib was started. A CT scan at the start of pazopanib showed a necrotizing metastasis in the left lung (Figure 1A, B). A month later a left-sided pneumothorax occurred after a skiing trip at 3000 meters height, persisting after drainage and later also a right sided pneumothorax occurred. The CT scan detecting the pneumothorax on the left side, also showed cystic degeneration of metastases in the right lower lobe (Figure 1 C, D). The

persistent bilateral pneumothorax was complicated by a pyothorax on the left side. He died six months after the start of pazopanib, which was continued until his death.

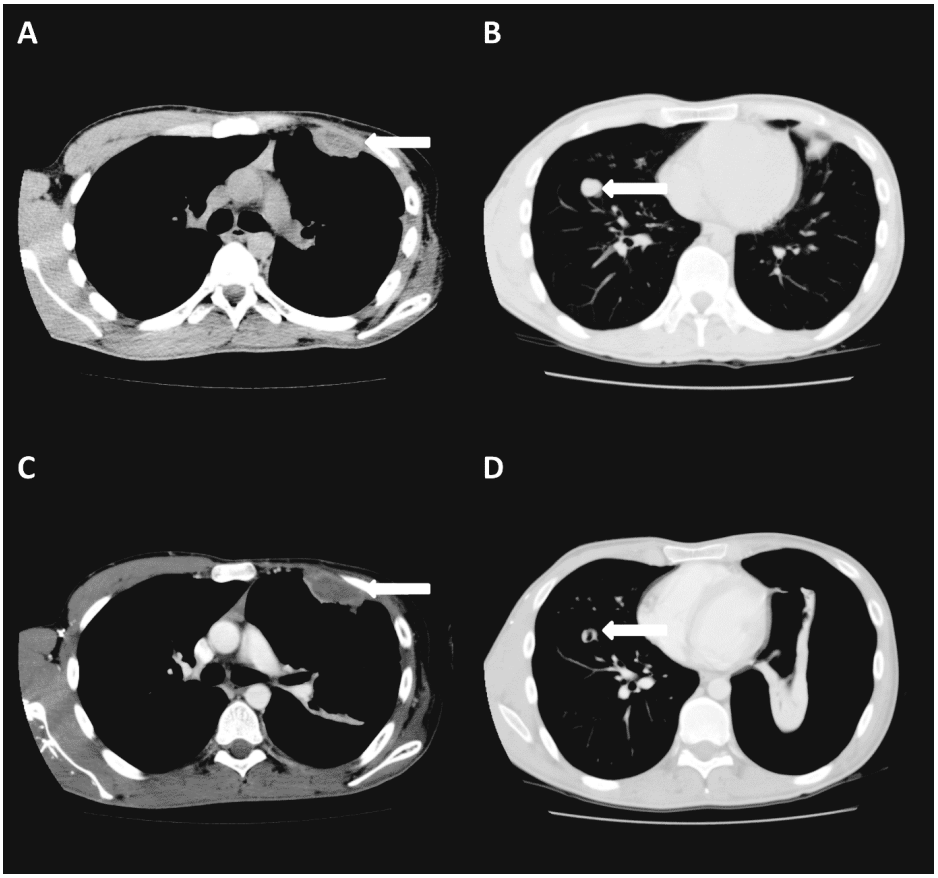

Figure 1 CT scans of patient 1. A and B: CT scan of the thorax at start of pazopanib, showing a pleural metastasis of the left lung with central hypodensities suggesting necrosis (A, arrow) and showing a pulmonary metastasis in the right lung (B, arrow). C and B: CT scan, when presenting with a left-sided pneumothorax (D), showing progressive hypodensity of the pleural metastasis on the left side (C, arrow) and central cavitation in the metastasis in the right lung (D, arrow).

Patient 2 is a 79-year old male, who was diagnosed two years before with an angiosarcoma of the scalp. Primary treatment was combined paclitaxel and radiotherapy. However, one year later a local recurrence was diagnosed and a CT scan showed pulmonary metastases, of which some were pleural, for which 3-weekly doxorubicin 75 mg/m2 was started. The local recurrence was progressive after six months and pazopanib was initiated, which was stopped three months thereafter because of progressive disease. Some of the pulmonary metastases already showing

cavitation at start of pazopanib (Figure 2A) were increasing in number, size and cavitation during treatment (Figure 2B, C). One week after the start of pazopanib a right sided pneumothorax occurred (Figure 2D), which was treated with drainage, but without pleurodesis, however it recurred one week later and again drained. A month thereafter a left-sided pneumothorax was diagnosed, which was left untreated. He died one week later due to disease progression, four months after the start of pazopanib.

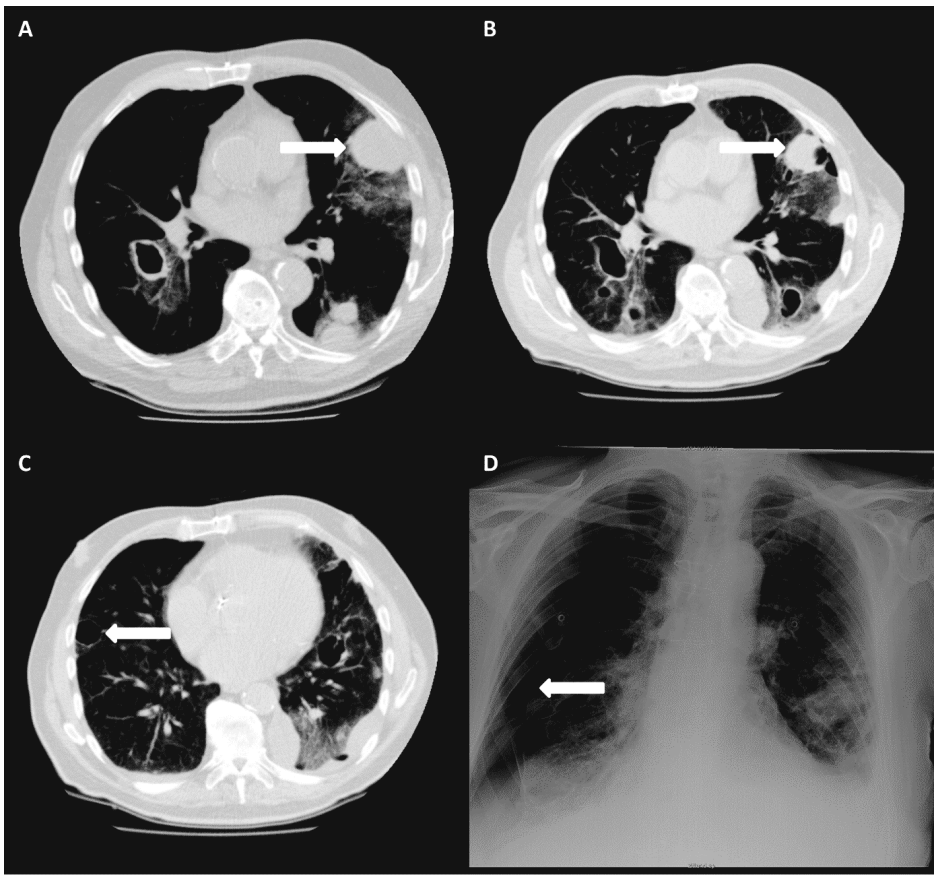

Figure 2 CT scans and X-thorax of patient 2. A: CT scan at start of pazopanib showing metastases in both lungs with a large necrotizing metastasis on the left side. The pleural metastasis indicated by the arrow is also visible in B, which is a CT scan after 3 months of pazopanib treatment, now showing cavitations. C is also an image from the CT scan after 3 months of pazopanib treatment showing a metastasis (arrow) with cavitation next to the pleura. D: The X-thorax shows the right sided pneumothorax. The visceral pleural line is indicated by the arrow.

The third patient is a 34-year old male, three years before diagnosed with a synovial sarcoma of the left femur with synchronous lung metastases, some with a pleural

localisation, and malignant pleural effusion. Treatment consisted of resection of the primary tumour and doxorubicin/ifosfamide chemotherapy followed by pulmonary metastasectomy and isolated melphalan lung perfusion. Treatment with trabectedin was started, but stopped after nine cycles because of progressive disease and pazopanib was started. He was treated for a remarkable 15 months when progression occurred and a hydropneumothorax was diagnosed on a routine follow-up CT scan (Figure 3A, B), treated with drainage and talc pleurodesis. Pazopanib was stopped. The CT scan did not show necrotizing metastases. Two weeks later the pleural effusion recurred and persisted until he died 2 months later.

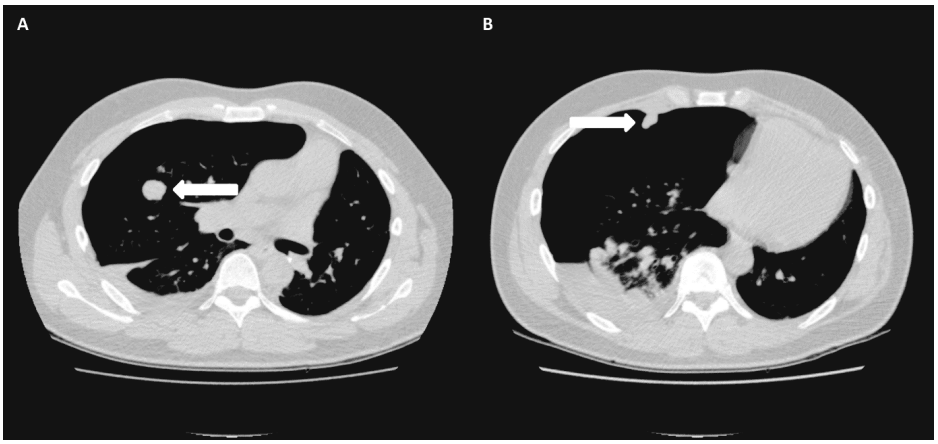

Figure 3 CT scans of patient 3. Routine follow-up CT scan showing the pneumothorax on the right side. A shows one of the pulmonary metastasis, B shows a pleural metastasis.

The fourth patient is a 53-year old female, who had resection of a low-grade fibromyxomatoid sarcoma of the left lower extremity 13 years before. Nine years later, pulmonary, liver and lymph node metastases were diagnosed, treated with 2 cycles of liposomal doxorubicin, which was stopped because of toxicity. Some of the pulmonary metastases were localised adjacent to the pleura. Treatment was continued with low dose doxorubicin weekly for 3 months, which was repeated one year later because of progressive disease. Three months after the last doxorubicin treatment progressive disease was diagnosed and pazopanib was prescribed. After seven months treatment with pazopanib she developed a left-sided pneumothorax (Figure 4), successfully treated with drainage. No cavitation of the metastases was found. At the moment, treated for 31 months with pazopanib, she has stable disease.

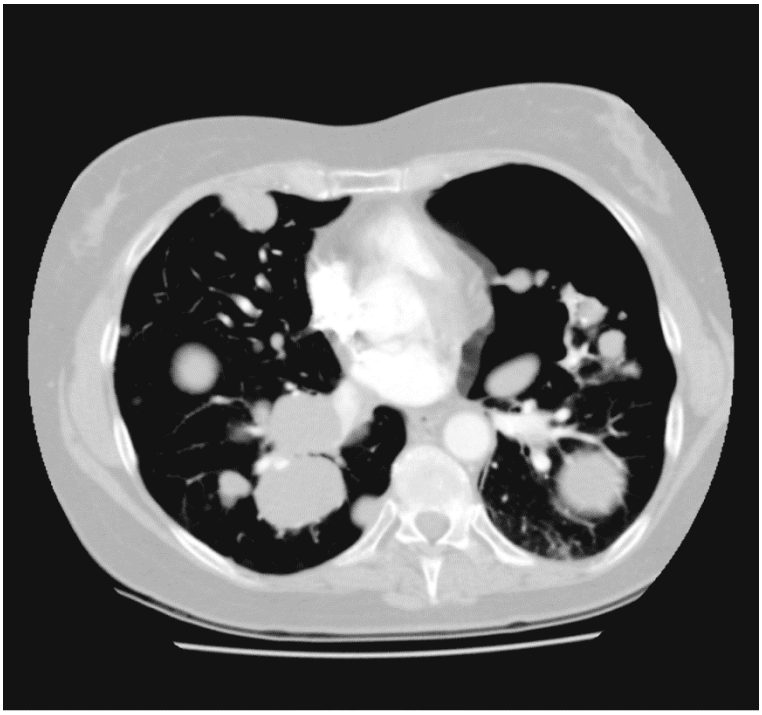

Figure 4 CT scan of patient 4. The CT scan shows the massive pulmonary metastases and a left-sided pneumothorax.

Patient five is a 72-year old female, who presented with a high grade undifferentiated pleomorphic sarcoma of the right lower extremity with pulmonary metastases, of which some are localised next to the pleura, one year before. She was treated with local resection, radiotherapy and 3-weekly doxorubicin 75 mg/m2. Five months after the start of doxorubicin progressive disease was diagnosed and pazopanib was prescribed (Figure 5A). After two months of treatment she developed a left-sided pneumothorax, treated with drainage and pleural rubbing (Figure 5B). Part of the pulmonary metastases showed cavitation. During admission a right-sided pneumothorax occurred and was drained successfully. However, she died one week later due to progressive disease.

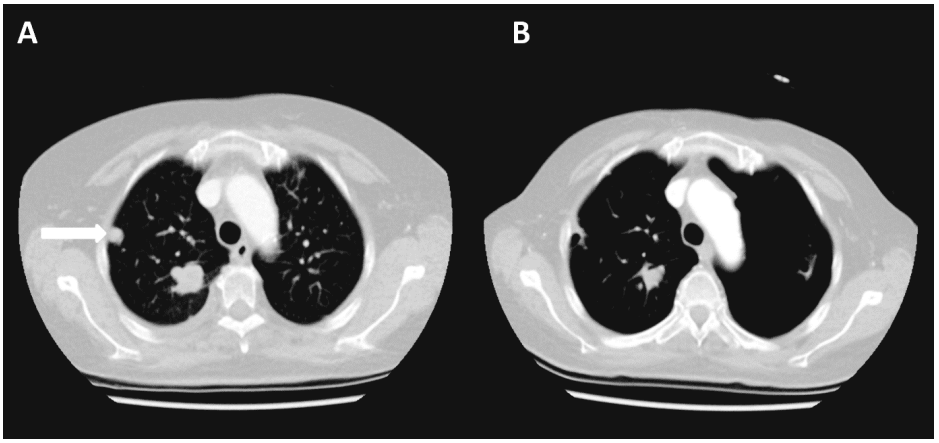

Figure 5 CT scans of patient 5. A: CT scan before the start of pazopanib showing multiple metastases in the right lung, one is indicated by the arrow. B: Routine follow-up CT scan during pazopanib treatment showing the left-sided pneumothorax and the earlier mentioned metastasis in the right lung is now showing cavitation.

The sixth patient is a 40-year old female diagnosed with a low grade endometrial stromal sarcoma, six years before, after a uterus extirpation for uterine myomatosis. When she presented four years later with thoracic pain, CT scan of the thorax showed a large mediastinal mass and pulmonary metastases, also localised next to the pleural space. Treatment with doxorubicin was started and resulted in partial regression of the tumour masses. Eighteen months later pazopanib was started under the supervision of the reference centre because of progression of the pulmonary metastases. Due to liver toxicity the pazopanib dose was tapered to a minimum dose of 200 mg with short pauses in treatment, however treatment was successful (Figure 6A, B). Treatment was permanently stopped after 33 months because of a bilateral pneumothorax and disease progression (Figure 6C). She was successfully treated with drainage.

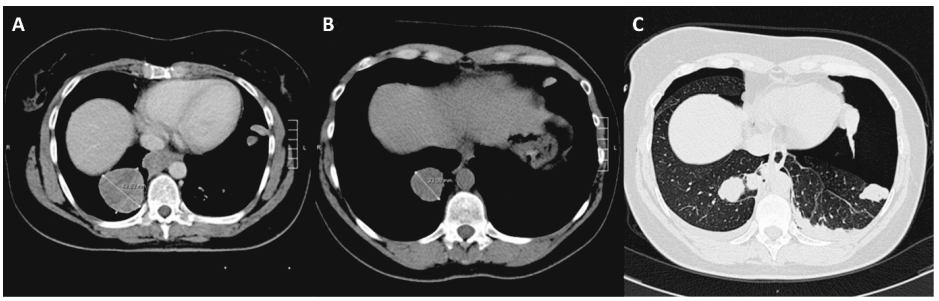

Figure 6 CT scan of patient 6. A: CT scan at start of pazopanib showing a metastasis in the right lower lobe with a diameter of 49.6 mm. B: CT scan after 12 weeks of pazopanib (6 weeks of treatment and 6 weeks on hold due to liver toxicity), showing a decrease in diameter of the metastasis to 33.1 mm. C: CT scan showing the bilateral pneumothorax.

Discussion

The incidence of pneumothorax of 14.0% in our institution was higher than the previous reported incidence (3.3%) in the PALETTE trial.[5] Literature does not provide the incidence of secondary spontaneous pneumothorax in STS patients, but it is probably uncommon. Other trials with pazopanib in for example urothelial cancer, renal cell cancer, pancreatic neuroendocrine tumours and cervical cancer did not report pneumothorax as an adverse event.[6-11] Trials with sunitinib, another VEGFR inhibitor, in renal cell carcinoma also do not report pneumothorax as an adverse event.[12,13] Only, two cases are published in literature of patients with a spontaneous pneumothorax during sunitinib treatment for renal cell carcinoma.[14,15] This suggests that this is a specific adverse event in metastatic STS treated with pazopanib, however, it could still be due to underreporting in other studies or due to the natural course of this disease that predominantly metastasizes to the lungs.

One of the proposed mechanisms is necrosis of a metastasis due to therapy, resulting in a pleural defect. Another possible explanation would be a check valve mechanism due to compression of bronchioles by a lung metastasis causing hyperinflation of a lung segment and rupture of lung parenchyma.[16] In our patients all cases of pneumothorax were related to pleural or subpleural lung metastases, and were observed in both progressive and responding patients. Smoking is a risk factor for primary spontaneous pneumothorax, but only one of our six patients had a smoking history. We do not think smoking history is relevant for the occurrence of a pneumothorax in these patients. As with other cancer related pneumothoraxes they were difficult to treat. One of the explanations for the difficult treatment in these patients could be the use of pazopanib, which inhibits angiogenesis and thereby tissue regeneration.

A larger series is needed in a case control setting to gain more understanding of this phenomenon.

Conclusion

The risk of a difficult to treat pneumothorax during pazopanib therapy should be discussed with the patient before initiation of treatment for a pulmonary metastasized sarcoma and physicians should be alert to the occurrence of such an event.

Consent

Written informed consent was obtained from every patient in the PALETTE study or the pazopanib compassionate use program for use of their medical data for scientific purposes. A copy of the written informed consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

STS, Soft tissue sarcoma; VEGFR, Vascular endothelial growth factor receptor.

Competing interests

AJV and HG declare to have no competing interests.

Authors' contributions

AJV participated in the collection of the data and the literature search and drafted the manuscript. HG participated in the design of the study and corrected the manuscript. Both authors have read and approved the final manuscript.

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PART II

Bone tumours


10

Incidence and demographics of giant cell tumour of bone in the Netherlands:

first nationwide pathology registry study

Acta Orthop. 2018;10:1-5.

A.J. Verschoor, J.V.M.G. Bovée, M.J.L. Mastboom, P.D.S. Dijkstra, M.A.J. van de Sande, H. Gelderblom

Abstract

Background and purpose

Giant cell tumours of bone (GCT-B) are rare, locally aggressive tumours characterized by an abundance of giant cells. Incidence studies for GCT-B are rare. This is the first study using a fully automated 100% covering pathology database, the nationwide Dutch Pathology Registry (17 million inhabitants), PALGA, to calculate incidence rates for GCT-B.

Patients and methods

From PALGA, all pathology excerpts were retrieved for patients diagnosed with GCT-B, giant cell tumours of tenosynovium and giant cell tumours of soft tissue between January 1, 2009 and December 31, 2013. The incidence of GCT-B was calculated.

Results

In total, 8156 excerpts of 5922 patients were retrieved; these included 138 first GCT-B diagnosis. For GCT-B the incidence was 1.7 per million inhabitants per year with a male to female ratio of 1:1.38 and a median age of 35 years (9-77). Most common localization was the femur (35%), followed by the tibia (18%). No differences in localization according to age and sex were found. Incidence rate of local recurrence was 0.40 per million inhabitants per year.

Interpretation

This is the first nationwide study reporting the incidence of GCT-B, based on a nationwide pathology database with 100% coverage of pathology departments. Current incidence calculations are based only on doctor-driven registries. We confirmed that GCT-B is a rare disease with an incidence that is slightly higher than previously published. The relatively young median age of patients and the high incidence of recurrence stresses the importance to develop more effective treatments for this disease.

Introduction

Giant Cell Tumour of Bone (GCT-B) is a locally aggressive neoplasm composed of sheets of mononuclear cells admixed with uniformly distributed large osteoclast-like giant cells, primarily affecting the metaphysis of long bones.[1] These cells express receptor of nuclear factor kappa-B ligand (RANKL).[2,3] GCT-B are rare; however, the incidence is not exactly known and is for example not stated in the World Health Organization (WHO) classification of Tumours of Soft Tissue and Bone.[1] The incidence was recently estimated at between 1.03 and 1.33 per million per year based on cancer registries in Australia, Japan and Sweden (Table 1).[4,5] Median age of onset ranges between 20 and 40 years with an equal distribution between the sexes or a slight female predominance.[1,5]

Patients with GCT-B typically present with pain, swelling and often decreased joint movement. In 5-30% of patients a pathologic fracture is noted.[1,6] Although this tumour rarely metastasizes, it is known to be locally aggressive, which may result in joint destruction and, uncommonly, neurological deficit in axial tumours. [1] Treatment options are curettage, curettage with an adjuvant treatment or resection with joint replacement.[7] In GCT-B the local recurrence rate is 6-42%.[6,8] Recently, denosumab, a human IgG2 monoclonal antibody against RANKL, was registered for use in GCT-B and showed tumour response in 2 phase II studies.[9,10]

Table 1 Review of all available incidence data on GCT-B

Article	**Nation**	**Type**	**Incidence** per million inhabitants	**Age** median (years) (range)		**Percentage men**
Liede, 2014*	Sweden, Australia, Japan	Doctor-driven	1.03-1.33	20-40	(na)	na
Amelio, 2016*	Sweden	Doctor-driven	1.3	34	(10-88)	48%
Current study	The Netherlands	Nation-wide pathology registry	1.66	35	(9-77)	42%

na: not available. The study by Liede does not report an exact median age, but only a median age group.
**These studies probably also included patients with a giant cell tumour of the small bones of hands or feet and patients with central giant cell granulomas of the jaw.*

According to our knowledge, current literature in GCT-B contains incidence calculations based solely on cancer registry studies. These studies are doctor-driven with a risk of underreporting (Table 1).[4,5] In this study we use the non-profit nationwide network and

registry of histo- and cytopathology in the Netherlands, PALGA. This fully automated nationwide database contains all pathology reports in the Netherlands (17 million inhabitants).[11] In an effort not to miss GCT-B cases, our search included the following giant cell containing tumours: GCT-B, tenosynovial giant cell tumours and giant cell tumours of soft tissue.

We calculated the incidence, demographics and localizations of GCT-B in a nationwide pathology database study between January 1, 2009 and December 31, 2013.

Methods

Patients

PALGA covers all pathology reports of all pathology laboratories in the Netherlands since 1993.[11] Patient registration in PALGA is based on social service number and thereby multiple reports of one patient will be grouped and not lead to double registration of one patient. Excerpts matching our search criteria were retrieved from PALGA: encoded either as giant cell tumour of bone (PALGA code m9250*) or giant cell tumour of tenosynovium (m9252*) or pigmented villonodular synovitis (m9252*) or giant cell tumour of soft tissue (m9251*) and terms separately used as free text between January 1, 2009 and December 31, 2013.[11] In our search, giant cell tumours of soft tissue and tenosynovium were included, to be as comprehensive as possible. Additionally, for all these patients historical excerpts were retrieved matching our search criteria. When date of first diagnosis met our 5-year timeframe, the patient was included for incidence calculations. Patients with a giant cell tumour of the small bones of the hands or feet were excluded, since these are considered a separate entity according to the current WHO classification of tumours of soft tissue and bone.[12] Patients with a GCT-B affecting the mandible were also excluded, because these are probably central giant cell granulomas of the jaw.[13]

Based on the combination of the historical and current excerpts we could calculate the incidence of first local recurrences during the 5-year study period. It is essential to note that this is not the same as the incidence of recurrences for the patients diagnosed during these 5 years of study. To calculate the latter, a longer interval between the study period and the moment of reporting would be necessary.

Excerpts contained an encrypted patient identification number (allowing to identify multiple excerpts of one patient), data on age and sex, date of arrival of the histological tissue, and the conclusion of the pathology report. AJV extracted the data and uncertain pathology conclusions in the reports were discussed with HG and JVMGB.

Disaggregated incidence rate calculations for localized and diffuse-type are necessary in giant cell tumours of tenosynovium. The PALGA database lacks information on tumour-type (i.e., whether a giant cell tumour of tenosynovium is a localized type or a diffuse

type as this is a combined diagnosis of radiological and pathological examinations), therefore additional chart review in giant cell tumours of tenosynovium was performed and published elsewhere.[14]

Data collection

Anonymized data were collected on age, sex, year of diagnosis, localization, GCT type, date of local recurrence.

Statistics

For statistical analysis, the Statistical Package for Social Sciences (SPSS) version 23.0.0 (IBM Corp, Armonk, NY, USA) was used. Incidence of GCT-Bs was calculated per million inhabitants per year and standardized for 5 year age groups and sex for the Dutch population in 2012, as published by the Central Bureau of Statistics (CBS).[15] Incidence standardized to the WHO standard population for 5-year age groups was also calculated.[16]

We estimated first recurrences, defined as biopsied lesions or surgically treated recurrences, as the registry only contained reports for histological specimens. Both 95% confidence intervals (CI) for incidence rates (Mid-P exact) and frequencies (Wilson score) were calculated using www.openepi.com.

Ethics, source of funding and potential conflicts of interest

As pathology excerpts were fully anonymized, no ethics approval was necessary for this study. This work was supported by Daiichi-Sankyo with an unconditional financial grant. There are no potential conflicts of interest.

Results

Search results

From PALGA, 8156 excerpts of 5922 patients were retrieved matching the search criteria (Figure 1). Of these 5922 patients, 5756 patients were excluded. 151 new cases of GCT-B were identified; however, 13 of these new cases were actually not GCT-B, but either giant cell tumours of the small bones of hands or feet or central giant cell granulomas of the jaw. 15 patients were only diagnosed with a first recurrence during the study period and had a primary tumour before the study period.

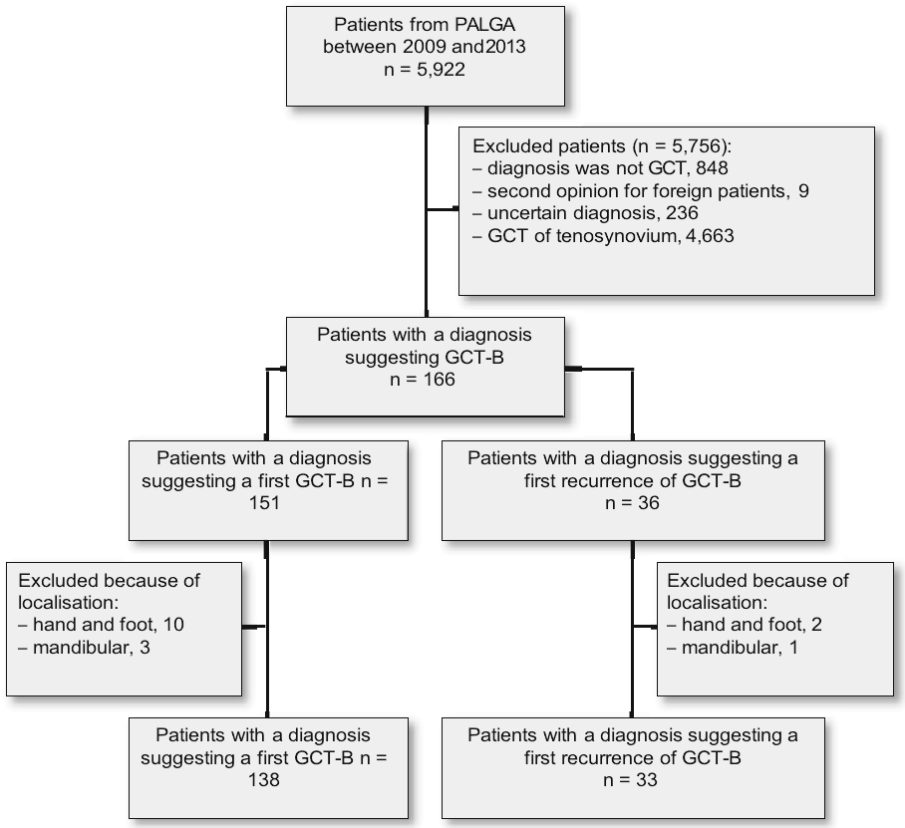

Figure 1 Diagram showing in- and exclusion of all patients with GCT in the Netherlands between 2009 and 2013

This resulted in 138 cases with a crude incidence ranging from 1.3 to 2.1 per million inhabitants per year (mean: 1.7; standard deviation (SD) 0.3; CI 1.4-2.0), age and sex corrected incidence ranged between 1.3 and 2.1 per million inhabitants per year (mean: 1.7; SD 0.3; CI 1.4-1.9), and the WHO standardized incidence was 1.4 to 2.3 per million inhabitants per year (mean: 1.7; SD 0.3; CI 1.4-2.0. Table 2 and Figure 2). 42% of patients were male (CI 34 - 50). The median age of patients was 35 years (9-77). 6% were below 18 years of age. The age distribution of GCT-B seems to be bimodal with a peak incidence between 20 and 39 and between 50 and 59 years (Figure 3). Most affected localization was the femur (35%), followed by the tibia (18%) (Table 3).

Table 2 Overview of incidence rates

	Crude incidence per million inhabitants per year (CI)	Age median (range)	Percentage males (CI)
GCT-B total	1.7 (1.4-1.9)	35 (9-77)	42 (34-50)
Long bones	1.3 (1.1 – 1.6)	35 (9-77)	41 (33-51)
Axial	0.35 (0.21 – 0.45)	38 (17-73)	46 (29-65)

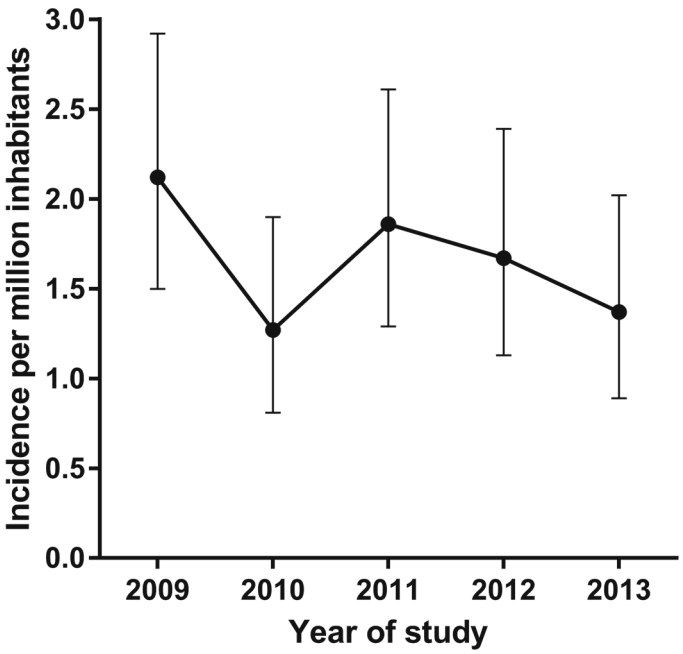

Figure 2 Crude incidence rates of GCT-B in the Netherlands with 95% confidence interval.

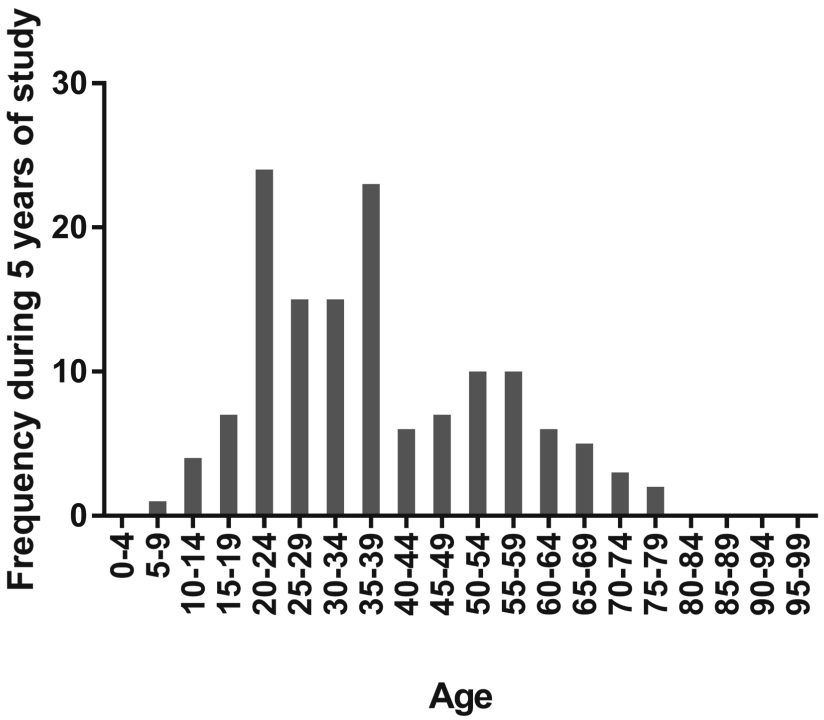

Figure 3 Age distribution of GCT-B in the Netherlands.

During these 5 years, 33 patients were diagnosed with a first recurrence. Consequently, crude incidence of pathology confirmed first recurrences was 0.40 per million inhabitants per year (CI 0.28-0.55). Median age of patients with a first recurrence was 32 years (10-63). Median time between first diagnosis and first recurrence was 23 months (range 2 – 142). 30% of the recurrences occurred within 1 year, 24% in the second year and 30% in the third year after diagnosis. Most common localization of recurrence were the femur and tibia (both 30%; Table 4).

Incidence rates for the long bones and the axial skeleton were 1.3 (CI 1.1 – 1.6) and 0.31 (CI 0.21 – 0.45) per million inhabitants per year, respectively (1 patient could not be allocated to one of the groups). WHO standardized incidence rates were 1.40 and 0.31 per million per year. Incidence of recurrence were 0.32 (CI 0.21 – 0.47) and 0.07 (CI 0.03 – 0.15) per million per year. The median age of patients for the 2 groups was 35 (9-77) and 38 (17-73) years. Percentage of males was 41% (CI 33-51) and 46% (CI 29-65) respectively.

Table 3 Frequencies of localizations of GCT-B

Localisation	Absolute frequency	Percentage (CI)
Femur	48	35 (27–43)
Tibia	25	18 (12–25)
Radius	14	10 (6 – 16)
Fibula	13	9 (6 – 15)
Spine	13	9 (6 – 15)
Ulna	5	4 (2 – 8)
Pelvis	5	4 (2 – 8)
Humerus	2	1 (0 – 5)
Mastoid	2	1 (0 – 5)
Patella	2	1 (0 – 5)
Scapula	2	1 (0 – 5)
Other*	3	2 (1 – 6)
Unknown	4	3 (1 – 7)
Total	**138**	**100**

**Other: 4th rib, maxilla and petrous bone*

Table 4 Localization of recurrences

Localisation	Frequency	Percentage (95% CI)
Femur	10	30 (17–47)
Tibia	10	30 (17–47)
Spine	4	12 (5–27)
Radius	3	9 (3–24)
Humerus	2	6 (2–20)
Fibula	1	3 (1–15)
Ulna	1	3 (1–15)
Scapula	1	3 (1–15)
Pelvis	1	3 (1–15)
Total	**33**	**100**

The localization of the tumours did not differ according to sex. Only 1 of the patients below 18 years of age had an axial localization of his GCT-B. However, this difference could be attributed to the low incidence of axial GCT-B.

During the 5-year study period, only 1 malignant GCT-B was reported.

Discussion

This is the first study on GCT-B incidence, based on a fully automated pathology database covering 100% of pathology reports in the Netherlands. Our calculated GCT-B incidence shows a higher number, compared with previously reported incidence rates (Table 1).[4,5] In addition, the study by Amelio et al. does not seem to exclude giant cell tumours of the small bones of the hands or feet and central giant cell granulomas of the jaw, suggesting that the actual incidence of giant cell tumours of bone in this study is actually lower.[5] However, this is not exactly stated in the paper, but derived from the graphs showing localizations. For the study by Liede *et al* (2014), no data on localization were reported. The higher incidence may be explained by the use of the 100% covering Dutch nationwide pathology database PALGA. Incidence of GCT-B seems to decrease slightly during the 5 years of study; this could be attributed to a normal variation in the low absolute count of GCT-B per year. As expected, most GCT-Bs were localized in the lower, weight-bearing extremities, as described in previous studies.[4,5] Both slight female preponderance and age distribution are comparable to these earlier reports.[4,5] Age distribution seems to be bimodal (between 20 and 39 years and 50 and 59 years of age), which is comparable to data described by Liede, *et al* (2014). However, this variation could also be due to the small number.

GCT-Bs generally affect young patients (median age 35 years) and 6% are younger than 18 years. This is lower compared to the 14% in the Swedish study and the approximately 8% in Japan (manually calculated, based on published data).[4,5] Reporting bias could be the cause of the higher percentage of patients < 18 years with a GCT-B in the Swedish and Japanese registries, because these are doctor-driven registries.

Although we do not calculate an exact incidence rate of first local recurrences for the patients diagnosed between 2009 and 2013 in this study, we calculated an incidence of all first recurrences during this time period of 0.40 per million inhabitants per year. This results in a rate of recurrence of approximately 24% (although the denominator is not exactly known), which is lower compared to the Swedish study (recurrence rate 41%).[4,5] 2 retrospective cohort studies reported rates of recurrence between 6 and 42%.[6,8] The relatively higher recurrence rate in the Swedish study could be attributed to an effect of reporting bias (patients with a recurrence will have a higher chance of being registered). The differences in recurrence could be caused by different treatment strategies, which

cannot be studied in these studies due to a lack of data in our study and the other studies.[6]

Compared with the other studies, the reported incidence of malignant GCT-B (1 patient in 5 years, 1 of 138 patients) during these years was much lower than in the study by Liede *et al.* (27/337). We have no explanation for this difference.

In the future, additional nationwide studies are needed to calculate a more accurate worldwide incidence, because at the moment only incidence rates for countries in North and West Europe are available. Furthermore, the incidence calculations should include information on the incidence of GCT-B subdivided into long bones and the axial skeleton.

Concluding, this study is the first to report incidence of GCT-B based on a 100% coverage nationwide pathology database. These incidence numbers are of value for research and healthcare planning.

Author contributions

AJV, JVMGB, HG designed the study. AJV did the data collection and primary analysis of the data. All authors interpreted the data. AJV wrote the manuscript. All authors critically reviewed the manuscript and approved the final version.

Acknowledgments

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11

Single centre experience with ifosfamide monotherapy as second line treatment of recurrent/ metastatic osteosarcoma

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Abstract

Background

The effectiveness of second-line palliative chemotherapy in patients with recurrent/metastatic osteosarcoma is not well defined. Several small studies (6-19 patients) have reported on ifosfamide as second-line treatment. In this study we report our single centre experience, with second-line ifosfamide monotherapy in patients treated for recurrent/metastatic osteosarcoma.

Methods

Of all osteosarcoma patients treated with ifosfamide from 1978 until 2017 a chart review was conducted. Until 1997 a 5 gram/m^2 regimen was used and from 1997 onwards 9 gram/m^2 regimen was used. Overall survival (OS) from start of ifosfamide was the primary end point. Progression free survival (PFS) from start of treatment was also studied. To assess difference in survival between groups the log rank test was applied. To investigate the effect of ifosfamide dose and WHO performance status (PS) a Cox proportional hazard regression model was estimated.

Results

Sixty-two patients were selected with recurrent/metastatic osteosarcoma treated with second-line ifosfamide monotherapy (26 dose of 5 gram/m^2 and 36 9 gram/m^2). OS was significantly better in univariate analysis for 9 gram/m^2 compared to 5 gram/m^2 (10.9 (95% confidence interval (95%CI) 9.3–12.6) vs. 6.7 months (95%CI 5.9-7.6) respectively) and for PS (median OS PS 0: 13.0 months (95%CI 2.3-23.8), PS 1 8.2 months (95%CI 5.4-11.1) PS$\geq$2 6.2 months (95%CI 2.2-10.3) and unknown 5.4 months (95%CI 2.2-8.5). In multivariate analysis only PS showed a significant difference. No difference in PFS was found between 5 and 9 gram/m^2 ifosfamide treatment or PS.

Conclusion

This study suggests that ifosfamide is an effective second-line treatment for patients with recurrent/metastatic osteosarcoma.

Introduction

Osteosarcoma is the most common primary bone malignancy, but remains a rare tumour affecting predominantly adolescents and patients of advanced age. Primary treatment of high-grade osteosarcoma in case of local disease or local disease with pulmonary metastases is perioperative chemotherapy combined with surgery. The 3-year event free survival is approximately 60-70%.[1-4] Current first line treatment in most of the Western world is combination chemotherapy consisting of methotrexate, doxorubicin and cisplatin. The EURAMOS study tried to improve cure rate in patients with a poor pathological response to the first cycles of chemotherapy by the addition of ifosfamide and etoposide to the perioperative regimen of methotrexate, doxorubicin and cisplatin, but this study failed to reach its primary endpoint.[5] At present, more than 40% of all osteosarcoma patients continue to develop local recurrent or distant metastatic disease after primary treatment. These patients may still be cured when recurrence or metastases are limited and amenable to surgery.[6,7]

When cure is no longer possible, different palliative chemotherapeutic regimens are available, e.g. ifosfamide, etoposide, ifosfamide/etoposide and gemcitabine/docetaxel.[8-14] These treatment regimens were studied in small, single arm, studies and case series. No randomized phase II or III trials are available. Reported outcomes of these treatments are poor with response rates of 17% for gemcitabine/docetaxel, one out of eight patients for etoposide, and a higher response rate of 48-59% for ifosfamide/etoposide, but as first line treatment.[8-11] Progression free survival (PFS) for gemcitabine/docetaxel was 3.5 months.[11] Ifosfamide as second line treatment was studied in several small studies (between 6 and 19 patients per study) studying varying ifosfamide doses, ranging from 5 gram/m^2 in one day to a total of 14 gram/m^2 continuously over 7 days.[12-15] None of these studies reported the overall survival (OS) and/or PFS. Overall response rates varied between 24% and 44%.

A retrospective analysis of 7 Children's Oncology Group studies, all with inactive drugs (according to the study criteria), by Lagmay *et al.* showed an event free survival (which is usually called PFS) of 12% at 4 months, which can be used as reference for new single arm studies.[16] In a recently published small randomised phase II study, including 43 patients, regorafenib was shown to have an 8 weeks PFS of 65% versus 0% for the placebo group.[17]

This study reports the Leiden University Medical Center experience with ifosfamide monotherapy as palliative treatment in patients with osteosarcoma. It also studies (to the authors knowledge for the first time in literature) whether the currently used dose of 9 gram/m^2 over 3 days continuously is better than the previously used 5 gram/m^2 as bolus infusion.

Methods

Patients

From our hospital cancer registry all patients treated palliatively with ifosfamide monotherapy for an osteosarcoma were selected. Sixty-two patients were identified, of which 2 were excluded (1 was actually a salivary gland tumour and 1 was a uterine leiomyosarcoma treated as osteosarcoma). Three additional patients had the outdated diagnosis malignant fibrous histiocytoma (MFH). All three patients with so-called malignant fibrous histiocytoma of bone had pathology review before study entry by an expert bone tumour pathologist (JVMGB). For two patients osteoid deposition by tumour cells was focally observed and the diagnosis was changed to high grade osteosarcoma, and these two patients were included. The third patient was diagnosed with undifferentiated pleomorphic sarcoma after revision and was excluded. Patients were grouped based on their actual primary ifosfamide dose being $\leq$6 grams/m^2 (hereafter called intended dose 5 gram/m^2) or >6 grams/m^2 (called intended dose 9 gram/m^2). In our reference centre ifosfamide 9 gram/m^2 was introduced in 1997. Before 1997, 5 gram/m^2 was used. The cut-off of 6 gram/m^2 was chosen because this cut-off takes into account a little overdosing in the 5 gram/m^2 dosed patients and a small dose reduction in patients with an intended dose of 9 gram/m^2.

For all of these patients a chart review was conducted. Data was collected on age and sex, date of primary diagnosis, primary localization, histological subtype, primary treatment, primary intend of treatment (palliative or curative), metastases at diagnosis, localization of metastases at diagnosis, date of recurrence, date of start ifosfamide, planned dose of ifosfamide, actual primary dose of ifosfamide given, number of cycles of ifosfamide, given dose of ifosfamide, dates of response evaluation, outcomes of response evaluations and treatment after progression on ifosfamide.

Endpoints

The primary endpoint was OS, calculated as the time between start of ifosfamide and death. Secondary endpoints were PFS, calculated as time between start of ifosfamide and first documented progression and overall response rate, *i.e.* complete remission, partial remission, stable disease and progressive disease according to RECIST 1.1 or in case of only clinical evaluation clinical benefit. Covariates studied were histological subtype, WHO performance status (PS) at start of ifosfamide treatment and time between primary diagnosis and start of ifosfamide treatment. Toxicity was graded according to the NCI CTCAE version 4.0.

Statistics

Statistical analysis was performed with IBM Statistical Package for Social Sciences (SPSS) Statistics 24. Categorical data were summarized by frequencies and percentages, continuous variables were summarized by median and overall range. These were

presented according to the two different groups. The characteristics were compared with χ^2-test for categorical variables and a Mann-Whitney U test for the continuous variables. A χ^2-test was used to compare response rates between the two treatment groups. Kaplan Meier's methodology was used to estimate OS and PFS. Univariate and multivariate Cox proportional hazard regression model was estimated to investigate the effect of prognostic factors on OS and PFS.

To compare with existing literature, 8 weeks and 3 months PFS and 9- and 12-months OS were estimated by using Kaplan Meier's methodology.

The Medical Ethics Committee provided us a waiver for informed consent (registration number C14.167).

Results

Patients

In total, 62 patients treated with palliative ifosfamide treatment for osteosarcoma were identified from our hospital cancer registry. Thirty-six patients had a primary intended dose of 9 gram/m^2 ifosfamide and the other 26 had an intended dose of 5 gram/m^2. Table 1 shows the characteristics of the included patients. Patients with an intended dose of 9 gram/m^2 were older (30.0 (17-70) years vs. 22.5 (15-56) years), received more radiotherapy before start of ifosfamide and received more cycles of ifosfamide treatment (median 3 vs 4 cycles). As expected, mean cycle dose and cumulative dose of ifosfamide was higher in patients with an intended dose of 9 gram/m^2. Only, 1 patient (9 gram/m^2) was pretreated with a regimen containing ifosfamide. (Supplementary table 2) More patients were treated with chemotherapy or other treatment options after the end of ifosfamide in the dose 9 gram/m^2 group (21 vs 12 patients). (Supplementary table 4 and 5)

Table 1: baseline characteristics

	Ifosfamide		
	Intended dose of 5 gram/m2 N=26	**Intended dose 9 gram/m2 N=36**	**P**
Age (in years, median, range)	22.5 (15-56)	30.0 (17-70)	0.031
Male	18 (69%)	20 (56%)	0.275
Primary localization			0.593
Lower extremity	21 (81%)	26 (72%)	
Upper extremity	4 (15%)	4 (11%)	
Pelvis	1 (4%)	4 (11%)	
Thorax		1 (3%)	
Head		1 (3%)	
WHO Performance status			0.306
0	5 (33%)	18 (51%)	
1	6 (40%)	11 (31%)	
2	3 (20%)	4 (11%)	
3	1 (7%)	2 (6%)	
Subtotal	15	35	
Unknown	11 (42%)	1 (3%)	
Grade			0.344
High	24 (92%)	35 (97%)	
Intermediate/low	1 (4%)	1 (3%)	
Unknown[a]	1 (4%)		
Metastases			0.395
Local recurrence only	1 (4%)	1 (3%)	
Pulmonary only	14 (54%)	24 (67%)	
Both pulmonary and primary localisation	1 (4%)	1 (3%)	
Other	10 (48%)	10 (28%)	

Table 1: Continued.

	Ifosfamide		
	Intended dose of 5 gram/m2 N=26	**Intended dose 9 gram/m2 N=36**	**P**
Number of previous lines of chemotherapy			0.072
0		1 (3%)	
1	21 (81%)	34 (94%)	
2	5 (19%)	1 (3%)	
Previous surgery	23 (89%)	29 (81%)	0.404
Previous radiotherapy	1 (4%)	10 (28%)	0.018
Number of cycles Median (range)	3 (1-16)	4 (1-13)	0.059
Mean dose/cycle (range)	4.9 gram/m2 (3.6-6.1)	8.3 gram/m2 (5.6-9.6)	Not calculated[b]
Cumulative dose (range)	18.0 gram/m2 (5.0-92.7)	40.5 gram/m2 (6.7-110.5)	Not calculated[b]
Histologic subtype			0.257
Conventional	16 (62%)	27 (75%)	
Other[c]	10 (38%)	9 (25%)	

[a] Treated as high grade. [b] Mean dose/cycle and cumulative dose were not statistically compared because these were the subject of our study. [c] See also supplementary table 1.

Overall survival

Median OS was 9.1 months (95%CI 7.8 – 10.4) after start of ifosfamide (this is also the median follow-up of the patients because all patients died).(Figure 1A) The OS was significantly different between the intended dose of 5 gram/m^2 and 9 gram/m^2 (*P*=0.046). For the intended dose of 5 gram/m^2 the median OS was 6.7 months (95%CI 5.9-7.6) versus 10.9 months (95%CI 9.3 – 12.6) for the intended dose of 9 gram/m^2.(Figure 1B) The OS was also significantly different between PS 0, 1 and ≥2 (*P*=0.012) with a median OS for PS 0 of 13.0 months (95%CI 2.3-23.8), PS 1 8.2 months (95%CI 5.4-11.1) PS ≥2 6.2 months (95%CI 2.2-10.3) and PS unknown 5.4 months (95%CI 2.2-8.5).(Figure 1C). In multivariate analysis only PS was statistically significant associated to OS. (Table 2) The 9- and 12-month OS were estimated to compare with other studies. (Table 3)

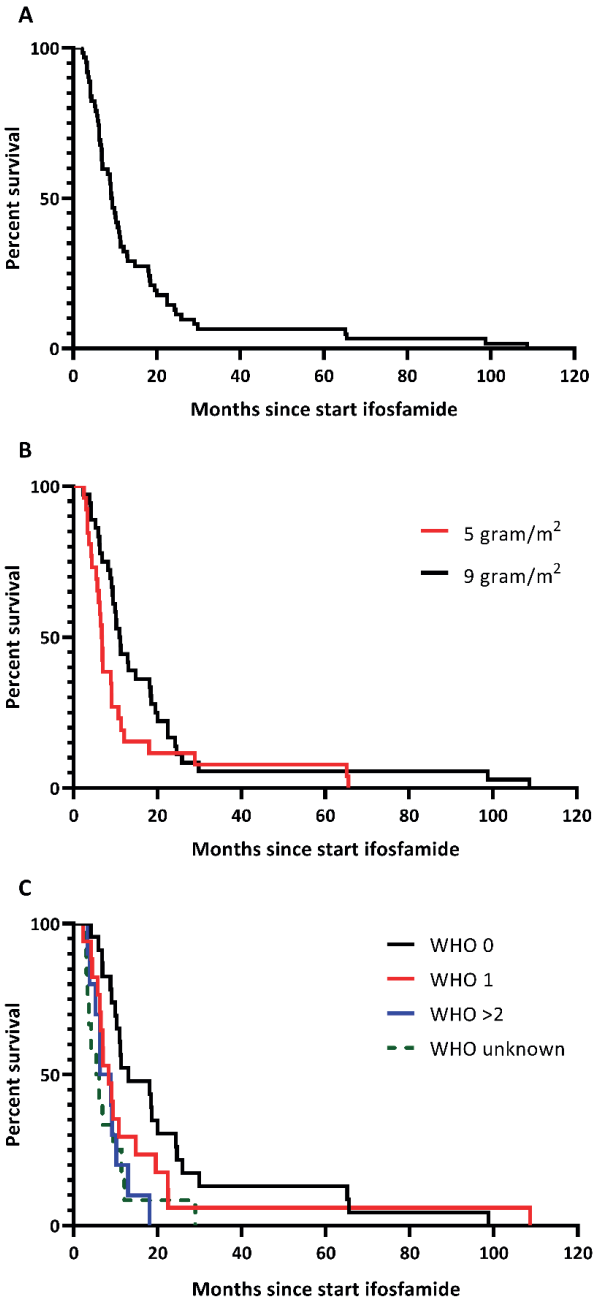

Figure 1: Overall survival, A all patients, B split based on dose, C split based on WHO performance score

Table 2 Multivariate analysis for prognostic factors for overall survival

		Overall survival	
		Adjusted hazard ratio	**P-value**
WHO performance score	**0**	1.00	0.016 (df=3)
	1	1.54 (0.81-2.93)	
	≥2	2.74 (1.26-5.97)	
	Unknown	2.70 (1.32-5.52)	

Progression free survival

The overall median PFS was 2.6 months (95%CI 2.2-3.0) after start of ifosfamide.(Figure 2A) The PFS showed a trend towards a better PFS for patients treated with an intended dose of 9 gram/m^2.(*P*=0.098) (Figure 2B) For the intended dose of 5 gram/m^2 the median PFS was 2.1 months (95%CI 1.3-2.9) versus 3.8 months (95%CI 2.2-5.4) for the intended dose of 9 gram/m^2.(Figure 2B) The PFS did not differ between the WHO performance states.(Figure 2C) The results of multivariate analysis resembled the univariate analysis. The 8 weeks and 3 months PFS were estimated to compare with other studies. (Table 3)

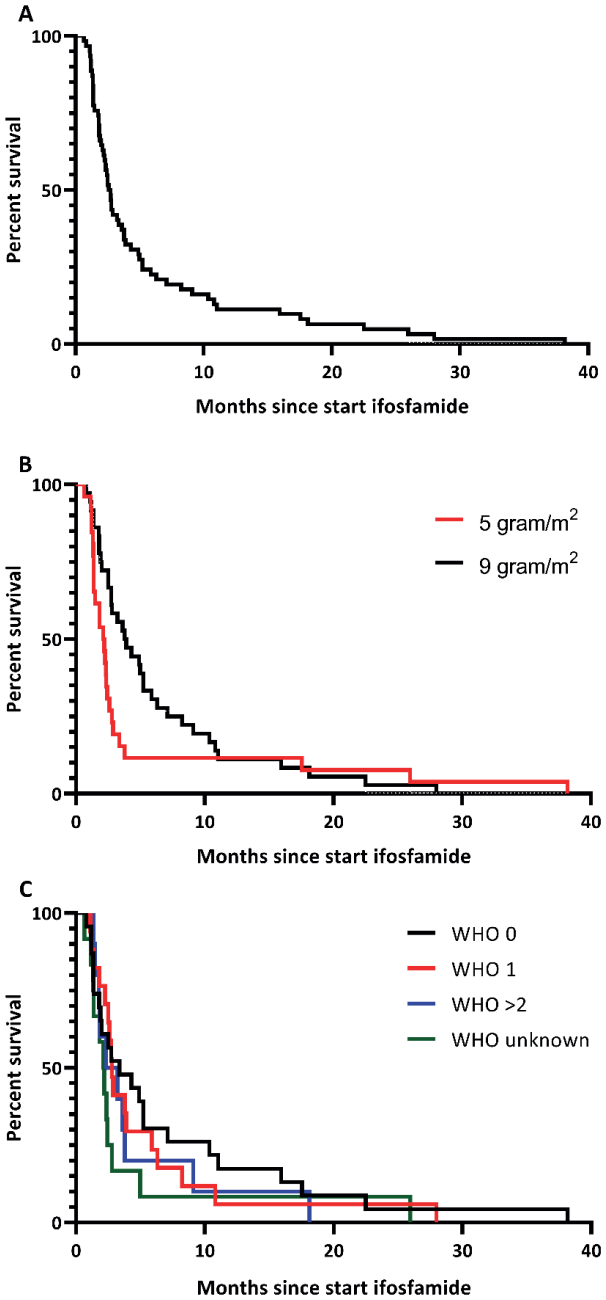

Figure 2: Progression free survival, A all patients, B split based on dose, C split based on WHO performance score

Table 3 Overall survival and progression free survival percentages at specific time points

	Intended dose 5 gram/m2	Intended dose 9 gram/m2
Overall survival 9 months	35% (95%CI 17 – 52)	69% (95%CI 52 – 82)
Overall survival 12 months	19% (95%CI 7 – 36)	44% (95%CI 28 – 60)
Progression free survival 8 weeks	54% (95%CI 33 – 71)	78% (95%CI 60 - 88)
Progression free survival 4 months	12% (95%CI 3 - 27)	44% (95%CI 28 – 60)

Overall response rate

Best overall responses are reported in table 4. Significant more patients had at least stable disease (78% vs 42%) when treated with ifosfamide 9 gram/m^2(*P*=0.005). Overall response rate did not differ significantly (36% vs 25%, p=0.27).

Table 4 Best overall response

		Best response				Total
		CR/PR/ clinical benefit	**SD**	**PD**	**Not evaluable**	
Intended dose	**5 gram/ m²**	6 (23%)	5 (19%)	15 (58%)	0 (0%)	26 (100%)
	9 gram/ m²	13 (36%)	15 (42%)	7 (19%)	1 (3%)	36 (100%)
Total		19 (31%)	20 (32%)	22 (35%)	1 (2%)	62 (100%)

Toxicity

As this is a retrospective study, toxicity was based on the reported toxicity in both the medical and nursing charts. This data is available in the supplementary data, table 5.

Discussion

This study is the largest study reporting the outcomes of ifosfamide monotherapy in the palliative treatment of osteosarcoma patients. Until now, only small studies with 6 to 19 patients reported outcome for patients treated with ifosfamide monotherapy. It shows that PS is an important prognostic factor for overall survival of osteosarcoma, but it was unfortunately not possible to detect a significant difference between 9 gram/m^2 and 5 gram/m^2.

To our knowledge, this is the first study to report both OS and PFS of patients treated with second line or later line ifosfamide chemotherapy for locally advanced or metastatic osteosarcoma. The overall response rate in this study (intended dose 5 gram/m^2 23% and 9 gram/m^2 36%) is comparable to earlier reports on ifosfamide monotherapy in these patients.[12-15,18] Additionally, in an ASCO 2015 abstract, results of ifosfamide 15 gram/m^2 continuously over 5 days were reported.[18] The overall response percentage was 22%, OS at 1 year was 60% and PFS at 6 months was 53%. Compared to these data, our study reports probably a lower 1 year OS and 6 months PFS in a patient population with worse PS and older age, but their results were not yet published.[18] In the French REGOBONE study, a placebo group was included with an 8 weeks PFS of 0% and in the regorafenib arm 65%.[17] In our study, ifosfamide showed an 8 week PFS of 54% (95%CI 33 – 71) for 5 gram/m^2 and 78% (95%CI 60 - 88) for 9 gram/m^2, suggesting a higher PFS for ifosfamide 9 gram/m^2 compared to regorafenib. The 4 month PFS of ifosfamide 9 gram/m^2 also compares favourably to the 4 months PFS defined in the retrospective study of the COG (44% (95%CI 28 – 60) vs. 12% (95% CI 6 – 19).[16] Also, an increase in clinical benefit rate is shown, when comparing 5 gram/m2 to 9 gram/m2.

One of the important results of this study is the prognostic impact of PS. This was already shown for some other tumours, e.g. soft tissue sarcoma.[19]

This study is limited by its retrospective character, the long study period and no routine monitoring interval of CT scan. All patients underwent CT scan at least each 2-3 cycles. We did an effort to report the toxicity of ifosfamide therapy, but this is probably an underestimation of the real toxicity and is probably also biased. The toxicity of ifosfamide monotherapy is well known. The long study period and the different time periods the study groups were treated in (5 gram/m^2 until 1997 and 9 gram/m^2 from 1997 until now) hamper the study because supportive care has improved during the years and this could cause a difference in OS. Also, the improvements in imaging could result in an earlier diagnosis of recurrent disease and thereby a suggested improvement in OS. Although in univariate analysis overall survival was better for 9 gram/m^2 and there was a trend towards a better PFS for patients treated with 9 gram/m^2, no significant impact of the dose on OS was found in multivariate analysis. This study is still underpowered because of the still small number of patients included, but also other causes are present. At baseline, there were differences in the number of pretreated patients between both groups (higher number of patients with 2 lines of chemotherapy in the 5 gram/m^2 group). This could have an impact on the results in several ways: selecting for patients with a more indolent disease and a more chemosensitive tumour or creating more chemoresistant tumours. It is not possible to determine what the most dominant effect is. Also, PS was slightly imbalanced at baseline, favouring the 9 gram/m^2 group, which could improve the OS in this patient group. Due to the still small patient group it is not possible to distinguish the effect of PS and ifosfamide dose. Although being the largest series, the small number of patients did not allow us to detect differences in for example

histologic subtypes of osteosarcoma. Lastly, we could not compare the outcomes of ifosfamide treatment to an untreated patient cohort of the Leiden University Medical Center. Although an untreated patient group exists, most of these patients had a reason why they were not treated and the comparison would result in a biased study. However, we did compare the data with the placebo arm of the REGOBONE study and with the retrospective study of the COG, showing that ifosfamide is an effective treatment (as reported above).[16,17]

This is the largest study until now, reporting data on OS and PFS of ifosfamide monotherapy as palliative treatment of osteosarcoma. This study suggests that ifosfamide is an effective second line treatment for patients with recurrent osteosarcoma.

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Supplementary material

Supplementary table 1: Osteosarcoma subtype

	Ifosfamide	
	Intended dose 5 gram/m² N=26	**Intended dose 9 gram/m² N=36**
Osteosarcoma subtype		
Conventional	16 (62%)	27 (75%)
Teleangiectatic	5 (19%)	1 (3%)
Small cell	1 (4%)	0 (0%)
Chondroblastic	4 (15%)	5 (14%)
Extraskeletal	0 (0%)	3 (8%)

Supplementary table 2: Pretreatment

	Intended dose 5 gram/m² N=26	**Intended dose 9 gram/m² N=36**
Pretreatment 1		
Doxorubicin/cisplatin	20 (77%)	27 (75%)
Doxorubicin/cisplatin/MTX	5 (15%)	6 (17%)
Doxorubicin/cisplatin/ ifosfamide/MTX*	1 (4%)	0
MTX/vincristin/doxorubicin	1 (4%)	0
Doxorubicin	0	2 (6%)
No treatment	0	1 (3%)
Pretreatment 2		
Doxorubicin/cisplatin	2	1
Doxorubicin	1	0
Iproplatin	1	0
MTX	1	1
No treatment	21	34

* Patient received only one cycle of this treatment

Supplementary table 3: Post ifosfamide treatment

	Intended dose 5 gram/m² N=26	Intended dose 9 gram/m² N=36
None	14	15
MTX < 1 gram/m2	7	2
MTX > 1 gram/m2		3
Radiotherapy	6	13
Metastasectomy	1	3
Caelyx	1	
Low dose doxorubicin	1	1
Iproplatin	1	
Carboplatin/etoposide		3
VEGF inhibition		4
EGFR inhibition		1
Docetaxel		1
Other systemic treatment, mainly phase I		4
Embolization/ Radiofrequency ablation		2

Supplementary table 4: Number of post ifosfamide treatment

	Intended dose 5 gram/m² N=26	Intended dose 9 gram/m² N=36
0	14	15
1	7	10
2	4	7
>2	1	4

Supplementary table 5: Toxicity (NCI CTCAE grade 3-5)

	Intended dose 5 gram/m² N=26	**Intended dose 9 gram/m² N=36**
No reported grade 3-5 toxicity	**18 (69%)**	**13 (36%)**
Febrile neutropenia	1 (4%)	7 (19%)
Neutropenia	3 (12%)	7 (19%)
Anaemia		3 (8%)
Vomiting	3 (12%)	
Nausea		5 (14%)
Syncope	1 (4%)	
Encephalopathy		3 (8%)
Hypophosphatemia		1 (3%)
Constipation		1 (3%)
Mucositis		1 (3%)
Anorexia		1 (3%)
Acute kidney injury		2 (6%)
Dehydration		1 (3%)


12

Discussion and future perspectives

This thesis discusses several retrospective studies in mesenchymal tumours. As mesenchymal tumours are rare, the use of all available data is essential for a rapid progress of scientific research without the need of large patient groups. Although retrospective studies have their limitations, these studies use the available patient data as much as possible. The results of the retrospective studies in this thesis are essential for the design of future studies and daily patient care.

Soft tissue tumours

Desmoid-type fibromatosis

The first two studies consider several aspects of desmoid-type fibromatosis, a disease with a highly variable natural behaviour varying from spontaneous regression to rapidly progressive disease with debilitating effects. Until several years ago primary treatment consisted of surgery, but now a wait and see policy or other, non-surgical, treatment options such as systemic treatment or radiotherapy are preferred first line therapies.[1] In **chapter 2**, we studied the frequencies and results of current non-surgical first-line treatment options of desmoid-type fibromatosis in the Netherlands. The frequency of non-surgical treatment has clearly increased between 1993 and 2013 (0.6% of patients in the period 1993-1998 up to 12.8% in 2009-2013). Still, surgery is the most common treatment modality for desmoid-type fibromatosis. As this disease is rare, the study included only 37 patients with active surveillance, 35 with radiotherapy and 19 with systemic therapy in first line. Of the patients with a wait and see policy, 16.2% had a partial remission or better and 56.8% stable disease as best response, suggesting that a wait and see policy is safe. Radiotherapy also showed good results with a best response of partial remission or better of 42.8% and stable disease in 45.7%. However, the results of our study should be interpreted with care because patients were, at least partially, selected for a wait and see policy after referral from another hospital to a tertiary sarcoma referral hospital and so there was already knowledge of the natural behaviour of the disease. On the other hand, it shows that there is, as earlier mentioned, a wide variety in natural behaviour as some patients also had progressive disease when a wait and see policy was applied. This study is not able to provide a suggestion on which treatment would be best for which patient. Previous studies have shown predictive factors for natural behaviour, such as age, tumour localization and *CTNNB1* mutation. In the future, studies on desmoid-type fibromatosis should preferably be randomised controlled trials to account for this variable natural behaviour and these studies should also incorporate known predictive factors.[2-7]

Chapter 3 focusses on a potential side effect of one of the treatment modalities in desmoid-type fibromatosis. Radiotherapy is an established treatment option for desmoid-type fibromatosis, but, as this tumour is frequently a chronic disease, there are concerns about its long-term toxicity especially in young adults. In a study by Keus *et al.* radiotherapy has shown a local control rate of 80% with an average dose of 56 Gy.[8]

In this study we report 6 unique cases of radiation induced sarcoma from 4 different referral hospitals and investigate whether these sarcomas occurring after radiotherapy originate from the desmoid-type fibromatosis or from the surrounding tissue. The first observation in this study is that radiotherapy induced sarcomas are very rare. Second, it was shown that sarcomas occurring after radiation of desmoid-type fibromatosis can develop as a new primary sarcoma (not harbouring a *CTNNB1* mutation) or as a malignant transformation of the desmoid-type fibromatosis (retaining the *CTNNB1* mutation). Different *CTNNB1* mutations were found in our series and so, no association between *CTNNB1* mutation and a higher risk of a radiotherapy induced sarcoma was found. However, our series only contained six cases. Thus, radiotherapy induced sarcoma in desmoid-type fibromatosis is extremely rare and may arise either de novo or from malignant transformation of desmoid-type fibromatosis cells.

Gastro-intestinal stromal cell tumour

Chapters 4 and 5 study gastro-intestinal stromal cell tumours (GIST), a rare tumour which has now a relatively favourable prognosis due to the introduction of imatinib in 2002 and thereafter sunitinib and regorafenib.[9–15] New drugs are currently studied, such as ripretinib and avapritinib (BLU-285), and are showing promising results.[16,17] The discovery of KIT and later DOG-1 as immunohistochemical markers for GIST enabled pathologists to distinguish GIST from leiomyosarcomas.[18,19] As a consequence GIST could be studied as a separate entity, thereby allowing the introduction of imatinib and improving the prognosis of these patients. Due to the introduction of imatinib the importance of correctly diagnosing GIST has further increased. In 2005, a Dutch nationwide population based study on the incidence of GIST was published studying the impact of the introduction of imatinib on the incidence of GIST, probably due to increased recognition by pathologists, showing a reported incidence of 12.7 patients per million inhabitants in the Netherlands, which was 2.1 in 1995.[20] As incidence numbers are important for both health care planning and study design, **chapter 4** studied the development of the incidence of diagnosed GIST between 2003 and 2012, again showing an increase; from 12.2 to 17.7 patients per million inhabitants per year. This is in line with other studies in amongst others the United States, Taiwan and Shanghai.[21–23] The reason for this increase cannot be derived from this study. Improvements in diagnostic procedures and increased awareness are probably at least partially the cause for this increase. A real increase in the incidence is also possible, but causal or risk factors for GIST are not known. The incidence in The Netherlands is on the higher end as compared to other reported incidences, which is probably due to the use of PALGA, the Dutch nationwide pathology registry, which fully automatically archives all Dutch pathology reports and so also registers small and incidental GISTs.[21–24]

In this study, the adherence to the ESMO guideline was also evaluated, which gives amongst others recommendations on mutational analysis and pathology review.[25] Only a minority of patients had pathology revision in a reference centre with mutation

analysis. For the high-risk patients, 67% had a mutational status and 67% had a pathology revision in a reference centre. Of all high-risk patients, revision in a reference centre and mutation analysis was performed in 92.3% of patients while only 16.7% of high-risk patients in one of the other centres had mutation analysis done. In conclusion, this second nationwide GIST incidence study in the Netherlands showed an increase in incidence during the years and a low adherence to the guidelines. The low rate of mutation analysis in the non-reference centres stresses the importance of pathology revision in a reference centre and of adherence to international guidelines.

As already mentioned, the introduction of imatinib had a great impact on the overall survival (OS) of patients with metastatic GIST. Side effects are often limited, but drug-induced agranulocytosis (neutrophil count $<0.5*10^3$/ml) is a rare, but serious adverse event. It can result in potentially life-threatening infections. Imatinib is used both in chronic myeloid leukaemia (CML) and in GIST. In CML patients treated with imatinib, grade 3-4 neutropenia (neutrophil count 0.5-1.0 and <0.5) is common, occurring in approximately 35-45% of patients treated with 400 mg/day.[26] However, this is expected as imatinib administration results in the suppression of the malignant cells by inhibition of the BCR-ABL fusion gene. However, imatinib induced myelosuppression is also seen in GIST patients with an assumed normal bone marrow function. Although the *KIT* proto-oncogene (the target of imatinib) is present in several cell types, in vitro studies show that the effect of imatinib is also independent of c-kit.[27-29] **Chapter 5** reports our experience with imatinib induced agranulocytosis. Four patients were identified in three Dutch GIST reference centres. All four patients showed rapid and full recovery after the discontinuation of imatinib. One patient could restart with a reduced dose without further events, one patient could continue with imatinib concomitantly with prednisolone, one patient had a recurrence after first rechallenge, but could continue with a reduced dose in a second rechallenge. Patient 4 was treated neo-adjuvant and had surgery after recovery of the neutropenia. Two patients were also treated with granulocyte colony stimulating factor, maybe resulting in a more rapid recovery of granulocyte count. Unfortunately, no imatinib drug levels were monitored in our study and we do not know what caused the imatinib-induced agranulocytosis in these patients. Our study suggests a possible management algorithm for imatinib induced agranulocytosis, with the suggestion of stopping imatinib until recovery. After full recovery, restart imatinib at the same dose. In case of recurrence after the rechallenge, consider restarting imatinib at a reduced dose and/or together with low dose corticosteroids (e.g. prednisolone 10 mg/day) and/or granulocyte-colony stimulating factor (G-CSF). If corticosteroids are started, the dose should be tapered slowly under strict monitoring of the hemogram. This study provides some guidance for treating imatinib-induced agranulocytosis.

Soft tissue sarcomas

Chapter 6, 7, 8 and 9 in this thesis are studies in soft tissue sarcoma. **Chapter 6 and 7** are two retrospective European Organisation for Research and Treatment of Cancer (EORTC)

database studies. **Chapter 6** describes the differences in survival between patients with locally advanced disease, patients with distant metastatic disease only or patients with both locally advanced disease and distant metastases. **Chapter 7** was a result of the development of a maintenance study with trabectedin after doxorubicin first line treatment and reports the survival after completing doxorubicin monotherapy as first line palliative treatment in soft tissue sarcomas. This study provides data on OS and progression-free survival (PFS) in patients completing at least 6 cycles of doxorubicin treatment.

As soft tissue sarcomas are rare, and the specific subtypes even rarer, stratification for prognostic factors is often difficult to apply in phase III studies. However, in **chapter 6** it is shown that an important difference in OS, PFS and overall response rate (ORR) exists between patients with only locally advanced disease versus patients with only distant metastatic disease versus patients with both locally advanced and distant metastatic disease (OS 15.4, 12.9 and 10.6 months, respectively and PFS 5.8, 4.3 and 3.2 months, respectively). The improved survival in patients with locally advanced disease only could be due to additional radiotherapy or surgery after chemotherapeutical treatment, but no data was available to test this. Prognostic factors, such as time since initial diagnosis, localization of primary tumour, histologic subtype and performance status had a different impact between the different disease stage groups. Major limitation of this study is the long time period this study stretches.

A second EORTC database study was done as prework for a study with trabectedin as maintenance therapy after first line doxorubicin treatment in patients with soft tissue sarcoma. **Chapter 7** describes the results of this study. The knowledge of data on the number of patients completing 6 cycles (the current standard maximum number of doxorubicin 75 mg/m^2 cycles) of doxorubicin without progression and data on OS and PFS after completing 6 cycles of doxorubicin is essential when designing studies of maintenance treatment after doxorubicin. As continuation for a longer time with doxorubicin is not possible due to its cardiotoxic effects, other ways to improve survival are explored. Survival of patients with metastatic soft tissue sarcoma remains poor with a median OS ranging between 13 and 18 months.[30-33] Olaratumab, a monoclonal antibody against platelet -derived growth factor alpha (PDGFRα), was thought to improve the survival of patients in a phase II study, but this could not be confirmed in the phase III study.[34,35] Another way of improving survival would be to start maintenance treatment after doxorubicin treatment. This is a well-established concept in e.g. colorectal cancer, non-small cell lung cancer and ovarian cancer.[36-38] Progression after first line treatment can result in deterioration of condition and thereby making it difficult to administer second line treatment. Maintenance treatment tries to improve the PFS, but at the cost of continuing adverse events. Our study shows that approximately 36.6% of all patients treated with first-line doxorubicin qualify for maintenance treatment, so a major patient group will not be considered for this treatment modality. The PFS of 8.7 months and the

OS of 20.1 months after randomisation is much longer than the commonly reported PFS and OS, but this is due to the selection of responding patients. However, this is an important factor to account for when designing phase II studies on maintenance treatment. One of the major limitations is, again, the long-time interval of inclusion of patients and thereby with time the addition of new treatment options as pazopanib, eribulin and trabectedin.

The data of these two database studies is essential for designing future studies. The study in **chapter 6** stresses the importance of stratifying for disease stage or including only patients with distant metastatic disease. Not accounting for the difference in disease stage and/or the different prognostic factors could cause serious imbalances and thereby causing a reduction in value of the study results. The database study of **chapter 7** reports important data for the design of maintenance studies after doxorubicin monotherapy and without these data designing phase II studies would be a wild guess.

Chapters 8 and 9 report adverse events of pazopanib treatment, a new drug in soft tissue sarcoma treatment. The phase III study with pazopanib versus placebo (PALETTE) showed a significant improvement in PFS of 4.6 months over 1.6 months with placebo.[39] OS was not improved by pazopanib in this study. One of the major adverse events causing treatment discontinuation is hepatic toxicity (grade $\geq$ 2 elevated alanine aminotransferase (ALAT) was 10% (placebo 3%) and aspartate aminotransferase (ASAT) was 8% (placebo 2%) in the PALETTE study). **Chapter 8** describes a patient with an endometrial stromal sarcoma and liver function test abnormalities**.** The mechanism for this hepatic toxicity is until now unknown. No liver biopsy was done in the patient described so the cause is also unknown in our patient. For this patient the dose of pazopanib was decreased to 200 mg every second day in several steps. Treatment was still effective with a time on treatment of 9 months. Currently the summary of product characteristics of pazopanib contains guidelines on handling liver toxicity that suggest to stop pazopanib in case of ASAT or ALAT elevations >8x upper limit of normal and restart it after near-normalisation of liver function abnormalities with a dose of 400 mg. In case of reoccurrence pazopanib should be stopped permanently. The results in our patient suggest that pazopanib can be continued safely in a lower dose under strict follow up of liver functions. Recently also a strategy with the addition of prednisolone was reported in literature to be effective.[40] The second message of this case report is the long PFS of a patient with an endometrial stromal cell sarcoma treated with pazopanib.

The second chapter **(chapter 9)** focusses on the development of a spontaneous pneumothorax as another side effect of pazopanib, that is reported for six patients treated with pazopanib for a metastatic soft tissue sarcoma. In total, we found a pneumothorax in 14% of soft tissue sarcoma patients treated with pazopanib in our centre, which was considerably higher than in the PALETTE study (3.3%).[39] Other trials with

pazopanib in other cancers did not report pneumothorax as an adverse event, which suggests that it is a specific adverse event in metastatic soft tissue sarcoma.[41-46] All cases developing a pneumothorax had pleural or subpleural metastases and showed some necrosis. The treatment of pazopanib associated pneumothorax was difficult, probably due to the fact that pazopanib inhibits VEGFR (Vascular Endothelial Growth Factor Receptor).

The reported cases in **chapter 8 and 9** are important as on one hand these report new treatment strategies for common side effects and thereby enabling continuation of pazopanib in case of toxicity, and on the other hand report new observations concerning side effects not earlier noted.

Bone tumours

The last part of this thesis focuses on two rare bone tumours, i.e. giant cell tumours of bone (GCT-B) and osteosarcoma.

Giant cell tumour of bone

GCT-B is an intermediate, locally aggressive tumour causing a lot of morbidity. Recently, denosumab, a monoclonal antibody against RANKL (receptor of nuclear factor kappa-B ligand), was introduced as a medical treatment for GCT-B. The incidence of GCT-B was not exactly known. Approximately 5% of all bone tumours are GCT-B and the incidence is estimated between 1.03-1.33 per million per year in doctor-driven cancer registries.[47-49] **Chapter 10** reports the results of a study on the incidence of GCT-B in the Netherlands based on the Dutch nationwide pathology registry, PALGA. The incidence is approximately 1.7 patients per million inhabitants in the Netherlands. The median age of patients was 35 years (range 9-77) and the tumours were most commonly localized in the femur (35%) and tibia (18%). The incidence of local recurrence was 0.40 patients per million inhabitants per year. The incidence we report is higher than previously reported in literature, probably due to the use of PALGA, which covers all Dutch pathology reports and is archiving these automatically.[48,49] Previous studies were based on doctor-driven registries. The recurrence rate was probably lower than in previous studies, which could be due to reporting bias. A recurrent tumour will be reported more frequently than an innocent primary tumour in a doctor-driven registry.

In summary, this study is the first to report incidence of GCT-B based on a 100% covering nationwide pathology database. Without these numbers it is difficult to plan health care and future research.

Osteosarcoma

The last tumour studied in this thesis is osteosarcoma. This is the most common malignant bone tumour, but is still very rare. First line treatment is well-defined,

consisting of doxorubicin and cisplatin with or without high dose methotrexate. Currently, approximately 40% of all osteosarcoma patients develop local recurrence or distant metastatic disease after first line treatment. Second-line treatment is not well-established. Chemotherapeutic regimens as ifosfamide, etoposide, ifosfamide/etoposide and gemcitabine/docetaxel are used.[50-56] Ifosfamide as second line treatment was studied in several small studies (between 6 and 19 patients per study) studying varying ifosfamide doses, ranging from 5 g/m^2 in one day to a total of 14 g/m^2 continuously over 7 days.[54-57] None of these studies reported the OS and/or PFS. **Chapter 11** reports the results of ifosfamide monotherapy as palliative treatment in osteosarcoma patients. Sixty-two patients treated with ifosfamide monotherapy were identified in the Leiden University Medical Center of which 26 were treated with an intended dose of 5 g/m^2 and 36 with an intended dose of 9 g/m^2. This study shows an improvement in OS for patients treated with 9 g/m^2 compared to 5 g/m^2 in univariate analysis (10.9 months (95%CI 9.3 – 12.6) versus 6.7 months (95%CI 5.9-7.6) resp.), but not in multi-variate analysis. PFS was not significantly different, but showed a trend towards a better PFS for the intended dose of 9 g/m^2 compared to 5 g/m^2 (3.8 months (95%CI 2.2-5.4) versus 2.1 months (95%CI 1.3-2.9) (P=0.098)). To our knowledge, this is the first study to report both OS and PFS of patients treated with second or later line ifosfamide chemotherapy for locally advanced or metastatic osteosarcoma. The placebo arm of the French REGOBONE study could be used as a surrogate arm for comparison.[58] The placebo group had an 8 weeks PFS of 0% and in the regorafenib arm 65%. In our study, ifosfamide showed an 8 week PFS of 54% (95%CI 33 – 71) for 5 gram/m^2 and 78% (95%CI 60 - 88) for 9 gram/m^2, suggesting a higher PFS for ifosfamide 9 gram/m^2 compared to regorafenib. The 4 month PFS of ifosfamide 9 gram/m^2 also compares favourably to the 4 months PFS defined in the retrospective study of the COG (44% (95%CI 28 – 60) vs. 12% (95% CI 6 – 19).[59] One of the other important results of this study is the prognostic impact of WHO performance status, *i.e.* a better performance status is associated with a better survival. Unfortunately, this study has still some major limitations. Patients in the lower dosed group were treated until 1997 and the patients with higher dosed ifosfamide were treated from 1997 onwards. In this time period new treatment options became available and diagnostics have improved, leading to earlier diagnosis of recurrence and so to a longer OS. This study is the largest until now reporting survival data for ifosfamide monotherapy as palliative treatment in osteosarcoma. The results of the study can be used as benchmark for future studies, when comparing new treatment options in phase II studies.

Future perspectives

Half of the studies in this thesis provide evidence for the improvement of future clinical trials. To improve care for patients with mesenchymal tumours it is essential to use the data already available as much as possible. Based on the results of the two incidence studies (**chapters 4 and 10**) future studies in gastro-intestinal stromal cell tumours and

giant cell tumours of bone can be developed without the risk of too low accrual due to an overestimation of the incidence. Also, health care authorities and providers have insight in the incidence of these tumours, which helps to predict health care consumption caused by these diseases.

The two EORTC database studies (**chapters 6 and 7**) provide evidence for future soft tissue sarcoma trials. It is important that future studies stratify or at least in some way account for differences in prognosis between different disease stages and for prognostic factors. These studies should also try to prospectively confirm the differences in survival found. The study proves that, although splitting sarcoma patients in different subgroups based on different disease stage or histologic subtype results in smaller subgroups, splitting in subgroups improves the validity of study results. The low incidence of these tumours remains a difficulty for further studies in soft tissue sarcoma and international cooperation is of utmost importance to include enough patients in studies. A way forward could be the implementation of registries of soft tissue sarcoma patients and thereby making the accrual of patients with specific subtypes easier. The integration of biobanking in these registrations will help to rapidly screen patients for studies.

These research infrastructures will help to improve the survival of soft tissue sarcoma patients, which is currently poor. As earlier mentioned, new studies will be necessary to study new drugs, but also other strategies should be explored, such as combining drugs, maintenance treatment with relatively low toxic drugs and the combination of treatment modalities. The data provided on survival after doxorubicin-based first line treatment helps the design of maintenance studies after first line doxorubicin-based treatment.

The study on ifosfamide as palliative treatment for osteosarcoma patients (**chapter 11**) provides evidence for the effectivity of ifosfamide monotherapy as second line palliative treatment in osteosarcoma. It sets a reference standard for the design of new phase II studies. Also, these future studies should concentrate on new drugs, new combinations of drugs and new strategies e.g. maintenance treatment. Due to the low incidence it is again of high importance that for these studies international collaboration is sought.

The results of non-surgical strategies as first-line in desmoid-type fibromatosis (**chapter 2**) show that the natural behaviour of this tumour is highly variable when a wait and see policy is applied. This stresses the importance of randomized trials in this tumour, because this will account for the variation in natural behaviour of this tumour. Second, non-surgical management of desmoid-type fibromatosis should be further developed and be compared to surgery to determine which is the best treatment for which patient.

The last studies (**chapters 3, 5, 8 and 9**), studying side effects, show that case reports and case series have great value in detecting good responding rare tumours, finding

new serious adverse event and regimens for the treatment of adverse events. Although these do not provide the highest level of evidence, these do provide hypotheses and suggestions for further research. It should be encouraged to publish case reports of interesting findings to generate new hypothesis.

In general, one of the major problems in mesenchymal tumour care is the availability of drugs and the regulatory process of these drugs. Currently registration of most drugs is based on large randomised phase III trials, including high numbers of patients. This is not possible for very rare subtypes of mesenchymal tumours. On one hand, to achieve large studies, international collaboration should be encouraged and made as easy as possible by health care authorities, but on the other hand new study designs should be developed in collaboration with health care authorities, needing lower numbers of patients, but designed in such way that health care authorities accept it as registration studies. As already mentioned, large patient registries/biobanks should be developed. These registries/biobanks allow for rapid patient identification for studies, screening for specific treatment targets and thereby allowing for faster accrual in studies.

In order to improve the medical care for these rare group of mesenchymal tumour patients and guarantee the possibility to offer studies to every patient, each patient should be treated in a network with expertise in mesenchymal tumour/sarcoma care. Each case should be discussed at essential moments in the care process in an expert team. Based on disease stage, type of treatment and patient wishes, the hospital of treatment should be chosen. If necessary, it should be centralised, but if possible, it should be as close to the patient as possible. This could imply for some very rare mesenchymal tumours, that only one expert centre exists in The Netherlands, to which all patients are referred at least at diagnosis and thereafter are treated at a subsite. Even international multidisciplinary team meetings should be considered for daily patient care. However, with all changes in the organisation of care for patients with mesenchymal tumours, at every moment the patient's preferences should be considered.

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English summary

This thesis consists of several retrospective studies in mesenchymal tumours. As mesenchymal tumours are rare, the use of all available data is essential for a rapid progress of scientific research without the need of large patient groups. Although retrospective studies have their limitations, these studies use the available patient data as much as possible. The results of the retrospective studies in this thesis will improve the design of future studies and daily patient care.

Soft tissue tumours

Desmoid-type fibromatosis

Chapter 2 studies the non-surgical treatment of desmoid-type fibromatosis, a disease with a highly variable natural behaviour. Based on pathology reports from PALGA, the Dutch nationwide pathology registry, this study shows that the incidence of non-surgical treatment has increased between 1993 to 2013 from 0.6% to 12.8%, but that surgery is still the primary treatment in most patients. The study shows a favourable outcome in patients with active surveillance or treated with radiotherapy or with systemic therapy. Because of the rarity of the non-surgical treatments and the variable natural behaviour of this disease, these results should be interpreted with care, but provide a base for further studying non-surgical treatments.

Chapter 3 focusses on a potential side effect of radiotherapy as one of the established treatment modalities in desmoid-type fibromatosis. Radiotherapy has shown an 80% control rate with an average dose of 56 Gy. This study reports six unique cases of radiation induced sarcoma from four different referral hospitals which indicates that these radiation induced sarcomas arising in desmoid–type fibromatosis are extremely rare. It was investigated whether these sarcomas occurring after radiotherapy originate from the desmoid-type fibromatosis or from the surrounding tissue. The results show that sarcomas occurring after radiation of desmoid-type fibromatosis can develop as a new primary sarcoma (not harbouring a CTNNB1 mutation, which was present in the desmoid-type fibromatosis) or as a malignant transformation of the desmoid-type fibromatosis (retaining the CTNNB1 mutation). We did not find an association between the type of CTNNB1 mutations and a higher risk of a radiotherapy induced sarcoma.

Gastro-intestinal stromal cell tumour

In **chapters 4 and 5** gastro-intestinal stromal cell tumours (GIST) are studied. GISTs are the most frequent mesenchymal tumours of the gastrointestinal tract. This rare tumour has a relatively favourable prognosis due to treatment with tyrosine kinase inhibitors, such as imatinib, sunitinib and regorafenib. The discovery of CD117 (KIT) and later DOG-1 as immunohistochemical markers for GIST enabled pathologists to distinguish GIST more easily as a separate entity and so it could also be studied as

separate entity for drug trials. The introduction of imatinib made it even more important to diagnose GIST correctly. A Dutch nationwide population based study on the incidence of GIST was published in 2005 and showed a reported incidence of 12.7 patients per million inhabitants. As incidence numbers are important for both health care planning and study design, **chapter 4** studied the development of the incidence of diagnosed GIST between 2003 and 2012, showing an increase from 12.2 to 17.7 patients per million inhabitants per year. Improvements in diagnostic procedures and increased awareness are probably at least partially the cause for this increase. A real increase in the incidence is also possible, but causal or risk factors for GIST are not known. This study also evaluates the adherence to the current ESMO (European Society for Medical Oncology) guidelines and shows that only a minority of patients had pathology revision in a reference centre and/or mutation analysis. Both increased for tumours with a higher risk of metastases. Due to the importance of a correct diagnosis of GIST for a good prognosis, it is important to adhere to these guidelines.

Chapter 5 reports our experience with imatinib-induced agranulocytosis in patients with metastatic GIST. In general imatinib has limited side effects and is well tolerated. Although neutropenia is rare, imatinib is the most effective drug in GIST and it is important to continue treatment if possible for the best overall outcome. In three Dutch GIST reference centres, four patients were identified. All four patients showed rapid and full recovery after the discontinuation of imatinib. Several treatment options for the prevention of a recurrence of this side effect are discussed such as dose reduction, cotreatment with prednisolone and granulocyte colony stimulating factor. The study suggests a possible management algorithm for imatinib induced agranulocytosis.

Soft tissue sarcomas

The next four chapters **(chapters 6, 7, 8 and 9)** discuss studies in soft tissue sarcoma. Soft tissue sarcomas are a group of rare tumours originating from connective tissue, such as muscles, adipose tissue, nerves and so on. **Chapter 6 and 7** are two retrospective European Organisation for Research and Treatment of Cancer (EORTC) database studies. **Chapter 6** describes the differences in survival between patients with locally advanced disease, patients with distant metastatic disease only and patients with both locally advanced disease and distant metastases. **Chapter 7** reports the survival after completing doxorubicin monotherapy as first line palliative treatment in soft tissue sarcomas and provides data on overall survival and progression-free survival in patients completing at least 6 cycles of doxorubicin treatment.

Because of the rarity of soft tissue sarcomas these tumours are often studied as one group, despite differences in prognosis for different histologic subtype and other prognostic factors. **Chapter 6** shows an important difference in overall survival, progression free survival and overall response rate between patients with only locally advanced disease versus patients with only distant metastatic disease versus patients

with both locally advanced and distant metastatic disease. Prognostic factors, such as time since initial diagnosis, localization of primary tumour, histologic subtype and performance status, had a different impact between the different disease stage groups. Prospective validation of these results is necessary.

To improve prognosis of patients with soft tissue sarcoma new treatment strategies are studied, such as maintenance treatment after first line doxorubicin. **Chapter 7** describes the overall survival and progression free survival of patients completing 6 cycles of doxorubicin without progression. This data is essential when designing these maintenance studies. The study shows that only approximately 36.6% of all patients treated with first-line doxorubicin qualify for maintenance treatment. The progression free survival of 8.7 months and the overall survival of 20.1 months after randomisation is much longer than the commonly reported progression free survival and overall survival, but this is due to the selection of responding patients. However, this increased survival for these patients should be accounted for in maintenance trials.

One of the new drugs in the treatment of soft tissue sarcoma is pazopanib, a tyrosine kinase inhibitor, that has shown a 3 months increase of progression free survival compared to placebo. **Chapters 8 and 9** report adverse events of pazopanib: hepatic toxicity and pneumothorax. Hepatic toxicity is one of the major adverse events causing treatment discontinuation. **Chapter 8** describes a patient with an endometrial stromal sarcoma and liver function test abnormalities**.** In this patient the dose was reduced in several steps to 200 mg every second day (usual dose 800 mg/day). In this dose, treatment was still effective with a time on treatment of 9 months. This report suggests that dose reduction lower than the recommended minimal dose of 400 mg per day can be safe and effective in patients with hepatic toxicity. This study also reports a remarkable long progression free survival in a patient with endometrial stromal cell sarcoma treated with pazopanib.

Pneumothorax as side effect of pazopanib is studied in **chapter 9.** It reports the development of a spontaneous pneumothorax in six patients treated with pazopanib for a soft tissue sarcoma. The incidence of spontaneous pneumothorax as side effect in patients treated for soft tissue sarcoma was estimated to be 14% in our centre. Literature suggests this side effect to be sarcoma specific as it is not reported in other cancers. In all patients reported in this study pleural or subpleural metastases were present and some of these showed necrosis, which could be the cause of the occurrence of the pneumothorax. The treatment of the pneumothorax was difficult, probably because pazopanib inhibits VEGFR 1, 2 and 3 (Vascular Endothelial Growth Factor Receptor).

The results of **chapter 8 and 9** are important as these chapters report new side effects or new treatments for side effects of a relatively new drug.

Bone tumours

The last part of the thesis focuses on two rare bone tumours: giant cell tumours of bone (GCT-B) and osteosarcoma.

Giant cell tumour of bone

GCT-B is an intermediate, locally aggressive tumour causing a lot of morbidity. Denosumab, a monoclonal antibody against RANKL (receptor of nuclear factor kappa-B ligand), was recently introduced as treatment for GCT-B. Until now, the incidence of GCT-B is not exactly known. **Chapter 10** reports the results of a study on the incidence of GCT-B in the Netherlands based on the Dutch nationwide pathology registry, PALGA. The incidence is approximately 1.7 patients per million inhabitants in the Netherlands. The median age of patients was 35 years (range 9-77) and the tumours were most commonly localized in the femur (35%) and tibia (18%). The incidence of local recurrence was 0.40 patients per million inhabitants per year. The incidence we report is higher than previously reported in literature, probably due to the use of PALGA, which covers all Dutch pathology reports and is archiving these automatically. The data of this study help to plan care for these patients and to plan future research.

Osteosarcoma

Although osteosarcoma is the most common malignant bone tumour, it is still very rare. First line treatment with doxorubicin and cisplatin with or without methotrexate is well defined, but second line treatment is not well-established. Several regimens are used. In the Leiden University Medical Center ifosfamide is currently used as a second line treatment, but literature lacks data on overall and progression free survival. **Chapter 11** reports the results of ifosfamide monotherapy in the Leiden University Medical Center. Sixty-two patients treated with ifosfamide monotherapy were identified in the Leiden University Medical Center treated with an intended dose of 5 g/m^2 or 9 g/m^2. This study shows an improvement in overall survival for patients treated with 9 g/m^2 compared to 5 g/m^2 in univariate analysis (10.9 versus 6.7 months resp.), but not in multi-variate analysis. Progression free survival was not significantly different, but showed a trend towards a better PFS for the intended dose of 9 g/m^2 compared to 5 g/m^2 (3.8 vs 2.1 months resp.). One of the other important results of this study is the prognostic impact of WHO performance status, i.e. a better performance status is associated with a better survival. This study can be used as benchmark for future studies, when comparing new treatment options in phase II studies.

Discussion and future perspectives

Chapter 12 summarizes the evidence generated in the retrospective studies reported in this thesis and discusses the results of the separate studies against the background of the other studies of this thesis and the current literature. It also describes future perspectives for sarcoma research and daily patient care.

Nederlandse samenvatting

Dit proefschrift omvat verschillende studies in mesenchymale tumoren. Omdat mesenchymale tumoren zeldzaam zijn, is het essentieel om alle beschikbare data te gebruiken voor een snelle vooruitgang in het wetenschappelijk onderzoek zonder dat grote patiëntengroepen noodzakelijk zijn. De resultaten van deze retrospectieve studies dragen bij aan het verbeteren van het ontwerp van toekomstige studies en aan verbeteringen in de dagelijkse patiëntenzorg.

Weke delen tumoren

Desmoïd-type fibromatose

Hoofdstuk 2 bestudeert de niet-chirurgische behandeling van desmoïd-type fibromatose, een ziekte met een sterk variabel natuurlijk beloop. Met behulp van pathologie verslagen uit PALGA, de Nederlandse landelijke pathologie registratie database, toont deze studie aan dat het gebruik van niet-chirurgische behandeling toegenomen is van 0,6% van de patiënten in 1993 naar 12,8% in 2013. Chirurgie blijft tot op heden de primaire behandeling in de meeste patiënten. De studie laat verder zien dat patiënten die actief vervolgd worden zonder dat ze een behandeling ondergaan, of na behandeling met radiotherapie of systemische behandelingen, een goede prognose hebben. Ondanks dat de resultaten met enig voorbehoud geïnterpreteerd moeten worden, vanwege de zeldzaamheid van niet-chirurgische behandelingen en door het variabele natuurlijke gedrag van deze ziekte, geven de resultaten een basis om verder onderzoek te doen naar niet-chirurgische strategieën.

Hoofdstuk 3 richt zich op een potentiële bijwerking van radiotherapie als één van de behandelingsmogelijkheden voor desmoïd-type fibromatose. Bestraling heeft een kans op ziektecontrole van ongeveer 80% bij een gemiddelde stralingsdosis van 56 Gy. Het onderzoek beschrijft zes unieke casus van stralingsgeïnduceerde sarcomen uit vier verschillende tertiaire verwijzingsziekenhuizen voor sarcomen. Dit geeft aan dat deze stralingsgeïnduceerde tumoren uiterst zeldzaam zijn. De studie onderzoekt of deze stralingsgeïnduceerde sarcomen zijn ontstaan als nieuwe primaire tumoren of dat deze sarcomen zijn ontstaan uit de bestraalde desmoïd-type fibromatosen. Het blijkt dat sarcomen die ontstaan na bestraling van desmoïd-type fibromatose zowel kunnen ontstaan als nieuwe primaire tumoren (sarcomen die geen CTNNB1 mutatie bevatten, welke wel aanwezig is in de desmoïd-type fibromatose) of als maligne transformatie vanuit de desmoïd-type fibromatose (met behoud van de CTNNB1 mutatie). Een associatie tussen de specifieke CTNNB1 mutatie in de desmoïd-type fibromatose en een hoger risico van een stralingsgeïnduceerd sarcoom wordt niet gevonden.

Gastro-intestinale stromaceltumor

In **hoofdstuk 4 en 5** worden gastro-intestinale stromaceltumoren (GIST) bestudeerd, de meest frequent voorkomende mesenchymale tumor in het maagdarmkanaal. Deze zeldzame tumor heeft een relatief goede prognose door de behandeling met tyrosine kinase remmers, te weten imatinib, sunitinib en regorafenib. De ontdekking van KIT en vervolgens DOG-1 als immunohistochemische markers voor GIST maakte het voor pathologen makkelijker om GIST als aparte entiteit te onderscheiden van andere sarcomen en zodoende kan het nu als aparte entiteit bestudeerd worden in geneesmiddelonderzoek. De introductie van imatinib maakte het nog belangrijker om de diagnose GIST correct te stellen, vanwege de sterk verbeterde prognose door imatinib. In 2005 werd een studie gepubliceerd naar het voorkomen, de incidentie, van GIST die gebaseerd was op de gehele Nederlandse bevolking. De studie rapporteerde een incidentie van 12,7 patiënten per miljoen inwoners per jaar. Omdat deze incidentiecijfers van belang zijn voor zowel gezondheidszorgplanning als ontwerp van toekomstige studies, wordt in **hoofdstuk 4** de verdere ontwikkeling van de gerapporteerde incidentie van GIST tussen 2003 en 2012 bestudeerd. De incidentie is in deze periode toegenomen van 12,2 naar 17,7 patiënten per miljoen inwoners per jaar. Waarschijnlijk is dit het gevolg van verbeteringen in diagnostische procedures en een toegenomen bewustzijn en daardoor betere herkenning van de ziekte. Alhoewel een daadwerkelijke toename in de incidentie ook een rol zou kunnen spelen, zijn hiervoor tot op heden geen oorzaken aan te wijzen. In dit onderzoek wordt tevens het gebruik van de huidige ESMO (European Society for Medical Oncology) richtlijn in de Nederlandse praktijk geëvalueerd, waarbij blijkt dat slechts voor een minderheid van de patiënten een revisie van de pathologie in een referentiecentrum verricht wordt en hetzelfde geldt voor het bepalen van de in GIST aanwezige mutatie. Dit wordt wel vaker gedaan indien sprake is van een GIST met een hoog risico op metastasen (uitzaaiingen). Gezien het belang van een correcte diagnose voor een goede prognose is het belangrijk om deze richtlijn te hanteren.

Hoofdstuk 5 beschrijft onze ervaring met imatinib geïnduceerde agranulocytose in patiënten met gemetastaseerd GIST. Over het algemeen heeft imatinib slechts milde bijwerkingen en wordt het goed verdragen. Neutropenie is een zeldzame bijwerking van imatinib. Het is echter voor de prognose van GIST patiënten van belang om imatinib, indien mogelijk, veilig te continueren, omdat dit het meest effectieve geneesmiddel is. In drie Nederlandse GIST verwijscentra werden vier patiënten gevonden met een door imatinib geïnduceerde neutropenie. Deze vier patiënten lieten een volledig herstel zien na het staken van de imatinib. In de studie worden een aantal mogelijke behandelopties besproken ter preventie van een recidief van de neutropenie, zoals dosisreductie, gelijktijdige behandeling met prednison en/of granulocyt kolonie stimulerende factoren. We introduceren een mogelijk behandelingsschema voor patiënten met een imatinib geïnduceerde agranulocytose.

Wekedelen sarcomen

De **hoofdstukken 6, 7, 8 en 9** presenteren de uitkomsten van studies in wekedelen sarcomen. Wekedelen sarcomen zijn tumoren uitgaande van het steun en bindweefsel, zoals spieren, vetweefsel en zenuwen. **Hoofdstukken 6 en 7** beschrijven de resultaten van twee retrospectieve studies op basis van gegevens uit de database van de EORTC (European Organisation for Research and Treatment of Cancer). **Hoofdstuk 6** rapporteert de verschillen in overleving tussen patiënten met lokaal gevorderde ziekte, patiënten met op afstand gemetastaseerde ziekte en patiënten die zowel lokale ziekte als afstandsmetastasen hebben. **Hoofdstuk 7** beschrijft vervolgens de overleving van patiënten na behandeling met doxorubicine monotherapie als eerstelijns behandeling voor patiënten met wekedelen sarcoom en geeft resultaten van de algehele overleving en progressievrije overleving in patiënten die tenminste 6 kuren doxorubicine volmaken.

Door de zeldzaamheid van wekedelen sarcomen worden ze vaak als één grote groep bestudeerd, ondanks verschillen in prognose op basis van histologisch subtype en andere prognostische factoren. **Hoofdstuk 6** laat belangrijke verschillen in algehele overleving, progressievrije overleving en response percentages zien tussen patiënten met lokaal gevorderde ziekte, patiënten met enkel afstandsmetastasen en patiënten met zowel lokale ziekte als afstandsmetastasen. Prognostische factoren, zoals tijd sinds primaire diagnose, lokalisatie van de primaire tumor, histologisch subtype en conditie (WHO performance status) hebben een verschillend effect in deze drie subgroepen. Deze resultaten moeten gevalideerd worden in een prospectieve studie.

Ten einde de prognose van patiënten met wekedelen sarcomen te verbeteren worden nieuwe behandelstrategieën bestudeerd, zoals onderhoudsbehandeling na eerstelijns behandeling met doxorubicine. **Hoofdstuk 7** beschrijft de algehele overleving en progressievrije overleving voor patiënten na behandeling met 6 kuren doxorubicine zonder progressie onder behandeling. Deze resultaten zijn nodig voor het ontwerp van studies naar onderhoudsbehandelingen. De studie laat zien dat slechts ongeveer 36,6% van alle patiënten die behandeld zijn met eerstelijns doxorubicine therapie in aanmerking komen voor een onderhoudsbehandeling. De progressievrije overleving van 8,7 maanden en de algehele overleving van 20,1 maanden na randomisatie zijn beduidend langer dan de overlevingscijfers die over het algemeen gerapporteerd worden, maar dit is het gevolg van de selectie op patiënten die goed reageerden op de therapie. Met deze verlenging van de algehele overleving en progressievrije overleving moet rekening gehouden worden bij het ontwerp van studies naar onderhoudsbehandelingen.

Eén van de nieuwe geneesmiddelen in de behandeling van wekedelen sarcoom is pazopanib, een tyrosine kinase remmer, met een aangetoonde verbetering van de progressievrije overleving van 3 maanden vergeleken met placebo. De **hoofdstukken**

8 en 9 rapporteren bijwerkingen van pazopanib, te weten leverchemieafwijkingen en pneumothorax (een klaplong). Levertoxiciteit is één van de belangrijkste bijwerkingen die leiden tot het staken van behandeling. **Hoofdstuk 8** beschrijft een patiënt met een sarcoom van de baarmoeder (endometriaal stromacel sarcoom) en leverfunctietest afwijkingen. In deze patiënt werd de dosis pazopanib geleidelijk aan afgebouwd naar 200mg elke tweede dag (standaarddosis 800 mg/dag). Deze dosis liet nog steeds effectiviteit zien met een behandelingsduur van in totaal 9 maanden. Dit hoofdstuk suggereert dat een verdere dosisreductie, lager dan de geadviseerde minimumdosis van 400 mg, veilig en effectief kan zijn in patiënten met levertoxiciteit. Daarnaast rapporteert deze studie een opmerkelijk lange progressievrije overleving van een patiënt met een endometriaal stromacel sarcoom, die behandeld werd met pazopanib.

Hoofdstuk 9 bestudeert de pneumothorax als bijwerking van behandeling met pazopanib. Het beschrijft het ontstaan van een spontane pneumothorax in zes patiënten, die behandeld werden met pazopanib voor een wekedelen sarcoom. Op basis van dit onderzoek wordt ingeschat dat deze bijwerking voorkomt bij ongeveer 14% van de patiënten in ons centrum. De literatuur suggereert dat dit een sarcoom specifieke bijwerkingen is, aangezien het niet in andere tumortypen beschreven is. In alle beschreven patiënten waren pleurale of subpleurale metastasen aanwezig en sommigen hiervan toonden necrose. Necrose in deze pleurale of subpleurale metastasen kan een verklaring zijn voor het ontwikkelen van de pneumothorax. De behandeling van de pneumothorax was vaak gecompliceerd, waarschijnlijk doordat pazopanib VEGFR 1, 2 en 3 (Vasculair Endotheliaal GroeiFactor Receptor) remt.

De uitkomsten van de **hoofdstukken 8 en 9** zijn belangrijk, omdat deze hoofdstukken nieuwe bijwerkingen beschrijven of nieuwe behandelingen voor bekende bijwerkingen geven.

Bottumoren

Het laatste deel richt zich op twee zeldzame bottumoren: reusceltumor van het bot en osteosarcoom.

Reusceltumoren van het bot

De reusceltumor van het bot is een lokaal agressieve tumor, die zorgt voor veel morbiditeit, ziektelast. Denosumab, een monoklonaal antilichaam tegen RANKL (receptor voor nucleair factor Kappa-B ligand), is recent geïntroduceerd als behandeling voor deze ziekte. Tot op heden is de incidentie van deze reusceltumoren van het bot niet exact bekend. **Hoofdstuk 10** beschrijft de resultaten van een studie naar de incidentie van reusceltumoren van het bot in Nederland, gebaseerd op data uit de Nederlandse landelijke pathologie database, PALGA. De incidentie wordt geschat op 1,7 patiënten per miljoen inwoners. De mediane leeftijd van patiënten was 35 jaar, spreiding 9-77 jaar, en de tumoren waren het vaakst gelokaliseerd in het femur (35%) en de tibia (18%). De

incidentie van een lokaal recidief was 0,40 per miljoen patiënten per jaar. De incidentie die wij rapporteren is hoger dan de eerder gerapporteerde incidentie in de literatuur, waarschijnlijk door het gebruik van PALGA, dat alle pathologie verslagen in Nederland bevat. De resultaten van deze studie helpen bij het plannen van toekomstig onderzoek en bij het plannen van dagelijkse patiëntenzorg voor deze patiëntengroep.

Osteosarcoom

Alhoewel het osteosarcoom de meest voorkomende kwaadaardige bottumor is, is het nog steeds erg zeldzaam. De primaire behandeling met chemotherapie met doxorubicine en cisplatina met of zonder methotrexaat is duidelijk vastgesteld, maar vervolgbehandelingen zijn dat niet. Verschillende combinaties worden voor deze situatie gebruikt in de wereld. In het Leids Universitair Medisch Centrum wordt ifosfamide momenteel als optie gebruikt in de tweedelijns behandeling van osteosarcomen, maar in de literatuur ontbreken gegevens over de algehele en progressievrije overleving van deze patiënten. **Hoofdstuk 11** beschrijft de resultaten met ifosfamide monotherapie in het Leids Universitair Medisch Centrum. Tweeënzestig patiënten werden geïdentificeerd, die behandeld zijn met een geplande dosis van 5 gram/m^2 of 9 gram/m^2. De studie toont een toename in algehele overleving voor patiënten behandeld met 9 gram/m^2 in vergelijking tot 5 gram/m^2 in univariate analyse (10,9 versus 6,7 maanden respectievelijk), maar niet in multivariate analyse. De progressievrije overleving is niet significant verschillend, maar laat een trend naar een betere overleving zien in patiënten behandeld met 9 gram/m^2 vergeleken met 5 gram/m^2 (3,8 versus 2,1 maanden resp.). Eén van de belangrijkste uitkomsten van deze studie is het prognostisch belang van WHO performance status, een betere conditie is geassocieerd met een betere overleving. De resultaten uit deze studie kunnen gebruikt worden als benchmark voor toekomstige studies, die nieuwe behandeling onderzoeken in fase II studies.

Discussie en toekomstperspectief

Hoofdstuk 12 vat de uitkomsten van de diverse studies in dit proefschrift samen en zet deze in het perspectief van de overige studies in dit proefschrift en die van de literatuur. Het beschrijft ook het toekomstperspectief van het onderzoek naar sarcomen en van de dagelijkse patiëntenzorg.

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Curriculum vitae

Arjan Verschoor werd geboren op 7 mei 1984 te De Lier. In 2002 behaalde hij cum laude zijn VWO-diploma aan CSG De Lage Waard te Papendrecht. In 2002 startte hij zijn studie Geneeskunde aan de Universiteit Leiden, waarbij hij in 2003 cum laude zijn propedeutisch examen en in 2007 cum laude zijn doctoraalexamen behaalde. In 2008 behaalde hij het artsexamen en begon hij als arts-assistent niet in opleiding bij de Interne Geneeskunde in het Groene Hart Ziekenhuis te Gouda, alwaar hij in januari 2010 startte met de opleiding tot internist (opleider dr. J.T.M. van der Heijden). In januari 2013 werd de opleiding voortgezet in het Leids Universitair Medisch Centrum (opleiders prof. dr. J.T. van Dissel, prof. dr. J.W. de Fijter). Gedurende 2014 onderbrak hij zijn opleiding voor een jaar en werd gestart met het onderzoek resulterende in dit proefschrift onder leiding van prof. dr. A.J. Gelderblom en prof. dr. J.V.M.G. Bovée. Vanaf januari 2015 werd de opleiding tot internist vervolgd binnen de differentiatie medische oncologie (opleider prof. dr. A.J. Gelderblom). In december 2016 volgde de registratie tot internist-oncoloog. Van januari 2017 tot en met september 2019 was hij werkzaam als staflid bij de afdeling medische oncologie van het Leids Universitair Medisch Centrum met als aandachtsgebieden sarcomen en tumoren van de hoge tractus digestivus. Sinds oktober 2019 is hij als internist-oncoloog verbonden aan het Reinier de Graaf Gasthuis, Delft, met als aandachtsgebied de gastro-intestinale oncologie.

Arjan is getrouwd met Marleen Verschoor - den Hooglander en heeft 1 dochter (Anne) en 2 zonen (Job en Stijn).

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