Treatment Advances in Locally Advanced and Metastatic Non-Small Cell Lung Cancer

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Vooruitgang in de behandeling van lokaal gevorderd en gemetastaseerd niet-kleincellig longcarcinoom

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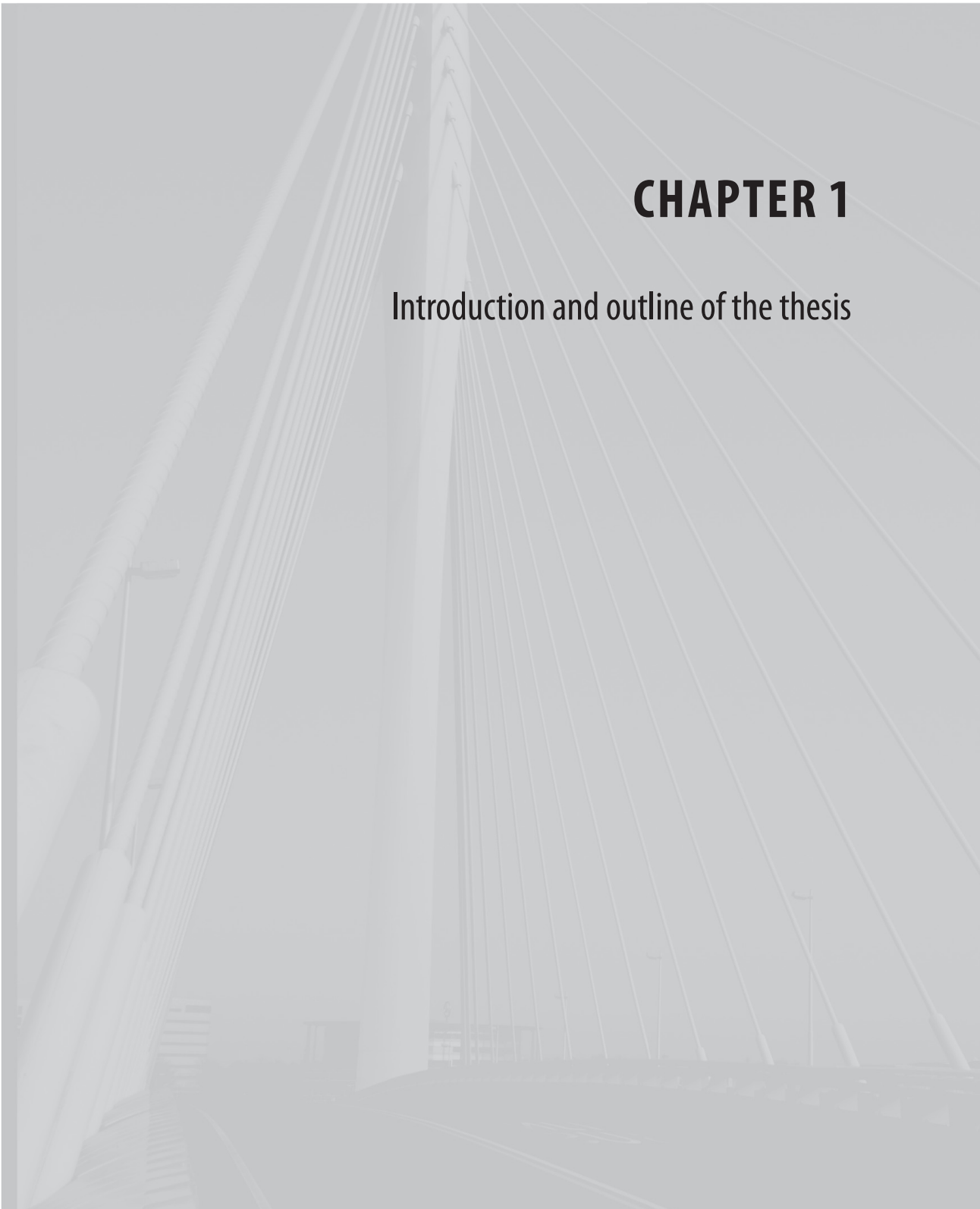
If you wish success in life,
make perseverance your bosom friend,
experience your wise counselor,
caution your elder brother and hope your guardian genius
Joseph Addison

Voor mijn ouders

CONTENT



CHAPTER 1

Introduction and outline of the thesis

Lung cancer is the leading cause of cancer mortality in the United States and Europe (1). Approximately 85% of the patients with lung cancer have non–small cell lung cancer (NSCLC), which can be classified into squamous, adeno, large cell and not otherwise specified (NOS) histologies. The most common histologies are: adenocarcinoma (~ 50%), squamous cell (~ 20%), and large cell (~ 10%) (2). More than two third of the patients have locally advanced or metastatic disease at the time of diagnosis (3,4).

LOCALLY ADVANCED NSCLC

Approximately one third of patients with non-small cell lung cancer are diagnosed with locally advanced (stage III) disease. Stage III includes a fairly heterogeneous group of tumours, including resectable and unresectable tumours, ranging from T3N1 to T4 N3 cancers. In stage IIIA, 5 subgroups are defined. (Table 1) A first subgroup of stage IIIA patients consists of tumours with locoregional extension without mediastinal lymph node involvement (IIIA-0). Due to the novel definitions for T3 and T4 and the inclusion of T4N0-1 tumours in stage IIIA in the 7th edition of the new TNM classification (Table 2 and 3), it is likely that this subgroup will numerically increase in the near future.
A second subgroup contains patients with so-called unexpected N2-involvement in the pathology specimen (pIIIA-1) or at thoracotomy (pIIIA2), found in 14-24% of the patients. The largest subgroup of stage IIIA consists of patients with clinical ipsilateral lymph node invasion at presentation, either demonstrated by non-invasive imaging or (minimally) invasive techniques (IIIA-3) or 'bulky' at imaging (IIIA-4). Patients from the IIIA-3 subgroup are variously considered 'resectable' or 'marginally resectable', depending on the number and location of the lymph node(s) involved, whereas patients from the IIIA-4 subcategory are considered 'primary unresectable'.

Table 1 Subclassification of stage IIIA (5)

Subgroup	Definition	Frequency
IIIA-0	T3N1 or T4N0-1 without N2 involvement	6% of NSCLC at presentation, 32% of stage IIIA
IIIA-1	Incidental nodal metastases found on final pathology examination of the resection specimen	Up to 14% of thoracotomies
IIIA-2	Nodal (single station) metastases recognized intraoperatively	
IIIA-3	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)	10% of NSCLC at presentation, 67% of clinical and pathological stage IIIA
IIIA-4	Bulky or fixed multistation N2 disease	

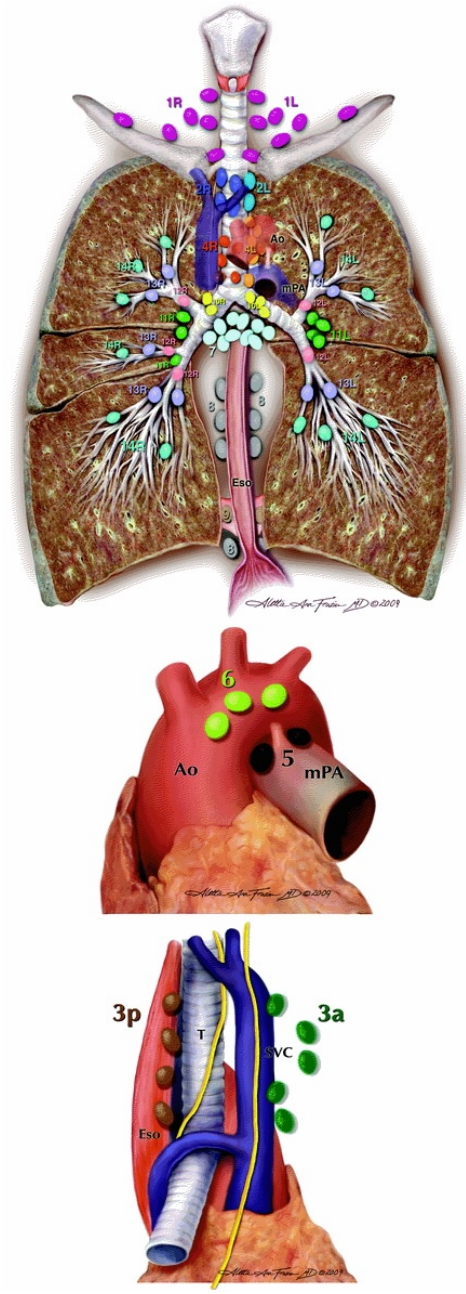
Table 2. Definitions for T, N, and M descriptors according to the seventh edition of the TNM classification.

T (Primary Tumour)	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumour ≤2 cm in greatest dimension
T1b	Tumour > 2 cm but ≤3 cm in greatest dimension
T2	Tumour > 3 cm but ≤7 cm or tumour with any of the following features Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour > 3 cm but ≤5 cm in greatest dimension
T2b	Tumour > 5 cm but ≤7 cm in greatest dimension
T3	Tumour > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus (< 2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumour nodule(s) in a different ipsilateral lobe
N (Regional Lymph Nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (Distant Metastasis)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion[b]
M1b	Distant metastasis

[a] The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

[b] Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3 or T4.

From Goldstraw et al.



Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

AORTIC NODES

AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
7 Subcarinal

Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

Figure 1: The IASLC lymph node map shown with the proposed amalgamation of lymph node levels into "zones**".**

Table 3 Stage Grouping

6th edition T/M	7th edition T/M	N0	N1	N2	N3
T1 (≤ 2cm)	T1a	IA	IIA	IIIA	IIIB
T1 (> 2-≤ 3cm)	T1b	IA	IIA	IIIA	IIIB
T2 (> 3-≤ 5cm)	T2a	IB	IIB→**IIA**	IIIA	IIIB
T2 (> 5-7cm)	T2b	IB→**IIA**	IIB	IIIA	IIIB
T2 (≥ 7cm)	T3	IB→**IIB**	IIB→**IIIA**	IIIA	IIIB
T3 (invasion)	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIIB→**IIB**	IIIB→**IIIA**	IIIB→**IIIA**	IIIB
T4 (extension)	T4	IIIB→**IIIA**	IIIB→**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)	T4	IV→**IIIA**	IV→**IIIA**	IV→**IIIB**	IV→**IIIB**
T4 (pleural effusion)	M1a	IIIB→**IV**	IIIB→**IV**	IIIB→**IV**	IIIB→**IV**
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Stage III patients are quite a heterogeneous group of patients with diffferent prognostic and therapeutic subsets.

Resectable stage pIIIA with incidental N2 disease should be treated with adjuvant platinum-based chemotherapy (6), whereas stage IIIB with pathologically confirmed involvement of the pleura (T4, pleural effusion) is synonymous with advanced disease and is preferably treated with palliative chemotherapy. For the remainder of the patients, who have potentially curable disease, treatment goals include local tumour control and eradication of distant micrometastases, while minimizing adverse events. For both stage IIIA and IIIB disease, combined modality therapy including chemotherapy, radiation and/or surgery is the treatment of choice. The evolving approaches for resectable and unresectable stage III NSCLC are described below.

Unresectable stage III non-small cell lung cancer

Stage III unresectable patients, candidate to radical treatment, include T4 without pleural effusions and/or bulky N2 or N3 tumours, although selected T4 patients may benefit from surgery.

Radiotherapy alone was initially considered the standard of care for these patients, but the disappointing 5-year survival of no more than 5%, mostly due to distant metastatic relapse, raised the need for systemic disease control. This observation led to further evaluations aimed at investigating the role of chemotherapy regimens in patients with unresectable disease, in order to eradicate the micrometastatic disease and improve patients outcome.

The first combination studies explored a *sequential approach*, with *chemotherapy followed by radiotherapy*. The role of induction chemotherapy has been investigated in

Tabel 4. Outcomes of sequential and concurrent chemoradiotherapy compared with radiotherapy alone.

Study	Randomized patients	Treatment	Median survival (mos)	5-year survival rate (%)	P value	Reference
CALGB 8433	155	Radiotherapy	10	6	0.01	Dillman, 1996 (7)
		Sequential Chemoradiotherapy	14	17		
Intergroup	458	Radiotherapy	11.4-12	5-6	0.04	Sause, 2000 (8)
		Sequential Chemoradiotherapy	13.2	8		
French	353	Radiotherapy	10	3	0.02	Le Chevalier, 1994 (9)
		Sequential Chemoradiotherapy	12	6		

three randomized trials including more than 900 patients with NSCLC which randomly assigned patients with unresectable locally advanced disease to radiotherapy alone or versus sequential chemo-radiotherapy (7-9, Table 4). All trials included platinum-based regimens and demonstrated a significant survival advantage favouring the addition of chemotherapy to radiation treatment, with median survival up to almost 14 months, mostly due to lower distant failure rates rather than improved local disease control. The meta-analysis performed in 1995 by the NSCLC Collaborative Group showed an advantage in survival favouring the addition of chemotherapy prior to radical radiation with a hazard ratio of 0.9 and a 5-year survival advantage of 5% (10).

A few years later different studies claimed *concurrent chemo-radiation* to be superior to sequential therapy with higher response rates and improved survival (11-17). The concomitant approach is compared to the sequential approach in several randomized trials. (14-17, Table 5). The first of these studies was performed by the West Japan Lung

Table 5 Outcomes of sequential vs. concurrent chemoradiotherapy.

Study	Randomized patients	Chemoradiotherapy treatment	Median survival (mos)	Survival rate (%)	P value	Reference
West Japan Lung Cancer Group	320	Concurrent	17	16 (5-yr)	0.039	Furuse,1999 (14)
		Sequential	13	9 (5-yr)		
RTOG 9410	610	Concurrent	17	21 (4-yr)	0.046	Curran,2003 (16)
		Sequential	14.6	12 (4-yr)		
Fournel NPC 95-01	200	Concurrent	16.3	21 (4-yr)	0.24	Fournel, 2005 (15)
		Sequential	14.5	14 (4 yr)		
Czech, phase II	102	Concurrent	16.6	18.6 (3y)	0.023	Zatloukal,2004 (17)
		Sequential	12.9	9.5 (3y)		

Table 6 Grade 3 or greater acute toxicities comparing sequential chemoradiotherapy with concurrent chemoradiotherapy in RTOG 9410 (Curran et al, 2003).

Toxicity (grade)	Sequential chemoradiotherapy (%)	Concurrent chemoradiotherapy (%)
Esophagitis (3-4)	4	25-47
Pneumonitis (3-5)	7	3-4
Neutropenia (4-5)	56	48-58
Thrombocytopenia (4-5)	2	4-8
Any Grade 5	3	2-3

Cancer Group and showed that patients treated with cisplatin/vindesine/mitomycine concurrently with radiotherapy gained prolonged survival compared with those who received sequential treatment (17 versus 13 months, $p< 0.04$) (14). Similar results have emerged from the 3-arm phase 3 RTOG 9410 trial, in which concurrent chemoradiation was compared with sequential chemoradiation. This study showed an improved overall survival for the concurrent standard radiotherapy arm compared with the sequential approach (17 versus 14.6 months, $p=0.046$), without benefit for patients who received hyperfractionated radiation with chemotherapy (16). A Czech phase II trial, with cisplatin and vinorelbine concurrent with radiotherapy, showed improved survival compared with the sequential arm (17). Overall available data indicate that concurrent chemoradiation is superior in terms of survival compared to the sequential approach, although higher toxicity, especially esophageal toxicity, limits the use to fit patients (Table 6).

In a meta-analysis and in the National Institute of Health and Clinical Excellence (NICE) guidelines, the use of concurrent chemo-radiotherapy is recommended only in selected patients, which means: patients with low co-morbidity, good performance status and pulmonary function and patients who are adequately staged (11,18). As a result the sequential approach is still widely used in Europe and a doublet of platinum combined with a third-generation chemotherapeutic agent is considered to be the most active induction regimen.

In the combined modality approach, the definitive dose thoracic radiotherapy should be no less than the biologic equivalent of 60 Gy, in 1.8-Gy to 2.0-Gy fractions to the planning target volume (PTV). Ideally, this requires 3-dimensional (3D) conformal radiotherapy, a technique characterized by beam outlines that match the shape of the PTV. Mapping of the PTV is improved when using information from FDG-PET/CT-scan and-whenever available- from the (minimally) invasive mediastinal staging techniques, to match the closest possible the actual 'involved field' (IF).

A major drawback in the treatment of locally advanced NSCLC is the high, 70% relapse rate, which occurs approximately one third locally, one third distantly and one third both locally and distantly (8-14). The challenge today is to reduce this high relapse rate by identifying the optimal radiation dose in combination with the most effective systemic

therapy. So far, neither the best drug combination nor the optimum radiation dose has been defined. Therefore, new chemo-radiotherapy combinations are needed and further research is warranted.

Potentially resectable stage III NSCLC

As mentioned before, this remains the most controversial area: some recommend chemotherapy with concurrent radiotherapy, others induction chemotherapy followed by surgery in downstaged patients (mediastinal clearance, pN0 after induction treatment) as the treatment of choice.
The potential role of a surgical resection following induction chemotherapy (with or without radiation) in stage IIIA and IIIB NSCLC remains controversial.

Preoperative chemotherapy and preoperative chemoradiotherapy.

Several small phase 2 studies have been published on the outcome of patients with stage IIIA NSCLC treated with neoadjuvant chemotherapy (19). A systematic review from six prospective phase II trials reported tumour response to preoperative (primary) chemotherapy in patients with stage IIIA or IIIB NSCLC (20). The review reported a non-weighted average effect size for radiological response rate of 64%, a disease progression of 4% and for histological complete response of 24% of patients. Survival was improved as compared with historical controls and was influenced by patients age, complete resection, pathologic stage, nodal downstaging and extent of resection, but not by the type of induction regimen, i.e. chemo-or chemoradiotherapy (21-23). Three randomized trials have compared chemotherapy and chemoradiotherapy as induction regimen in stage III NSCLC (24-26). These trials suggest that induction chemoradiotherapy results in better rates of resectability, pathological downstaging and pathological complete remissions than chemotherapy alone, but without significant benefit for overall or progression-free survival. This issue is currently being addressed by the Swiss Group for Clincal Cancer Research, conducting a phase III randomized trial of preoperative cisplatin and docetaxel chemotherapy versus chemoradiotherapy with the same agents followed by surgical resection (27).
Twelve randomized trials have compared neoadjuvant chemotherapy followed by surgery vs surgery alone in patients with stage IIIA NSCLC with variable numbers of N2-involvement (20,28,29). It can be concluded from the meta-analysis (29) that a significant benefit in favour of neoadjuvant chemotherapy is present ranging at 5 years from 6-14%,

Table 7. OS at 5 years comparing surgery with radiotherapy after induction therapy.

Study	Randomized patients	Surgical resection	Radiotherapy	P value	Reference
EORTC 08941	332	15.7%	14%	0.60	van Meerbeeck, 2007 (30)
Intergroup 0139	396	27%	20%	0.10	Albain, 2009 (31)

albeit weakened by confounding factors as the inhomogeneity of the patients included, the inadequate sample size and the variable addition of postoperative treatments.

Surgical resection following neoadjuvant therapy versus radiotherapy following neoadjuvant therapy.

The role of surgical resection, in comparison to RT, following induction therapy in patients with stage IIIA disease is unclear. Two large randomized phase III trials have not found a survival benefit for surgery in comparison to RT following chemotherapy or for surgery following concurrent chemoradiotherapy (Table 7).

The European Organization for Research and Treatment of Cancer (EORTC) study 08941 examined the issue of radiotherapy versus surgical resection following induction chemotherapy in patients with clinical stage IIIA-N2 NSCLC (30). In this study, 579 patients received induction chemotherapy with three cycles of platinum-based chemotherapy. Following chemotherapy, 332 patients with at least stable disease were randomized to receive definitive RT 60-62.5 Gy to the primary tumour and involved mediastinum, with 40-46 Gy to the uninvolved mediastinum versus surgical resection. Surgical resection did not improve overall survival or progression free survival compared with RT. In a posthoc unplanned univariate subgroup analysis of the surgical arm, 5 year survival was longer if radical resection was performed, nodal downstaging was present or if a lobectomy was performed.

The Intergroup 0139 trial evaluated 429 patients with stage IIIA NSCLC that were treated initially with concurrent RT (45 Gy) plus chemotherapy with cisplatin 50 mg/m^2 on days 1, 8, 29, and 35 plus etoposide 50 mg/m^2 on days 1 to 5, and 29 to 33; 396 patients with at least stable disease were then randomized to surgical resection or a continuation of RT to 61 Gy (31). Two additional cycles of chemotherapy were given to both groups. Median overall survival was 23.6 moths in the surgical group versus 22.2 months in the radiotherapy group.(p=0.24). In an unplanned exploratory analysis, overall survival was improved for patients who underwent lobectomy, but not pneumonectomy compared to matched irradiated patients.

As many controversies exist in locally advanced NSCLC, there is vast room for improving outcomes for these patients. A multidisciplinary approach to managing this diverse group of patients is strongly recommended.

METASTATIC NON-SMALL CELL LUNG CANCER

Patients with malignant pleural and pericardial effusions are classified as stage IIIB under the current staging system, but their prognosis and treatment is similar as for patients with metastatic disease. Therefore, in the new staging system they will be classified as stage IV disease. Depending on the primary tumour size, 30-40% of the patients with early-stage disease will subsequently relapse with metastatic disease (32). Thus, the vast majority of patients with NSCLC will potentially be candidate for chemotherapy for metastatic disease.

In patients with advanced stage NSCLC, the patient's performance status (PS) is used to estimate a patient's prognosis, as well as their tolerance of and potential benefit from chemotherapy. The Eastern Cooperative Oncology Group (ECOG) or Zubrod and Karnofsky (33,34) scales are commonly used to assess the PS. Standard of care for patients with a good PS, defined as asymptomatic or ambulatory but restricted from strenuous activities, is platinum-based doublet chemotherapy (35,36). Treatment with chemotherapy has been shown to extend survival, reduce disease-related symptoms and improve quality of life (Qol) in comparison to best supportive care (BSC) in this patient population (37,38). Patients with performance status 2, defined as ambulatory and active more than 50% of the time but unable to carry out work activities, have a worse prognosis, and the role of chemotherapy in this patient population is less certain. For patients who are only capable of limited self care and confined to a bed or chair more than 50% of the time or incapable of self care, BSC is the standard of care. Thus, a detailed history of the patient's daily activities and a careful assessment of his or her PS are critical to selection of the appropriate therapy.

Trials comparing different platinum-based combinations have, in general, revealed equal efficacy but different toxicity profiles (37). This led by some investigators to the defaitistic view that we might have reached a "therapeutic plateau" with standard cytotoxic chemotherapy (38). Recent trials have explored the addition of a so called "targeted agent" to platinum-based chemotherapy. These agents are active against a specific pathway involved in the pathogenesis and metastases of NSCLC. Currently two types of therapeutic targets are developed successfully: anti-angiogenesic agents and epidermal growth factor receptor (EGFR) inhibitors. There was initial enthusiasm for the integration of targeted agents into the treatment of advanced NSCLC; however, after the sobering results of several phase III trials, it became apparent that the integration of targeted agents would be more difficult than anticipated. For example, the EGFR tyrosine kinase inhibitors (TKI), gefitinib and erlotinib, have shown promising activity in phase II trials (39,40) and four phase III trials of chemotherapy with and without EGFR TKI

therapy were performed (41-44). Unfortunately, none of these trials revealed a survival benefit with the addition of EGFR TKI therapies to the standard chemotherapy. In North America bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), is approved in advanced NSCLC for patients with non-squamous histology based on the result of the ECOG 4599 and is in combination with chemotherapy accepted as standard care (45). The AVAIL trial performed in Europe has raised issues about the clinical benefit of bevacizumab in combination with cisplatin-gemcitabine; in this trial progression free survival was improved in patients receiving chemotherapy plus bevacizumab, overall survival was not improved (46). The FLEX trial, a randomized phase III trial comparing cisplatin, vinorelbine versus cisplatin, vinorelbine and the monoclonal antibody cetuximab, showed improved overall survival in favour of the cetuximab arm (47). Today there is strong evidence from the IPASS study that patients harbouring EGFR mutations, should be treated with EGFR-TKI's in first line and that the conclusions of this study are not geographical but biological determined (48). This thesis will not further deal with targeted agents in the treatment of NSCLC.

First-line therapy

The benefit of first-line chemotherapy in patients with a good PS is well established. In the past decades the optimal number of agents, selection of agents and the duration of chemotherapy has been evaluated in different trials and meta-analyses. The optimal *number of agents* was assessed in a meta-analysis performed by Delbaldo and colleagues (49). 13601 patients were included from 65 trials; platinum-based doublets yielded a superior response and survival rates compared with non-platinum based single-agent chemotherapy (50). The addition of a third cytotoxic agent did not improve survival and resulted in greater toxicity in comparison to two chemotherapeutic agents (51). Thus, most trials currently consist of platinum compound (cis- or carboplatinum) with a 3rd generation non-platinum agent, usually paclitaxel, gemcitabine, vinorelbine or docetaxel and more recently pemetrexed in patients with non-squamous histology (35–37,50). However, there is a continuing debate on *the type of the platinum compound* used. In two meta-analyses cisplatin has been compared with carboplatin. Both meta-analyses showed a superior response for cisplatin compared with carboplatin-based therapies, but similar overall survival (51,52). In the meta-analysis by Ardizzoni and coworkers, carboplatin treatment was associated with a non–statistically significant increase in the HR for mortality relative to treatment with cisplatin (hazard ratio [HR], 1.07; 95% confidence interval [CI], 0.99–1.15; $P = 0.10$) (52). In a subgroup analysis, patients with non-squamous histology and those treated with a third-generation chemotherapy,

carboplatin-based chemotherapy was associated with a statistically significant increase in mortality (HR, 1.12; 95% CI, 1.01–1.23 and HR, 1.11; 95% CI, 1.01–1.21, respectively). In the meta-analysis by Hotta et al., cisplatin-based chemotherapy was associated with a non-significant survival advantage (HR, 1.050; 95% CI, 0.907–1.216; $P = 0.515$), but in a subset analysis a superior survival was found for cisplatin in combination with 3rd generation chemotherapy than for carboplatin in combination with a 3rd generation drug (HR, 1.106; 95% CI, 1.005–1.218; $P = 0.039$) (51). These meta-analyses indicate that cisplatin is the more active agent when combined with new chemotherapy agents. Both meta-analyses revealed an increase in nausea, vomiting and renal toxicity for cisplatin-based therapy. Carboplatin-based therapy was associated with an increased rate of thrombocytopenia. At this time, both therapies are considered acceptable. Those in favour of cisplatin base their arguments on the improved efficacy, while those in favour of carboplatin refer to the lower toxicity of carboplatin.

Another issue in advanced stage NSCLC is *the optimal duration of chemotherapy* and this has been an area of investigation as well. Five trials have compared a shorter duration of platinum-based therapy (three or four cycles) with a longer duration of therapy (six cycles or until disease progression) (53–57). Four trials (51-53, 57) showed that a short course of therapy was not associated with impaired survival, while prolonged therapy had equivalent or greater toxicity compared with a short course (54,55). The quality of life has been equivalent (54,56) or better with a shorter duration of therapy (54,57). Recently four cycles of carboplatin-based therapy have been compared with six cycles. Preliminary results revealed a significant improvement in overall survival for the long course therapy (56). The cumulative data of the currently available phase III trials favour a short course of platinum-based chemotherapy because a short course of chemotherapy does not compromise overall survival while there is an increased risk of toxicity and loss in quality of life with a longer duration of therapy. The sequential use of non-cross resistant chemotherapy might be an approach to overcome these problems. Sequential chemotherapy administration offers the possibility to increase drug diversity while maintaining dose intensity, potentially leading to less dose reductions, an optimal dose intensity and prolonged treatment duration and disease control.

Second-line therapy

Second-line therapy is generally defined as therapy given after disease progression after first-line therapy. Approximately 40 to 50% of patients enrolled in first-line trials have subsequently received second-line therapy (53). Patients with a good PS, non-squamous histology and female gender appear to be more likely to receive second-line therapy

(58). There are currently three agents approved by the FDA for second-line therapy; two cytotoxic agents, docetaxel and pemetrexed, and an EGFR TKI, erlotinib.

Docetaxel was the first agent approved based on two phase III trials. In the TAX 317 trial, in which docetaxel was compared with BSC the initial docetaxel dose was 100 mg/m^2 every 3 weeks, but because of excessive toxicity the trial was amended and the dose was reduced to 75 mg/m^2 every 3 weeks. Patients receiving docetaxel at 75 mg/m^2 experienced a significantly longer time to tumour progression, median survival time, and a higher 1-year survival rate (59). The second phase III trial, TAX 320, compared docetaxel at two different doses, 100 mg/m^2 and 75 mg/m^2 every 3 weeks with the control arm of older chemotherapy agents of vinorelbine or ifosfamide (60). While the overall survival was not different among the three treatment groups, the 1-year survival rate was significantly higher for the treatment arm of docetaxel 75 mg/m^2. These trials led to FDA approval of docetaxel and established docetaxel at 75 mg/m^2 every 3 weeks as the standard of care. Subsequent trials have investigated docetaxel on a weekly schedule in comparison to the every-three-week schedule. A recent meta-analysis compared the two schedules and found equivalent efficacy and a similar rate haematological and non-hematological toxicities (61). The rate of febrile neutropenia was significantly lower on the weekly schedule and this schedule may be an option for patients who are at increased risk of infectious complications.

Pemetrexed was subsequently approved in the second-line setting on the basis of a phase III non-inferiority trial comparing pemetrexed versus docetaxel 75 mg/m^2 every 3 weeks (62). This trial differed from other second-line trials in that patients were only allowed to have received one previous line of therapy for advanced disease. Pemetrexed had a statistically significant lower rate of haematological toxicity and a similar rate of grade 3 or 4 non-hematologic toxicities. Based on the similar clinical activity of pemetrexed compared with docetaxel and the lower rate of myelosuppression, the FDA approved pemetrexed for treatment in the second-line setting (63). A retrospective analysis revealed that in patients with squamous histology treatment with pemetrexed led to an inferior overall survival compared with docetaxel (HR, 1.563; 95% CI, 1.079–2.264; median survival time of 6.2 and 7.4 mo, respectively) (64). In contrast, in patients with non-squamous histology pemetrexed yielded superior survival compared with docetaxel (HR, 0.778; 95% CI, 0.607–0.997; median survival time of 9.3 and 8.0 mo, respectively). The treatment by histology interaction test was statistically significant (P = 0.001). These data, in combination with prospective data from another trial (50), are suggestive that pemetrexed is more active in patients with non-squamous histology. Therefore, the FDA has recently changed the indication of pemetrexed to patients with non-squamous histology.

Erlotinib was approved by the FDA on the basis of the National Cancer Institute of Canada BR.21 trial, which compared erlotinib versus BSC in patients who had progressed on one line of therapy and were considered not candidates for further chemotherapy, and/or had progressed on two lines of therapy (65). This trial revealed a statistically significant improvement in progression free survival and overall survival with erlotinib in comparison to best supportive care. Erlotinib was well tolerated, with the principal toxicities being rash and diarrhea, and a low rate of myelosuppression and nausea and vomiting was observed. Erlotinib is approved in second- as well as third-line treatment settings and the fact that it is an oral agent may be more convenient for some patients. Early experience with the EGFR TKI therapies erlotinib and gefitinib revealed that some patients experienced a rapid and tremendous response to therapy, and that these responses were associated with a history of never-smoking, female sex, Asian ethnicity and adenocarcinoma histology (66). The clinical subgroups were subsequently found to have a higher prevalence of activating EGFR mutations in the tyrosine kinase domain that was associated with a high response rate to this EGFR TKI therapy (67–69). A separate analysis of the BR.21 revealed that smoking status appeared to be the most powerful predictor of survival benefit of erlotinib: never-smokers (defined as < 100 cigarettes in the entire lifetime) had a significantly higher survival rate (HR, 0.4; $P < 0.01$) (70). Current investigations are trying to determine the combination of clinical and molecular factors that will predict a survival benefit for EGFR TKI therapy.

Maintenance chemotherapy

In order to improve patients' outcomes, there has been a renewed interest in evaluating the role of maintenance or consolidation chemotherapy or both. In a recent randomized phase III trial of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care, progression free survival was 4 months in the pemetrexed arm versus 2 months in the placebo arm with an hazard ratio (HR) of 0.6 ($p< 0.00001$) and the overall survival was 13.4 months versus 10.6 months, respectively (HR 0.79, $p=0.012$) (71). The phase III trial of immediate versus delayed docetaxel after first line chemotherapy in advanced NSCLC showed also a superior progression free survival (5.7m versus 2.7m, $p=0.0001$) and a superior median overall survival (12.3m versus 9.7m), although not statistically significant for the arm with immediate docetaxel (72). In the Saturn trial the earlier initiation of erlotinib resulted in statistically significant improved PFS and overall survival. (73) These trials support the rationale of using a non-cross-resistant third generation agent before disease progression has occurred. However, question remains if we

could preserve the survival benefits if we delayed the second line treatment and allowed a treatment break?

Histology in the treatment of NSCLC

For the first time, randomized clinical trials in NSCLC now suggest that histology subtype can also be used as a marker for chemotherapy effectivity (50,74). In the Scagliotti trial, comparing pemetrexed/cisplatin versus gemcitabine/cisplatin, survival was superior in patients with non-squamous histology receiving the pemetrexed-based regimen (50). Conversely, gemcitabine/cisplatin resulted in superior survival in patients with squamous histology tumours. These data suggest that the histologic subtype can now be used to select individual patients who would benefit more or less from different chemotherapy regimens.

Personalized therapy in NSCLC

Some studies suggest evidence for a key role for the increased expression of ribonucleotide reductase subunit 1 (RRM1) in acquired gemcitabine resistance. (75,76) Recent trials report that patients with NSCLC with high excision repair cross-complementing 1 (ERCC1) expression do not benefit from cisplatin based chemotherapy (77,78). These data are sufficient to consider ERCC1 and RRM1 as possible molecular selection factors for platinum compounds and gemcitabine, respectively. These findings are important keys towards a "patient-specific individualized" therapy in NSCLC.

OUTLINE OF THE THESIS

As this introduction has pointed out, the optimal treatment of patients presenting with locally advanced and metastatic NSCLC is a moving target, as clinicians are constantly challenged with improvements in staging and therapy, resulting in evolving patterns of approach and research. In this thesis we describe chemotherapy and chemo-radiotherapy studies aimed to optimize treatment for patients with locally advanced and metastatic NSCLC.

For patients with locally advanced unresectable stage III NSCLC, the sequential chemo-radiotherapy approach is still widely used in Europe. A doublet of platinum combined with a third-generation chemotherapeutic agent is considered to be the most active induction regimen. Cisplatin-based chemotherapy regimens are not suitable for all patients because of the presence of comorbidity or a poor performance status. Carboplatin regimens are usually better tolerated in these circumstances, but the activity and toxicity of carboplatin-based induction regimens are yet unknown for this disease stage. Therefore, we decided to investigate the activity and toxicity of the combination of carboplatin and gemcitabine as an induction regimen for unresectable stage III NSCLC. This trial is described in **chapter 2.**

A major drawback in the treatment of locally advanced unresectable NSCLC is the high, 70% relapse rate, which occurs approximately one third locally, one third distantly and one third both locally and distantly.
A challenge today is to reduce this high relapse rate by identifying the optimal radiation dose in combination with the most effective systemic therapy. So far, neither the best drug combination nor the optimum radiation dose has been defined. The problem with most third generation chemotherapeutic drugs is that they cannot be administered in full systemic dose in combination with concurrent radiation therapy. Therefore, we decided to investigate if the combination of a new third generation agent, pemetrexed, with cisplatin could be administered at full systemic dosages with concurrent thoracic radiotherapy in patients with unresectable stage III NSCLC. The primary aim of this phase I study was to determine the MTD of pemetrexed and cisplatin in combination with conventional radiotherapy and secondly to determine the MTD of cisplatin and pemetrexed with hypofractionated radiotherapy. In **chapter 3** we describe the results of this phase I study.

Patients with stage IIIA and IIIB NSCLC who are downstaged after induction therapy may potentially benefit from surgery. The series published were usually limited to single institutional experiences. Proper and reliable restaging after induction therapy is crucial in order to prove downstaging. Therefore, the Lung Cancer Group of the European Organisation for Research and Treatment of Cancer (EORTC) decided, to investigate in patients with stage IIIB NSCLC, by study 08981, the feasibility of a tri-modality approach of chemoradiotherapy followed by restaging by means of the re-mediastinoscopy and resection in a multicenter setting. This trial is described and discussed in **chapter 4.**

The controversial issues in the management of patients with stage IIIA-N2 non-small cell lung cancer are being reviewed in **chapter 5**. It discusses the reasons of and the biases inherent to this controversy and discusses the different treatment approaches with emphasis on survival, as evidenced by meta-analyses and randomized clinical trials. Prospects on novel treatment modalities and future research opportunities are presented.

For patients with metastatic NSCLC, many North American physicians and Cooperative Groups prefer carboplatin-based therapies and also in Europe this regimen has become more popular. In the recommended 3-weekly schedule with gemcitabine (1250 mg/m^2) and carboplatin (AUC 5), both administered on day 1, patients frequently experience grade 3-4 neutropenia and/or grade 3-4 thrombocytopenia which requires special attention, repeated blood count controls and if needed, dose reductions and platelets transfusions. Question is whether administration of carboplatin on day 8 instead of on day 1 might lead to less toxicity while maintaining efficacy. In **chapter 6** we address this research question in a randomized phase II trial setting in which two schedules of carboplatin and gemcitabine are studied.

Sequential chemotherapy administration offers the possibility to increase drug diversity while maintaining dose intensity, potentially leading to less dose reductions, an optimal dose intensity and prolonged treatment duration and disease control. **Chapter 7** describes the results of a phase II trial, in which non-cross resistant sequential single agent chemotherapy is administered in first line metastatic NSCLC.

Currently many physicians select the second-line agent on the basis of physician and patient preference, patient co-morbidity, the toxicity profiles of the different therapies, and treatment convenience. Oral agents with few side effects are appealing in 2nd or 3rd line setting when patients are usually in a less favourable condition. In **chapter 8** we

report on the efficacy and toxicity of Uracil-Tegafur and etoposide in second and third line advanced stage, Caucasian NSCLC patients and compare the toxicity profile and costs of this regimen with historical series of the 2nd line therapy.

The studies described in this thesis are summarized in **chapter 9.** Futures perspectives towards an optimized and personalized treatment for NSCLC patients are highlighted.

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CHAPTER 2

A phase II study of induction therapy with carboplatin and gemcitabine among patients with locally advanced non-small cell lung cancer

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ABSTRACT

Introduction: The objectives of this trial were to evaluate the activity and safety of gemcitabine/carboplatin as induction therapy in patients with locally advanced non-small cell lung cancer.

Methods: Patients received two cycles of gemcitabine (1250 mg/m^2 on day 1 and 8), plus carboplatin (area under the curve = 5 on day 1), after which response was established. Patients received a third course only in the case of an objective response (OR). Non-responding patients were directly irradiated. Toxicity was assessed according to the NCI-CTC version 2, radiation toxicity was assessed according to RTOG criteria. Response evaluation was performed according to RECIST criteria.

Results: We identified 42 patients, of whom 37 were eligible. Of these, 51% (95% CI, 34%-68%) achieved an OR, all partial responses. No disease progression on therapy was established. Toxicity was mostly hematological: 35% trombocytopenia grade 3 and 4, and 40% neutropenia grade 3 and 4. No severe bleeding or hospitalization because of febrile neutropenia occurred.

Conclusions: Gemcitabine and carboplatin administered according to a 3-week schedule is an active and safe induction regimen. Pending the results of a phase III study, we believe that it is a reasonable alternative among patients for whom cisplatin-based chemotherapy is contraindicated.

The combination of platinum-based chemotherapy and thoracic irradiation is considered standard therapy in patients with unresectable locally advanced non-small cell lung cancer (NSCLC). In a number of randomized studies and a meta-analysis, chemotherapy added to radiotherapy improved survival compared with radiotherapy alone (1).
Recent studies claim concurrent chemo-irradiation to be superior to sequential therapy as it achieves higher response rates and adds 7% on long-term survival benefit (2,3). However, the optimal chemo- and radiotherapy combination is yet unknown, and its major drawback is its increase in toxicity, both hematologic and non-hematologic (mucositis, pneumonitis, and esophagitis). This is the reason that a recent meta-analysis and the NICE guideline restrict the use of concurrent chemo-radiotherapy to selected patients (2). Although sequential therapy is not the standard of care in the United States, it is still widely used in Europe, mainly because of logistical reasons.
In the sequential treatment setting, response to induction chemotherapy is an important variable in qualifying for subsequent radiotherapy (1,4). A doublet of platinum combined with a third-generation chemotherapeutic agent is considered to be the most active induction regimen. One of these third-generation agents is gemcitabine. In a recent meta-analysis, gemcitabine-containing regimens led to a better survival than other third-generation drug combinations in patients with advanced NSCLC (5).
Because of its more favourable toxicity profile, carboplatin is often preferred to cisplatin (6,7). The most frequently used regimen in the United States combines carboplatin and paclitaxel. In a recent meta-analysis, it was concluded that cisplatin combinations have a survival benefit compared with carboplatin combinations in advanced NSCLC (7), but in phase III studies in which gemcitabine-cisplatin and gemcitabine-carboplatin were compared, no survival benefit for the cisplatin combination could be demonstrated in advanced disease (6,8).
The aim of the present study was to investigate the activity and toxicity of the combination of carboplatin and gemcitabine as an induction regimen for stage III NSCLC.

PATIENTS AND METHODS

The study was conducted in three Dutch hospitals in Rotterdam (Erasmus MC, Sint Franciscus Gasthuis, and MCRZ) and was approved by the local ethical committees of each participating center.
Eligible chemonaive patients had to have a histological or cytological diagnosis of locally advanced NSCLC. In the case of presumed stage IIIA disease, tissue confirmation of N2 involvement was required. In the case of stage IIIB disease, patients with N3 (ex-

cluding supraclavicular lymphnodes) or T4 (excluding pleural fluid) were eligible. Other criteria were: measurable disease according to RECIST criteria, age older than 18 years, World Health Organization performance status 2 or less, adequate bone marrow reserve (hemoglobin >10 mg/dL or 6 mmol/L, white blood cell count higher then 4.0 $\times 10^9$/L, absolute neutrophil count >2.0 $\times$ 10^9/L, platelet count >100 $\times$ 10^9/L), and a calculated creatinine clearance of at least 60 mL/min. Women of child-bearing age were asked to use adequate contraceptive methods.

Exclusion criteria were the presence of other malignancies (previous or current), except adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin, or a previous malignancy more than 5 years ago without evidence of recurrence; pregnancy and/or breast feeding; use of any investigational agent in the month before enrolment into the study; uncontrolled infections and signs or symptoms of metastases; a weight loss of more than 10% in the preceding 3 months.

Pretreatment evaluation included a complete medical history and physical examination, chest radiograph and computed tomographic scanning of thorax and upper abdomen, pulmonary function testing with diffusion capacity, routine blood sampling, urine analysis and electrocardiogram. All patients had to give written informed consent.

Treatment

The treatment scheme is presented in Figure 1. Chemotherapy consisted of two courses of gemcitabine and carboplatin as a 21-day regimen. Gemcitabine was given at a dosage of 1250 mg/m^2 intravenously (over 30 minutes on days 1 and 8), carboplatin at an area under the curve of 5 (intravenous in 30 minutes on day 1) after gemcitabine. Routine anti-emetics were given according to institutional practice. No prophylactic growth factors were allowed. Dose adjustments were made according to the guidelines described in Table 1. In the case of non-hematological toxicity grade 4, a dose reduction with 25% of both gemcitabine and carboplatin was performed.

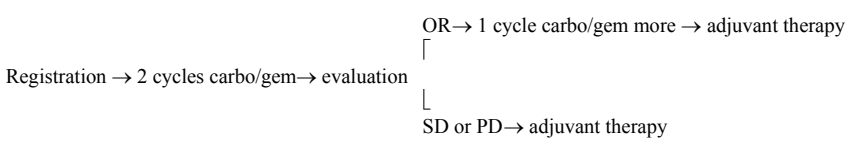

Figure 1. Treatment schedule

Table 1. Redosing schedule related to toxicity

Gemcitabine Dose (mg/m^2)	WBC x 10^9/L	ANC x 10^9/L and/or	Platelets x 10^9/L and/or
1250	> 2	> 1	>100
1000	1-2	0.5 – 1	50-100
0	<1	<0.5	<50

After two cycles, response evaluation was performed according to RECIST criteria. In case of a response, one more cycle was administered before the start of thoracic radiotherapy. In the case of stable disease or progressive disease, patients were immediately referred for radiotherapy. Radiotherapy was given with a radical intent. Dose was calculated taking into account lung toxicity (V20) and estimated esophagus toxicity. The interval between the start of the last chemotherapy and the start of radiotherapy had to be at least 4 weeks and less than 6 weeks. Toxicity was assessed weekly using the National Cancer Institute common toxicity criteria (NCI-CTC version 2). Radiation toxicity was scored according to RTOG criteria.

Statistics

The study was designed according to the two-step Simon design, with a response rate of interest after two cycles of chemotherapy of at least 70% with a type 1 error of 0.05 and a power of 80%; 37 patients had to be accrued to observe 26 responses. If less than 12 responses were seen in the first 24 patients, the study should have been discontinued. Response analysis was performed for eligible patients only. Toxicity analysis included all patients. Survival data were calculated using the Kaplan-Meier method.

RESULTS

Patient Characteristics

Between January 2002 and December 2004, 42 patients were enrolled (23 male, 19 female; mean age 61.3 years, range 42-78 years). All patients gave informed consent. Five patients were ineligible because of stage IV disease in four patients and stage IIIB disease with pleural effusion in one patient. Patient characteristics of the eligible patients are presented in Table 2.

Table 2. Patients Characteristics

	Characteristics	No. of Patients (%)
Male/female	19/18	(51/49)
Age (yr)	61.8	(51/49)
PS 0	14	(38)
PS 1	21	(57)
PS 2	2	(5)
Stage IIIA	16	(43)
Stage IIIB	21	(57)
Values are *n*(%) or mean (range)		

Activity

A total of 102 chemotherapy courses were administered, with a median of three cycles per patient (range, one to four). Two patients with a partial response received four cycles instead of the planned three because of a delay in the start of radiotherapy because of logistical problems.

The overall clinical response rate in the 37 eligible patients was 51% (95% CI, 34%-68%) and for stage IIIA and IIIB disease 38% (9 of 16) and 61.9% (13 of 21), respectively, with no complete responses. No disease progression was observed.

Toxicity and Dose Intensity

Five patients were excluded from the toxicity analysis, one because of erythropoietin administration and four because only data from cycle one were available. In the remaining 37 patients, grade 3 to 4 thrombocytopenia was seen in 13 patients (35.1%), with 12 (32.4%) grade 3 and 1 (2.6%) grade 4 (Table 3). Six patients required platelet transfusions, but no overt hemorrhages were observed. Grade 3 to 4 neutropenia was observed in 15 (40.5%) of patients: 13 (35.1%) grade 3 and 2 (5.2%) grade 4. No febrile neutropenia occurred. In one patient (2.6%) a grade 3 anemia was found, but erythrocyte transfusions were given in 10 patients (27%) (Table 3).

Except for dyspnea, which was found in five patients (13.2%), non-hematological toxicity was low. The planned dose intensity was 208 mg/wk for carboplatin and 1542 mg/wk

Table 3. Hematological toxicity

	Grade 3	Grade 4
Anemia	1 (2.7)	0 (0)
Thrombocytopenia	12 (32.4)	1 (2.7)
Leukopenia	9 (24.3)	0 (0)
Neutropenia	13 (35.1)	2 (5.4)
Values are *n*(%). *n* = 37.		

for gemcitabine. Relative dose intensity in the 37 patients equaled 99% for carboplatin and 91% for gemcitabine.

Radiation Therapy

Of the patients who received the planned treatment, 89% (33 of 37) underwent radiotherapeutic treatment. Four patients did not undergo radiotherapy. One patient died after chemotherapy before the start of radiation therapy because of myocardial infarction that was not related to chemotherapy. One patient had a marginal pulmonary function but was considered by a radiation oncologist to be fit for involved field radiotherapy. However, the patient's clinical condition deteriorated after chemotherapy, and he was subsequently judged to be unfit for radiotherapy. In two otherwise fit patients, the initial radiation fields were considered to be excessively large for radical radiotherapy, and we planned to irradiate the post-chemotherapy volume. A lack of response to chemotherapy led to the decision not to irradiate. These were the only two patients included in the study for who we planned to irradiate the post-chemotherapy volume. Mean dose was 42.5 Gy (range, 20-66 Gy). During and after radiotherapy, one patient developed grade 3 esophagitis. Radiation pneumonitis occurred in four patients (grade 1 in two patients and grade 3 in two patients).

Follow-Up

Median survival of all 37 patients was 13 months. The Kaplan-Meier survival curve is presented in Figure 2. Currently 78% of patients have progressed. Median time to disease progression is 9.1 months.

DISCUSSION

In this phase II study designed to investigate the activity and safety of the gemcitabine-carboplatin combination as an induction regimen in sequential chemo-radiation for locally advanced NSCLC, an overall response rate of 51% was achieved. Table 4 summarizes the characteristics of the published data on the combination of gemcitabine and platinum in locally advanced NSCLC. Because consolidation treatment is different among the studies, no valid information on time to progression can be provided. For the cisplatin-based schemes, response rates after chemotherapy differ between 40% and 70%. In the earlier studies, gemcitabine-cisplatin was given in a 4-week schedule. In

Table 4. Articles about gemcitabine platinum in locally advanced NSCLC

Author	Phase	Induction scheme	q	*n*	Stage IIIa/ IIIb (%)	Response rate (95% CI)
Van Zandwijk et al.[4]	II	Gemcitabine 1000 mg/m^2 d1,8,15 Cisplatin 100 mg/m^2 d2	4	47	100/0	70 (55-83)
Yang et al.[17]	II	Gemcitabine 1000 mg/m^2 d1,8,15 Cisplatin 90 mg/m^2 d15	4	52	50/50	64 (50-77)
Van Kooten et al.[18]	II	Gemcitabine 1250 mg/m^2 d1,8,15 Cisplatin 100 mg/m^2 d2	4	29	59/41	62(45-79)
De Pas et al.[13]	II	Gemcitabine 1000 mg/m^2 d1,8,15 (1250 mg/m^2 d1,8) Cisplatin 100 d1 (80 mg/m^2 d1)	4 (3)	10(40)	74/26	74 (60-85)
Santo et al.[14]	II	Gemcitabine 1250 mg/m^2 d1,8 Cisplatin 100 mg/m^2 d8	3	43	33/67	62 (NR)
Cappuzzo et al.[15]	II	Gemcitabine 1000 mg/m^2 d1,8 Cisplatin 70 mg/m^2 d2	3	129	44/56	62 (54-70)
Vokes et al.[12]	III	Gemcitabine 1250 mg/m^2 d1,8 Cisplatin 80 mg/m^2	3	62	67/33	40 (27-55)
Migliorino et al.[16]	II	Gemcitabine 1250 mg/m^2 d1,8 Cisplatin 70 mg/m^2 d2	3	69	67/33	57 (45-62)
Argiris et al. [9]	I/II	Gemcitabine 1000 mg/m^2 d1,8 Carboplatin AUC = 5	3	39	56/44	41 (26-56)
Current study	II	Gemcitabine 1250 mg/m^2 d1,8 Carboplatin AUC = 5	3	37	45/55	51 (34-68)

AUC = arca under the curve

later studies, this was changed to a 3-week schedule. This was done because of toxicity (mostly hematological), because of which the gemcitabine on day 15 was often omitted. Only one other study with gemcitabine-carboplatin used as an induction regimen in locally advanced NSCLC has been published, with a response rate of 41% (9). Recent data were presented in the same patient group showing a response rate of 74% (10). In the latter studies, the induction treatment was followed by concomitant treatment with chemoradiation.

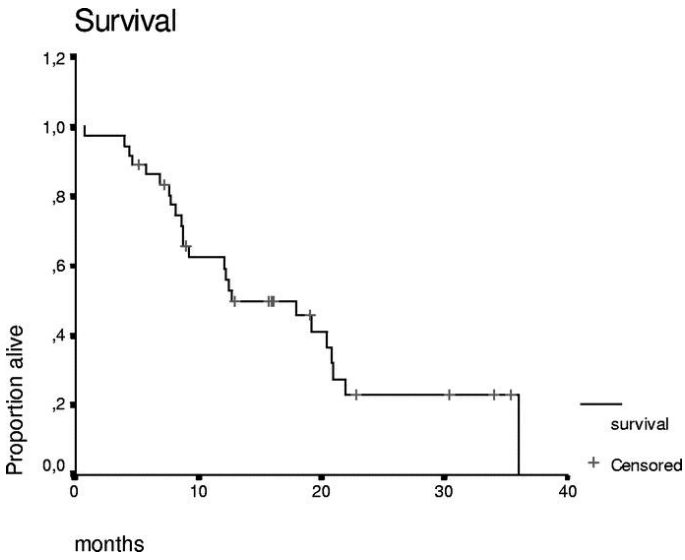

Figure 2. Survival curve for all 37 eligible patients.

In the absence of randomized data, no formal comparison can be made between cisplatin- and carboplatin-containing regimens for induction. It is unlikely that such a trial will ever be conducted because of the large sample size required to demonstrate a true difference. In advanced disease, such studies have been performed (6,8). In neither of these studies was a significant difference in response rate between gemcitabine cisplatin or gemcitabine carboplatin found. In both studies, the response rate in the cisplatin arm was higher, but this did not reach statistical significance.

Toxicity was limited in the study. The known dose-limiting toxicity of the gemcitabine-carboplatin combination is hematologic (6). Although thrombocytopenia grade 3 and 4 was present in 35% of cases, this was never associated with bleeding. Neutropenia grade 3 and 4 was present in 41% of patients, but no hospitalization because of febrile neutropenia was necessary. Anemia grade 3 was present in only one patient, but 10 patients received an erythrocyte transfusion, which may have influenced this number. Almost all transfusions were given after the completion of the second cycle. The high number of transfusions in relation to the objective toxicity numbers may be related to the fact that, in 12% of patients, grade 3 and 4 dyspnea was scored, which may have made physicians more prone to give blood transfusions. The toxicities are comparable to the numbers found in other studies (6,9,11). Survival of our patients was poor. We believe that this is related to the patient population included; most of our patients were stage IIIB. Patients

with minimal N2 disease were included into other study protocols. The recent publication of Fournel et al. (3) also included a large population of patients with stage IIIB disease, and survival in the sequential arm was comparable to ours. Similarly, the recent phase III CALGB study 39801 evaluating two concurrent chemo-radiotherapy schedules reported median survivals of 11.4 months for concurrent chemo-radiotherapy, and 13.7 months for induction chemotherapy followed by the same concurrent chemo-radiotherapy scheme (12).

In recent years, more and more data on the survival benefit of concurrent therapy have become available. At the time of the design of the study, these data were not published. It is therefore also likely that patients with good performance status were enrolled in this study. These patients will now preferably be treated with concurrent chemoradiotherapy. However, in a large group of patients, with poor performance status or with comorbid conditions, because of the toxicity of concurrent therapy, sequential therapy will remain standard of care. For these patients, the possibility of a lesser toxic chemotherapeutic agent is of importance, and, in these situations, carboplatin is preferred.

In conclusion, gemcitabine carboplatin is an active and safe chemotherapeutic regimen, especially for patients in whom cisplatin-based chemotherapy is contraindicated.

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CHAPTER 3

Pemetrexed and Cisplatin with concurrent radiotherapy for locally advanced non-small cell and limited disease small cell lung cancer: Results from 2 phase I studies

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Lung Cancer, accepted

ABSTRACT

Background: The objectives were to determine the maximum tolerated dose (MTD) of pemetrexed and cisplatin with concurrent radiotherapy. Secondary objectives include incidence and nature of acute and late toxicities, tumour response and overall survival.

Patients and methods: Treatment naïve patients received 1 cycle of cisplatin 80 mg/m^2 in study I (stage III NSCLC), 75 mg/m^2 in study II (LD-SCLC)) and pemetrexed 500 mg/m^2 before the phase I part. In Study I, patients were treated in cohorts with escalating cisplatin doses (60-80 mg/m^2), pemetrexed doses (400-500 mg/m^2) and concurrent escalating radiotherapy doses (66 Gy in 33-27 fractions). In study II, patients were treated with cisplatin 75 mg/m^2 and escalating pemetrexed doses (400-500 mg/m^2) with concurrent escalating radiotherapy doses (50-62 Gy).

Results: The trials closed prematurely: study I because of poor accrual, study II because of sponsor decision. Thirteen patients were treated : 4 with NSCLC, 9 with LD-SCLC. No dose-limiting toxicity was observed. There was no grade 4 toxicity, grade 3 hematological toxicity was mild. One patient developed grade 3 acute esophagitis, but was able to complete radiotherapy without delay. Two patients experienced grade 2 late pulmonary toxicity. 1 complete response, 6 partial responses and 1 progressive disease were observed.

Conclusions: Although the studies stopped too early to assess MTD, we have demonstrated that the combination of full doses of cisplatin (75-80 mg/m^2) and pemetrexed 500 mg/m^2 with concurrent radiotherapy up to 50 Gy (25 x 2 Gy) is well tolerated. Pemetrexed is the first 3rd generation cytotoxic found to be tolerable at full dose with concurrent radiotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the United States and Europe for both men and women. Non-small cell lung cancer (NSCLC) accounts for 87% of all lung cancer cases. One third of them presents with locally advanced disease, of which the majority is unresectable. Concomitant chemo-radiotherapy improves survival of patients with locally advanced NSCLC by 5.7% at 3 years compared to sequential chemo-radiotherapy, but at the cost of increased acute esophageal toxicity (1). The 70% relapse, occurring approximately one third locally, one third distantly and one third both locally and distantly (2-7), is a major drawback. A major challenge today is to reduce this high relapse rate by identifying the optimal radiation dose in combination with the most effective systemic therapy. So far, neither the best drug combination nor the optimum radiation dose has been defined. Therefore, new chemo-radiotherapy combinations are needed.

Small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancers diagnosed and about one third is limited-stage disease (LS-SCLC). Sequential chemo-radiotherapy has improved 5-year survival rates by 5 % compared to radiotherapy alone (8, 9) and has been further improved by the combination of early thoracic radiotherapy (TRT) and concurrent chemotherapy (10-13). Like in NSCLC, major challenge is to reduce the high relapse rate and to improve survival. Therefore, also for LS-SCLC new chemo-radiotherapy combinations are needed.

Pemetrexed is a multitargeted antifolate which has activity in a wide range of cancers. It has been approved by the U.S Food and Drug Administration for single agent second-line therapy in metastatic NSCLC (14-16) and for first-line treatment in malignant pleural mesothelioma in combination with cisplatin (17) and recently in first-line metastatic NSCLC in combination with cisplatin for non-squamous histology (18).

In preclinical studies, the combination of pemetrexed with radiotherapy appeared to be synergistic (19). Seiwert et al. was the first to demonstrate in a phase I study in patients with locally advanced NSCLC or esophageal cancer that the combination of pemetrexed (500 mg/m^2) and carboplatin (area under the curve 5 or 6) with concurrent radiation was well tolerated and active (20). However, in patients with NSCLC, cisplatin-based regimens are superior to carboplatin-based regimens in terms of response rate and, in certain subgroups (patients treated with third-generation platinum-based regimens and patients with non-squamous histology) in prolonging survival (21). Cisplatin is also a potent radiosensitizer, while the radiosensitizing properties of carboplatin are not as well established. Therefore, we decided to investigate the combination of pemetrexed and cisplatin with concurrent TRT in patients with LS-SCLC and stage III NSCLC in two

separate studies. Primary objective of these studies was to determine the maximum tolerated dose (MTD) of pemetrexed and cisplatin with concurrent TRT. Secondary objectives were acute and late toxicity, objective tumour response and overall survival.

PATIENTS AND METHODS

Study I was approved by the Ethical Committee of the Erasmus University Hospital Rotterdam, study II by the Ethical Committee Vrije Universiteit Amsterdam.

Patients and treatment plan

Enrolled were patients with histologically or cytologically proven stage III NSCLC not amenable for surgical resection (Study I, investigator initiated, Lilly supported) or histologcially or cytologically proven LS-SCLC (Study II, Lilly study number H3E-EW-S107). The in- and exclusion criteria and dose limiting toxicity definitions of these two studies are summarized in Table 1. Both the NSCLC and LD-SCLC patients received one cycle of cisplatin (80 mg/m^2 study I, 75 mg/m^2 study II) and pemetrexed 500 mg/m^2 before start of phase I. Starting with cycle 2, chemotherapy and radiotherapy doses differed between the cohorts as summarized in Table 2. Patients gave written informed consent before enrolment in the studies.

Chemotherapy

Patients were treated with cisplatin and pemetrexed on day 1 of a 21-day cycle. Pemetrexed was administered as a 10-minute and cisplatin as a 120-minute intravenous infusion 30 minutes after the end of the pemetrexed infusion. Folic acid supplementation (350-600μg) started 5 to 7 days prior to the first dose of pemetrexed and continued daily until 3 weeks after the last dose of pemetrexed. Vitamin B12 (1000μg) was administered as an intramuscular injection 1 to 2 weeks prior to the first dose of pemetrexed and was repeated every 9 weeks until 3 weeks after the last dose of pemetrexed. Patients were treated with dexamethasone the day before, the day of and the day after each dose of pemetrexed. For all cohorts, radiotherapy was administered 2 hours after the chemotherapy administration.

Table 1. Eligibility criteria and definition of dose limiting toxicity for patients with non-small cell lung cancer (study I) and small cell lung cancer (study II)

Eligibility criteria	No prior chemo- or radiotherapy
	ECOG 0 or 1
	ANC ≥ 1.5 X 10^9/L, platelets ≥ 100 X 10^9/L and hemoglobin ≥ 9.6 g/ dl
	Measurable disease (RECIST)
	Calculated creatinin clearance ≥ 60 ml/min (Cockroft and Gault)
	· FEV1 >30% predicted normal value
	· Diffusion capacity > 40% predicted normal value
	· V20 ≤ 36%
	Able to drain third space fluids
Exclusion criteria	Pleural effusion with positive cytology
	Stage III NSCLC with supraclavicular lymph node involvement
	Uncontrolled vena cava superior syndrome
	Serious concomitant systemic disorder
	Myocardial infarction <6 months or symptomatic heart disease
	Significant weight loss (>10%) over previous 6 weeks before study entry
	Inability to take folic acid or vitamin B12 supplementation
	Inability to take corticosteroids
DLT definition	Grade 4 neutropenia lasting > 5 days, or ANC < 0.5 x 10^9/L on two occasions 7 days apart
	Febrile neutropenia
	Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
	RTOG grade 3 pulmonary or esophageal toxicity that prohibits 5 or more consecutive days of radiation treatment or any RTOG grade 4 pulmonary or esophageal toxicity
	Any other grade 3 non-hematologic toxicity that prohibits 5 or more consecutive days of radiation treatment or grade 4 non-hematologic toxicity (except grade 3/4 alopecia, nausea and vomiting)
	Death due to toxicity
	Grade 2 to 4 myelosuppression prohibiting retreatment on day 22

Definitions of abbreviations: ANC : absolute neutrophil count; RECIST: Response Evaluation Criteria in Solid Tumors; FEV1: forced expiratory volume in one second; V20: lung volume minus the planned target volume receiving ≥20 Gy; DLT= dose limiting toxicity;

Radiation therapy

For study I, the initial radiotherapy dose in cohort one through four was 66 Gy administered over 45 days with daily fractions of 2 Gy, 5 days/week. For study II, the initial radiotherapy dose in cohort 1 and 2 was 50 Gy administered in 25 daily fractions of 2 Gy, 5 days/week. Patients with LS-SCLC who had a complete response, received prophylactic cranial irradiation with a total dose of 20-30 Gy, in fractions of 2-2.5 Gy/day over a period of 3 weeks.

Radiotherapy was administered according to the recommendations of the European Organisation For Research and Treatment of Cancer (EORTC) Radiotherapy Group, ICRU Report 50 and ICRU Report 62 (22). The gross tumor volume (GTV) encompassed all known pre-chemotherapy primary tumor and involved lymph node locations. Additional margins applied for microscopic tumor extension, mobility and daily setup

Tabel 2. Treatment plan for patients with non-small cell lung cancer (study I) and treatment plan for patients with small cell lung cancer.(study II)

Study I	Pemetrexed (mg/m^2)	Cisplatin (mg/m^2)	Radiotherapy (Gy/fractions/days)	Patients
Cycle 1				
All	500	80	None	All
Cycles 2-3				
Cohort 1	400	60	66/33/45	3-6 (9)
2	400	70	66/33/45	3-6 (9)
3	400	80	66/33/45	3-6 (9)
4	500	80	66/33/45	3-6 (9)
5	500	80	66/30/40	3-6 (9)
6	500	80	66/27/37	3-6 (9)
Study II	Pemetrexed (mg/m^2)	Cisplatin (mg/m^2)	Radiotherapy (Gy/fractions/days)	Patients
Cycle 1				
All	500	75	None	All
Cycles 2-3				
Cohort 1	400	75	50/25/25	3-6
2	500	75	50/25/25	3-6
3	500	75	56/28/28	3-6
4	500	75	62/31/31	3-6
Cycle 4				
All	500	75	None	all

Definitions of abbreviations: Gy= gray

errors in order to derive a planning target volume (PTV) did generally not exceed 1.5 cm. Mediastinal or hilar lymph nodes > 1cm in shortest diameter found histologically positive at cervical mediastinoscopy or endoscopic ultrasound and those considered positron-emission-tomography (PET) positive have been included in the PTV. The margins around visible, enlarged lymph nodes were 1.5 cm in the transverse and 2 cm in the longitudinal direction. The PTV has been irradiated by multiple field arrangement swith the use of 3D conformal techniques. Dose volume histograms for the PTV, normal lung, esophagus and heart have been calculated in order to gain full knowledge of the 3D dose distribution.

The spinal cord did not receive more than the equivalent of 50 Gy in 30 fractions using standard, biologically effective dose corrections at any point. The esophagus was included within the 95% isodose in most patients but the maximal length did not exceed 15 cm. The heart received a maximum tolerated dose < 30% of its volume and the volume of both lungs that received more than 20 Gy (V20) was ≤ 36%.

Dose escalations and dose-limiting toxicity

The definitions of the dose-limiting toxicities for the two studies (DLT) are summarized in Table 1. They apply to the complete chemo-radiation period up to 6 weeks after the last fraction of radiotherapy administration. If none of the patients experienced a DLT, the next dose level was explored and if 1 of the first 3 patients had DLT, 3 additional patients were enrolled at the same dose level. Dose escalation was only allowed if no more than 1 patient experienced a DLT.

If in study I, more than 1 out of 6 patients had a DLT, the cohort was expanded to 9 patients. If no more than 3 out of 9 patients experienced DLT, this dose was the maximum tolerated dose (MTD) and the dose used in the preceding cohort was the recommended phase II dose. If in study II more than 1 of the 6 patients had DLT, this dose was the MTD and the dose used in the preceding cohort the recommended phase II dose. In case of grade IV toxicity (except alopecia, nausea and vomiting), the recommended dose was defined as one dose level below the level at which the grade 4 toxicity occurred. To proceed to the next cohort, 6 weeks (Study I) or 2 weeks (Study II) must have elapsed after the last radiation fraction of the last patient.

Efficacy and tolerability assessments

Baseline assessments included physical examination, complete blood count, electrocardiogram (ECG) < 2 weeks before the start of treatment and chest-upper abdomen computed tomography (CT), CT or MRI brain, TRT planning CT and a PET scan within 4 weeks before treatment. The lung function test included a forced expiratory volume in one second (FEV1) and a diffusion capacity (DLCO) within 4 weeks before start of the treatment. Routine blood tests for blood chemistry and haematological toxicity were performed before each chemotherapy administration. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3 (NCI-CTC) and assessed on day 1, 8, 15 and 21 of each cycle by physical examination, direct questioning and appropriate hematological and biochemical values. Post treatment follow-up included a chest-upper abdomen CT at 1, 3, 6, 9 and 12 months, lung function tests at 3 and 12 months, NCI-CTC toxicity scoring and RTOG toxicity scoring at 1, 3, 6, 9 and 12 months, and an ECG at 1, 3, 6, 9 and 12 months. Tumor response was assessed according to RECIST criteria (23).

Statistical and analytical plan

Patients who received at least cycle 1 and 2 (concomitant chemo-radiotherapy) were included in the primary outcome analysis, i.e the MTD of cisplatin and pemetrexed with concurrent radiotherapy. All patients who received at least one 1 dose of pemetrexed or cisplatin were evaluated for safety analysis and tumour response assessment. This safety analysis included serious adverse events (SAES) related to study treatment, discontinuation, listings of CTCAE 3 toxicities and RTOG acute and late toxicities.

RESULTS

Study I was prematurely terminated because of poor accrual and study II because of the inferior activity of pemetrexed in SCLC based on the interim results of the GALES trial in SCLC-ED (24).

In study I, between April 2006 and January 2008, 3 males and 1 female were enrolled. Median age was 59 years (range 54-64); 3 had ECOG performance status (PS) 1, 1 PS 0; 3 had stage IIIA, 1 stage IIIB; 1 squamous cell carcinoma, 1 adenocarcinoma and 2 undifferentiated carcinomas were diagnosed.

In study II, between March 2007 and December 2007, 6 males and 3 females have been included with a median age of 70 years (range 50-80); 2 had PS 0, 7 PS 1.

In study I, 4 patients completed cohort 1 without DLT. All patients received 3 cycles of chemotherapy without dose reductions. In none of the patients radiation therapy was interrupted because of adverse events (AE). In one patient a non-study related SAE occurred 2 days after the end of the radiotherapy. He died of intracranial haemorrhage (at that time, the thrombocyte count was normal) as a result of a car accident This study participant was replaced in this cohort. Treatment-related grade 3 and 4 toxicities are summarized in Table 3. No febrile neutropenia or toxic deaths were observed. Acute and late pulmonary and esophageal toxicities are summarized in Table 4. In one patient grade 2 late pulmonary toxicity was diagnosed.

Two patients achieved a partial response, 1 patient had a complete response. One patient died with progressive disease at 21 months, the other patients are still alive at 3 years.

In study II, 9 patients were included in the safety analysis and 5 in the tumour response evaluation. Four of the 9 patients completed treatment. Three patients in cohort 2 discontinued treatment due to an AE; 1 because of renal failure after the first course of chemotherapy, 1 because of femoral artery occlusion and 1 because of grade 3 peripheral

Table 3. Treatment-related grade 3 and 4 toxicities after cisplatin and pemetrexed with concurrent radiotherapy in study I and II according to the National Cancer Institute Common Toxicity Criteria version 3 and RTOG toxicity scoring

Study I (NSCLC)				
Cohort	No	DLT	Hematological toxicity	Non-hematological toxicity
1	4	no	1: G3 leucopenia	1: G3 hyperglycemia
Study II (LD-SCLC)				
Cohort	No	DLT	Hematological toxicity	Non-hematological toxicity
1	3	no	1: G3 anemia, G3 thrombocytopenia 1: G3 thrombocytopenia, G3 neutropenia 1: G3 lymphopenia	1: G3 anorexia, G3 fatigue 1: G3 esophageal toxicity
2	6	no	2: G3 lymphopenia, 1: G3 neutropenia	1: G3 anorexia, G3 renal toxicity 1: G3 fatigue, G3 anorexia, G3 femoral artery occlusion 1: G3 peripheral sensory neuropathy

Definitions of abbreviations G3= grade3; DLT= dose limiting toxicity; NSCLC= non-small cell lung cancer; SCLC=small cell lung cancer

Table 4. Pulmonary and esophageal toxicity after treatment with cisplatin-pemetrexed and concurrent radiotherapy in study I and II, according to RTOG toxicity scoring

Study I (NSCLC)			Pulmonary toxicity	Esophageal toxicity
1	4	no	**Acute:** / **Late:** 1 G2	**Acute**: 1 G1 **Late:** /
Study II (LD-SCLC)				
Cohort	No	DLT	Pulmonary toxicity	Esophageal toxicity
1	3	no	**Acute:** 2 G1, 1 G2 **Late** : 2 G1	**Acute:** 3 G2, 1 G3 **Late :** 1 G2
2	6	no	**Acute:** 1 G1 **Late:** 1 G2	**Acute:** 2 G1 **Late:** /

Definitions of abbreviations G= grade; DLT= dose limiting toxicity; NSCLC= non-small cell lung cancer; SCLC=small cell lung cancer

sensory neuropathy. Two patients received only 1 cycle of chemotherapy because of premature closure of the trial. In total, 3 patients were replaced as they were not evaluable for DLT. None of the patients in cohort 1 or 2 experienced DLT. In one patient, dose reductions for pemetrexed and cisplatin were required because of dehydration at cycle 2. In one patient the cisplatin dose was reduced at cycle 4 because of decrease in renal function. Treatment-related grade 3 and 4 toxicities are summarized in Table 3. No febrile neutropenia or toxic deaths were observed. Acute and late pulmonary and esophageal toxicities are summarized in Table 4. One patient in cohort 1 experienced a grade 3 acute esophageal toxicity, this patient was able to complete radiation therapy without delay. One patient in cohort 2 developed grade 2 late pulmonary toxicity.

Four patients achieved a partial response, 1 patient progressed after 2 and 4 cycles of chemo-radiotherapy.
Of the 4 patients who completed treatment, 1 patient died 6 months, one 14 months and one 11.5 months after the start of treatment, all of them because of disease progression. One patient is still alive.

DISCUSSION

Because these two phase I trials were terminated prematurely and prior to the occurrence of DLT's, we are unable to establish the MTD of cisplatin and pemetrexed with concurrent radiotherapy in locally advanced NSCLC and LS- SCLC. However, these two studies provide additional data on the toxicity of this new combination and are important for future trials.
From our data we may conclude that systemic doses of pemetrexed and cisplatin up to 500 mg/m^2 and 75 mg/m^2, respectively, can safely be combined with radiotherapy up to 50 Gy in 25 fractions. Overall the toxicity profile is favourable. Hematological toxicities were mild and no dose reductions for haematological toxicity were needed. Similar results were presented at ASCO 2008 by Brade et al (25) and Gadgeel et al (26). They concluded that full dose of pemetexed and cisplatin with full dose of RT is well tolerated in stage III NSCLC. In our study, grade 3 and 4 acute or late pulmonary toxicities have not been observed. Although one patient experienced a grade 3 acute esophageal toxicity, this patient was able to complete radiation therapy. Because 2 out of 13 patients (15%) developed late grade 2 pulmonary toxicity, close follow-up for late pulmonary toxicity is recommended, especially in studies with higher radiation dosages.
Pemetrexed is the first 3rd generation cytotoxic which can be administered at full dose with concurrent chemoradiotherapy. Choy et al. demonstrated recently that a gemcitabine-carboplatin combination concurrent with thoracic radiotherapy is well tolerated with a MTD of gemcitabine of 450 mg/m^2 and carboplatin area under the curve (AUC) of 2 with thoracic radiation to 63 Gy. These dosages of gemcitabine and carboplatin are far below systemic effective dose levels (27). Recently, a phase III study in non-squamous unresectable locally advanced stage III NSCLC has started with full dose pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2 and radiotherapy 66 Gy in 33 fractions followed by consolidation pemetrexed.
Unfortunately, pemetrexed proved to be inactive in SCLC. Jalal et al. evaluated single-agent activity of pemetrexed in relapsed SCLC and reported disappointing response rates (28). The interim analysis of the GALES trial, a phase III trial comparing carboplatin

with etoposide versus carboplatin with pemetrexed, showed that the pemetrexed arm was unable to meet the predefined endpoint of noninferiority. Overall response rates were also inferior for the pemetrexed arm (24.9% versus 40.5%, $p<0.001$) (24). Recent evidence suggests that tumors associated with a high expression of thymidylate synthase (TS) may be resistant to the effects of pemetrexed; recently it is shown that TS expression is high in SCLC, explaining the minimal activity of pemetrexed in SCLC (29,30).

In conclusion, the combination of full doses of cisplatin (75-80 mg/m^2) and pemetrexed 500 mg/m^2 with concurrent radiotherapy up to 50 Gy (25 x 2 Gy) is well tolerated. Pemetrexed is the first 3rd generation cytotoxic found to be tolerable at full dose with concurrent radiotherapy. Further studies in locally advanced NSCLC are warranted.

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CHAPTER 4

Lessons to learn from EORTC study 08981: A feasibility study of induction chemoradiotherapy followed by surgical resection for stage IIIB non-small cell lung cancer

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ABSTRACT

The present EORTC phase II feasibility study in stage IIIB (T4-N3) NSCLC was conducted to investigate whether an induction regimen with concurrent chemo-radiotherapy followed by surgery after restaging by re-mediastinoscopy and /or fluorodeoxyglucose-positron emisson tomography (FDG-PET) was feasible in a multicenter setting. Unfortunately, the study closed prematurely because of poor accrual. The combination of more stringent selection criteria, the incorrect prevailing view of Ethical Boards that a trimodality approach is too toxic, competing studies in the participating centers and the fact that patients with N3 disease could only be enrolled if a re-mediastinoscopy could be performed, underlie the low accrual. Although this study illustrate that the conduct of a tri-modality study in centers across Europe appeared to be difficult at that time, the number of centers with highly qualified and experienced specialists involved in this kind of multi-modality approaches is rapidly increasing. Future initiatives should, therefore, certainly be encouraged. Minimally invasive procedures such as EUS and EBUS should preferably be used for up-front mediastinal staging, mediastinoscopy with or without EUS should preferably reserved for restaging, and right-sided pneumonectomies should be avoided. Though evident, the feasibility to complete this kind of studies within a reasonable time period, is still a condition sine qua non.

INTRODUCTION

The overall prognosis of locally advanced non-small cell lung cancer (NSCLC) stage IIIB (any T4 or N3) is poor, and primary surgery is rarely possible. Standard treatment for clearly unresectable disease is sequential or concurrent chemoradiotherapy with full dose chemotherapy (1). Several studies have demonstrated that locally advanced, potentially resectable and unresectable stage IIIA NSCLC may become operable after induction chemo- or chemo-radiotherapy (2,3). The strongest predictor of long-term survival after such an induction treatment appears to be the absence of residual tumor in the mediastinal lymph nodes at surgery, the so called down-staged patients (4-6).
Based on the promising results of induction therapy for stage IIIA (2, 7-9), the SWOG investigated if a tri-modality treatment was also feasible for stage IIIB NSCLC (study 8805) (2). A 3-year survival rate of about 25% was found, without survival difference between stage IIIA and IIIB. Again, the prognosis with persistent N2 or N3 disease after induction therapy was poor, with 5-year survival rates of about 15%. Although the induction treatment was different in subsequent trials (number of chemotherapy cycles, different drugs, standard or hyperfractionated radiotherapy), the resectability rate was similar at about 60%, with a pathologic complete remission rate of about 20% (10-14). It is evident now, that persistent N2 or N3 disease after induction treatment is a contra-indication for further surgery (3, 4, 15), and that only those who are downstaged benefit from induction therapy followed by resection. Despite these promising results, the potential role of a surgical resection following chemotherapy (with or without radiation) is still controversial. The series published so far are usually limited to single institutional experiences and are listed in Table 1 (2, 16-18). Proper and reliable restaging after induction therapy is crucial in order to prove down-staging. Except for the study by Stamatis et al., restaging has been based on CT evaluation, known to be inappropriate for mediastinal staging and restaging with a low accuracy (19). Therefore, the Lung Cancer Group of the European Organisation for Research and Treatment of Cancer (EORTC) decided, to investigate by study 08981 the feasibility of a tri-modality approach of chemoradiotherapy followed by restaging, with the re-mediastinoscopy and resection in a multicenter setting and this before the publication of the study by Stamatis et al. (16).

EORTC 08981 study design, methods and results

The EORTC 08981 study was designed as a prospective, non-randomized phase II feasibility study to determine the incidence of radically resected stage IIIB NSCLC following induction chemoradiotherapy. The secondary end-points were the toxicity of the

induction regimen, the toxicity of the surgical procedure, the clinical response rate after the induction therapy and pathological response after surgery. Based on the Simon one sample two stage testing procedure (20), considering an unacceptable and an acceptable success rate of respectively 40% and 60%, the total sample size was estimated to be 62 eligible patients with an alpha error of 0.10 and a power of 0.95. In this multi-center study only patients with clinical stage IIIB NSCLC (any T4 or N3) could be enrolled. Important selection criterion for the participating centres was, however, that the thoracic surgeon was capable to perform a re-mediastinoscopy in case of N3 disease. If that particular expertise was not present, only patients with T4N0M0 NSCLC were enrolled. The T4 status had to be histologically confirmed. Patients with pleuritis carcinomatosis or N3 due to scalene or supraclavicular lymph node involvement were excluded. Induction chemotherapy treatment consisted of 3 cycles of cisplatin 80 mg/m^2 on day one and etoposide 100 mg/m^2 on day 1-3 intravenously. Involved field radiotherapy consisted of 45 Gy in 1.8 Gy per fraction, for 5 days a week over a period of 5 weeks starting from day 2 of chemotherapy cycle 2. Patients with T4 N0-1M0 disease without progression during induction therapy, proceeded directly to surgery without re-staging. If a FDG-PET facility was available, a PET scan was done at baseline. If initial PET positive mediastinal lymph nodes became PET negative at restaging, patients were allowed to proceed directly to thoracotomy without re-mediastinoscopy. When the PET scan remained positive, however, a re-mediastinoscopy had to be performed to exclude persistent N2/3 disease. If there was no PET facility available, patients with N2 or N3 disease without progression during induction therapy had to undergo a re-mediastinoscopy.

Of the initial 10 European thoracic oncological centers expressing their interest in this trial, only 5 centers were eventually activated. Between May 2001 and August 2002, five male patients were enrolled in 2 centers. Median age was 67 years (range 60-74 years), all of them with WHO performance score 0 or 1. One patient progressed during induction treatment, and did not undergo restaging or surgery. One patient was restaged by endoesophageal ultrasound (EUS) instead of a re-mediastinoscopy. Grade 3/ 4 neutropenia or trombocytopenia occurred in 4 (80%) and 2 patients (40%), respectively. Half of them relapsed loco-regionally, the others on distant sites. Both patients who underwent a right-sided pneumonectomy developed a bronchopleural fistula.

DISCUSSION

Although it is evident that EORTC study 08981 is a negative study, several other investigators have demonstrated that a tri-modality approach is feasible with acceptable toxicity. Examples of this are the large Intergroup trial of North America, the German Lung Cancer Cooperative Group Study, the studies performed by the West German Cancer Center Consortium, the Italian and French tri-modality experiences and several phase-II studies performed in North America (11,16-18).

The participating centers in EORTC study 08981 were large institutions, experienced in chemo-radiation, where multidisciplinary tumor board meetings take place weekly. Therefore, other reasons may underlie the discrepancy found with the studies published before. One of them is that we used more stringent selection criteria (Table 1). In our trial the T4 status had to be confirmed histologically and patients with supraclavicular

Table 1. Differences in the selection criteria and restaging methods in trimodality trials for stage III non-small cell lung cancer.

	Stamatis (16)	Grunewald (17)	SWOG 8805 (2)	INT 0139 (18)	EORTC 08981
Number of patients	174 IIIB 218 IIIA	40 IIIB	51 IIIB 75 IIIA	429 IIIA	5 IIIB
Recruitment period	10 years	3 years	4 years	7 years	2 years
Participating institutes	Single	Single	Multiple	Multiple	Multiple
Supraclavicular LN's	No	Yes	Yes	No	No
T4 esophagus, aorta, vertebrae	No	No	Yes	Not	No
sattelite nodule	No	No	Not mentioned	applicable	No
myocardium	No	No	Not mentioned		No
malignant pleural/pericardial effusion	No	No	No		No
Lower lobe tumors with contralateral upper mediastinal LN's	Yes	Yes	Yes	Not applicable	No
N2 and N3 confirmation method	Histology	Histology	Histology	Histology	Histology
T4 confirmation method	CT or MRI	Histology	Histology	Not applicable	Histology
Restaging method	Mediastinoscopy	CT scan	CT scan	CT scan	Mediastinoscopy

lymph node involvement or lower lobe tumors with contralateral upper higher mediastinal lymph node involvement were excluded. In contrast, in the SWOG 8805 trial, 35% of the IIIB patients had N3 disease based on supraclavicular lymph node involvement. With the current available data, IIIB patients with supraclavicular lymph node involvement should, to our opinion, not be enrolled in tri-modality protocols. Machtay et al.

reported a prolonged survival in a non-randomized study in patients with supraclavicular node metastases treated with chemoradiotherapy (21). On the contrary, Lee et al. demonstrated that patients with supraclavicular lymph node involvement treated with chemoradiotherapy had a median survival of only 12 months while it was 28 months for patients without supraclavicular lymph node involvement, which was statistically significant (22).

A second major reason for the slow accrual is that our restaging method was different from those in the other studies (Table 1). CT evaluation is known to be inappropriate for the staging and restaging of the mediastinum (19) and only patients with cytological or histological confirmed downstaging (2,4) benefit from resection. Therefore, re-mediastinoscopy received a central role in the restaging of our patients. Even though two centers with surgeons experienced in performing re-mediastinoscopy participated, it appeared to be a major threshold for patient enrollement. Due to extensive fibrosis and difficult access, re-mediastinoscopy leads to more complications and often incomplete sampling of the mediastinum (23,24). Only few studies addressed the role of re-mediastinoscopy in the restaging of lung cancer (25-30). Although Van Schil et al. demonstrated that a re-mediastinoscopy has an accuracy of 85% and a negative predictive value of 75% (25), only a small number of patients had undergone radiotherapy, so that no final conclusions can be drawn for the role of the re-mediastinoscopy after chemoradiotherapy (29). De Leyn et al. showed in a prospective trial that re-mediastinoscopy is technically feasible, but the sensitivity and negative predictive value are low due to fibrosis (30). Although mediastinoscopy is still regarded the gold standard for mediastinal staging, minimally invasive staging procedures such as EUS (31-37) and EBUS (36) are attractive alternatives, available in an increasing number of institutions. A combined approach of EUS- and EBUS-fine needle aspiration even allows the investigation of both sides of the mediastinum (36). This evolution might lead in an increasing number of institutions to a shift in the sequence of mediastinal staging procedures. Upfront staging could be done by minimally invasive procedures such as EUS and EBUS, while surgical procedures could be reserved for playing a role in restaging after induction therapy (29). In this way, a technically more difficult re-mediastinoscopy is avoided. FDG-PET has not yet proven to be enough accurate in mediastinal restaging. Initial promising data for the assessment of downstaging of mediastinal lymph nodes could not be confirmed (37,38). Changes in the microenvironment of the tumor, such as altered perfusion after chemo- or chemoradiotherapy, may impair the presentation of FDG to the metastatic mediastinal node sites. Thus, PET-imaging is not performant enough to detect persistent N2/3 disease. Induction chemoradiotherapy results in a high percentage of false positive findings as a result of inflammatory reactions after radiotherapy. Therefore, restaging

should currently use invasive techniques, although FDG-PET may help to guide these procedures. Although the optimal restaging strategy is yet unknown, it should at least take place as soon as possible after the completion of the induction treatment to avoid long interruptions in the scheduled radiotherapy if no downstaging has been achieved.
Despite initial expression of interest in EORTC study 08981 by 10 large European cancer institutes, the Medical Ethical Boards of five institutes considered the tri-modality approach too controversial for this particular group of patients and did not gave their approval. On the other hand, in the centers that received Medical Ethical Board permission, competing studies targeting the same patient group appeared to be ongoing afterwards.
The prevailing view of many Medical Ethical Boards that a tri-modality approach for stage III NSCLC is inappropriate, is very debatable, given the fact that, for example, in superior sulcus tumors, a tri-modality approach is the standard of care.
The recent results of the EORTC 08941 and the Intergroup study 0139 have shown however, that the extent of surgery determines the postoperative mortality and that in a subgroup in which the resection was confined to a lobectomy there was a survival benefit. Although these two studies have not been designed to explore the effect of the extent of the resection, this subgroup analyses suggest that especially right-sided pneumonectomies should be avoided (5,12).
Although the number of participants in this trial is low and no final conclusion can be drawn, the results of the five included patients are disappointing with a high rate of pneumonectomies, major complications after a right-sided pneumonectomy and poor overall survival.
In conclusion, although this study illustrates that the conduct of a tri-modality study across Europe appeared to be difficult in the 1990s, the number of centers with highly qualified and experienced specialists involved in this kind of multi-modality approaches has rapidly increased since then. Future initiatives should, therefore, certainly be encouraged. Therefore it is very important to ensure full commitment of all investigators involved in tri-modality treatment. Minimally invasive procedures such as EUS and EBUS should preferably be used for up-front mediastinal staging, mediastinoscopy with or without EUS should preferably be reserved for restaging, and especially right-sided pneumonectomies should be avoided. Though evident, the feasibility to complete the study within a reasonable time period is still a condition sine qua non.

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Conflict of Interest Statement

None declared

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CHAPTER 5

Stage IIIA-N2 NSCLC: a review of its treatment approaches and future developments.

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ABSTRACT

Few issues are as controversial in non-smal cell lung cancer as the management of patients with stage IIIA-N2 non-small cell lung cancer. This manuscript reviews the reasons of and the biases inherent to this controversy and discusses the different treatment approaches with emphasis on survival, as evidenced by meta-analyses and large randomized clinical trials. Prospects on novel treatment modalities and future research opportunities are presented.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) represents 80% of all lung cancers, and approximately 15% of these are at presentation diagnosed with stage IIIA [1]. The definition of stage IIIA has changed with the successive editions of the UICC staging classification, since it was first coined (Table 1) [2]. According to the 6th edition, stage IIIA includes patients with either malignant involvement of one or several ipsilateral mediastinal lymph node(s) or T3N1 tumours [1]. In the new proposed classification, T4 tumours without mediastinal lymph node invasion (N0-1) will be added to this stage [3].

Table 1: definition of stage IIIA according to successive editions of the UICC TNM-staging classification of lung cancer

UICC edition	5	6	7 (proposed)
Reference	[2]	[1]	[3]
T and N categories included in IIIA	T3N0-1 T1-3 N2	T3N1 T1-3 N2	T3N1 T1-3 N2 T4N0-1

Ruckdeschel et al. [4] and André et al. [5] have proposed to subclassify stage IIIA according to the extent of mediastinal lymph node involvement, as the latter has an inverse correlation with survival. This classification has been the basis for the recent ACCP-guideline [6] and is presented in Table 2 in a slightly adapted version.

Table 2: subclassification of stage IIIA , adapted from [4-6]

Subcategory	Definition	Frequency
IIIA-0	T3N1 or T4N0-1 without N2 involvement	6% of NSCLC at presentation, 32% of stage IIIA [1]
IIIA-1	Incidental nodal metastases found on final pathology examination of the resection specimen	Up to 14% of thoracotomies [9,10]
IIIA-2	Nodal (single station) metastases recognized intraoperatively	
IIIA-3	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)	10% of NSCLC at presentation, 67% of clinical and pathological stage IIIA

A first subgroup of stage IIIA patients consists of tumours with locoregional extension without mediastinal lymph node involvement (IIIA-0). Due to the novel definitions of T3 and T4 and the inclusion of T4N0-1 tumours in stage IIIA in the new proposed classification, it is likely that this subgroup will numerically increase in the future from the present day one third fraction. The treatment of this subgroup is not the focus of the present review.

A second subgroup contains patients with so-called unexpected N2-involvement in the pathology specimen (IIIA-1) or at thoracotomy (IIIA2), found in 14-24% of patients [7, 8]. The introduction of more accurate preoperative staging techniques has resulted in conflicting data on the rate of unsuspected IIIA-1- involvement. Gonzalez et al. report a 8% false negative mediastinal lymphnode staging with systematic PET-scan and selective mediastinoscopy in 90 cM0 operable patients, which compares with their 6% false negative rate using routine mediastinoscopy approach in a similar prior cohort of patients [9]. Cerfolio et al. however still found 14% unsuspected microscopic N2 (IIIA-1) in their consecutive series of NSCLC, considered N2 negative after integrated PET-Ct scan [10]. The same authors picked up 16 of 22 cases with microscopic N2-disease using routine mediastinoscopy and endoscopic transesophageal ultrasound with fine needle aspiration (EUS-FNA) in 153 patients with clinically N2-negative mediastinum after integrated PET-Ct scan [11].

The largest subgroup of stage IIIA consists of patients with clinical ipsilateral lymph node invasion at presentation, either demonstrated by non-invasive imaging or (minimally) invasive techniques (IIIA-3) or 'bulky' at imaging (IIIA-4). Patients from the IIIA-3 subgroup are variously regarded 'resectable' or 'marginally resectable', depending on the number and location of the lymph node(s) involved, whereas patients from the IIIA-4 subcategory are considered 'primary unresectable' [12]. Table 3 summarizes the survival data of several registries and large data sets of these patients.

Table 3: Outcome of resected stage IIIA-N2 patients according to several registries

Source	UICC 5 data set		UICC 6 data set		JJC-LCR data set		German registry	Mayo Clinic	UICC 7 data set	
Reference	2		1		13		14	15	3	
Period	1975-1988		1975-1988		1999		1996-2005	1997-2003	1990-2000	
Clinical (C) or pathological (P)	C	P	C	P	C	P	P	C	C	P
N of pts with N2 (% of all pts in series)	NA	NA	471 (9)	344 (18)	1628 [2] (13)	1862 [2] (15)	431 [3] (21)	714 [4] (13)	2832 [5] (12)	4441 [5] (16)
Median survival (m)	12*	18*	12*	18*	36*	34*	24*	16.4	24*	24*
1 y (%)	50*	60*	50	64				62	71	69
2 y (%)	17*	45*	26	40	60*	60*	50*	38	50*	45*
3y (%)			19	32				26		
4 y (%)	12*	35*	15	26	44*	40*	32*	15	35*	29*
5 y (%)	10*	30*	13	23	38	33	30	8	31	22

UICC: Union Internationale Contre Le Cancer; JJC-LCR: Japanese Joint Committee-Lung Cancer Registry.

NA: not available; *: data extrapolated from Kaplan Meier curves; [2]: includes an unspecified number of T3N1; [3]: includes 9 cases of T4N2; [4]: includes 43 cases of T3N1 and 18 of TXNXM0; [5]: includes 134 cases of cT4N2 and 217 of pT4N2; all c patients were operated upon.

All percentages are rounded to the next unit

The observed variation in outcome reflects the stage-specific shift in survival by improving staging techniques and changing staging classifications and adds to the caution when using historical series in comparisons.
It is assumed that the fraction of IIIA-3 patients will remain unchanged in the near future: whereas on the one hand, the advent of FDG-PET/Ct-scan and endoscopic ultrasound techniques will upstage about 10% of stage III patients to either N3 or M1 [16], the same techniques will on the other hand upstage a number of lower stage patients to IIIA-3 [11]. When looking across the UICC datasets of 1997 and 2007 [1, 3], the fraction of clinical N2 patients has hence increased from 9 to 12%.

METHODS

This article reviews the treatment approach for stage IIIA-N2 NSCLC, with emphasis put on evidence obtained by randomized trials, systematic reviews, pooled analyses, meta-analyses and guidelines. This evidence was obtained as follows:

(i) a PubMed search using the key words as mentioned in the abstract, applying separately the instruments' default limits [Meta-Analysis], [Practice Guideline], [Randomized Controlled Trial] and [Review]
(ii) a manual search of recent guidelines [ESMO, ACCP, NICE, NCCN] and their cross-references, published between 2005 and 2008
(iii) a manual search of congres proceedings of ASCO, WCLC, ESMO since 2005.
(iv) a search of www.clinicaltrials.gov using the key words as mentioned in the abstract and cross referencing with (i) and (iii).
(v) Data were whenever possible recalculated for IIIA-N2 patients and the latest source used whenever double reports of the same series were retrieved.

Single modality surgery

Two studies have examined the survival of 79 patients following complete resection who were positive at mediastinoscopy [17]. The studies showed a 5-year survival of between 9% and 18%. It is less than the outcome of N2 patients with negative mediastinoscopy but involves few patients. A systematic review of 5 studies (735 patients with radiologically identified N2-disease prior to resection) found a variable 5-year survival ranging from 8-31% (weighted average 23%) [17]. However, three of the studies included adjuvant radiotherapy with or without chemotherapy. Failure was in more than half of the cases due to distant relapses, originating from occult micrometastatic disease

Table 4: Pooled analyses of outcome of stage IIIA patients treated with surgery with and without peri-operative therapy

Reference	Pignon et al [19]	Lim et al [20]	Stewart et al [21]	Le Péchoux et al [22]	PORT [23]	Berghmans et al[41]	Lim et al [20]	Burdett et al [40]
Type of perioperative therapy	+/- adjuvant chemotherapy	+/- adjuvant chemotherapy	+/- adjuvant chemotherapy	PORT +/-adjuvant chemotherapy	+/- adjuvant radiotherapy	+/- neoadjuvant chemotherapy	+/- neoadjuvant chemotherapy	+/- neoadjuvant chemotherapy
Type of analysis	Pooled data	Pooled data	Individual patient data	Individual patient data	Pooled data	Pooled data	Pooled data	Individual patient data
N trials in the analysis	5	22	15*	12	10	5	10	7
n patients with IIIA/ n patients with N2	1247/NA	NA	1020/NA	1596/NA	809/550	376/NA	NA	988/NA
HR (95% CI)	HR: 0.83 (0.73-0.95)	HR: 0.80 (0.74-0.87)	HR: 0.92 (0.78-1.08)	HR: 0.89 (0.81-0.97)	HR: 0.97 (0.82-1.14)	HR: 0.65 (0.41—1.04)	HR: 0.81 (0.67-0.97)	HR: 0.82 (0.69-0.97)
Absolute benefit at 5 year (95%CI)	13%	15%	3%	4.4% (1-8)	3%	Not specified	14%	6-7%

*: only trials not containing Tegafur/UFT; NA: not available; PORT: postoperative radiotherapy; HR: hazard ratio with 95% confidence intervals (CI)

missed at clinical staging. From series that have reported on prognostic subgroups of pN2, the only conclusion that can realistically drawn is that multistation nodal disease has a somewhat worse prognosis than single station involvement, but the site of a single metastatic nodal station probably has no significant effect [reviewed in 6]. This analysis was confirmed by the IASLC-staging committee database wherein three nodal groups were found to have significantly different survival rates: patients who had pN1 single-zone disease, those who had either multiple pN1 or single pN2 zone metastases, and those who had multiple pN2 lymph node zones involved [18].

Postoperative chemo- and radiotherapy

The poor survival rates with surgery has led to efforts at adding non-surgical (chemo- and/or radio-) therapy with hopes to improve long term survival by reducing the distant relapses. Several randomized trials have shown an improved survival with cisplatin-based postoperative chemotherapy. This evidence has been pooled in a recent meta-analysis in which the subgroup of pIIIA patients (mostly but not exclusively pN2) appear to have a 17-20% reduction in the risk of death (Table 4), improving their 5 year survival rate with 13-15% [19,20]. The benefit of overall survival was however, smaller in an individual patient data meta-analysis of randomized trials addressing the benefit of adjuvant chemotherapy on surgery [21], but included an improved local recurrence free interval and persisted when postoperative radiotherapy (PORT) was added to surgery [22].

Although PORT was shown to have a significant detrimental effect on overall survival in stage pI-II, the pooled data in pN2 patients show no clear difference but a small reduction in local recurrence [23]. Results from a subgroup analysis of a randomized trial addressing adjuvant chemotherapy [24] and from a retrospective epidemiological study [25] suggest benefit of PORT on overall outcome in stage IIIA .This issue is currently being prospectively studied in the LUNG-ART trial [26].

Post-induction surgery

Parallel to the abovementioned adjuvant therapies, the same non-surgical approaches were added preoperatively in order not only to reduce the distant relapse rate, but aiming at a possible parenchyma-sparing resection and better compliance to chemotherapy. The medical literature is replete with phase 2 series reporting the outcome of patients with stage IIIA NSCLC treated with this neoadjuvant approach [6]. A systematic review reported tumour response to preoperative (primary) chemotherapy from six prospective

phase II trials in patients with stage IIIA or IIIB NSCLC [27]. The review reported a non-weighted average effect size for radiological response rate of 64%, a disease progression of 4% and for histological complete response of 24% of patients. Survival is improved as compared with historical controls and is influenced by patient age, complete resection, pathologic stage, nodal downstaging and extent of resection, but not by the type of induction regimen, chemo-or chemoradiotherapy [28-30].

Most if not all series have administered 2 to 3 cycles of a platinum combination, as these regimens were consistedly used in advanced NSCLC and associated with the highest response rates. The latter are typically higher in stage IIIA, with figures varying from 50-70%. Although no formal randomized comparison between different neoadjuvant regimens in stage IIIA-N2 has been conducted, the available non-randomized evidence shows that 3-drug combinations are not superior to 2-drug ones, and that combinations of platinum and third generation drugs are equivalent and more active than combinations with second generation drugs [31]. For fear of toxic interaction, series with concomitant chemoradiotherapy have mostly used second generation combinations, e.g. cisplatin with either etoposide or a vinca alkaloid.

Three randomized trials have compared chemotherapy and chemoradiotherapy as induction regimen in stage III NSCLC [32-34]; 1 more is ongoing and 1 has been prematurely closed due to a lack of accrual (Table 5) [35-37]. Taken together, these trials suggest that induction chemoradiotherapy results in better rates of resectability, pathological downstaging and pathological complete remissions than chemotherapy alone, without significantly affecting overall or progression-free survival survival. Two small randomized trials have compared surgery preceded by either neoadjuvant chemotherapy or radiotherapy [38,39]. Their results are inconclusive and difficult to interprete due to a small sample size, per protocol analysis and the variable use of perioperative chemo- and radiotherapy across treatment arms.

Twelve randomized trials have compared neoadjuvant chemotherapy followed by surgery versus surgery alone in patients with stage IIIA NSCLC with variable numbers of N2-involvement [reviewed in 6]. A number of these trials have not yet been published as full papers. Table 4 summarizes the available evidence as pooled analyses of survival data of these trials [20, 40, 41]. It can be concluded that a significant benefit in favour of neoadjuvant chemotherapy is present ranging at 5 years from 6-14%, albeit weakened by confounding factors as the inhomogeneity of the patients included, the inadequate sample size and the variable addition of postoperative treatments. The use of chemotherapy prior to surgery has raised concern that surgical complications may be increased. A series of 335 patients (259 surgery alone, 76 chemotherapy followed by surgery) was studied out of 380 consecutive patients undergoing lobectomy or

Table 5: randomized trials comparing induction chemotherapy and chemoradiation in stage III NSCLC

Reference	N	Treatment	Complete resection rate (%)	Rate of pathological downstaging (pD) and complete remission (pCR) (%)	Progression free (PFS); overall survival (OS)
Fleck [32]	48	P-5FU + RT ->S-PORT	52	NA	PFS at 3y: 40%
	48	MVP->S->PE	31	NA	PFS at 3y: 21%
Sauvaget [33]	44	MVP->S	55	pD +pCR: 50	Median OS: 19 m
		MVP->P-5FU -> S	66	pD +pCR: 58	Median OS: 18.5 m
GLCCG [34]	260	PE ->S ->PORT	32%	pD: 11; pCR: 7	Median PFS: 9.5 m Median OS: 17.6 m
	264	PE->CV+HFRT ->S	37%	pD: 17; pCR: 22	Median PFS: 10 m Median OS: 15.7m
RTOG 0412 [35]	NA	Carbo-paclit -> S		Trial stopped due to low accrual	
		Carbo-paclit +RT ->S			
National Cancer Center, Korea [36]	NA	PE->S		Ongoing	
		PE + RT -> S			
SAKK 18/00 [37]	NA	PD -> S		Ongoing	
		PD -> RT ->S			

Abbreviations: S: Surgery; RTOG: Radiation Therapy Oncology Group; SAKK: Swiss Anti Cancer Coalition; CTRT: concomitant chemoradiation; PORT: postoperative radiotherapy; PE: cisplatin-etoposide; CV: carboplatin-vindesine; RT: radiotherapy; HFRT: hyperfractionated radiotherapy; PD: cisplatin-docetaxel; 5FU: 5-fluorouracil; MVP: mitomycin C-vindesin-cisplatin; NA: not available

larger resection [42]. The use of preoperative chemotherapy did not significantly affect morbidity or mortality overall, based on clinical stage, postoperative stage, or extent of resection. No significant differences in overall or subset mortality or morbidity including pneumonia, acute respiratory distress syndrome, reintubation, tracheostomy, wound complication or length of hospitalization were seen. In another series, 470 patients treated with induction chemotherapy and surgery from 1993 through 1999 were reviewed [43]. Univariate and multivariate methods for logistic regression model were used to identify predictors of adverse events. Overall, a surgical mortality rate of 4% was found, which compared favourably to other primary surgery studies. Total morbidity and major complication rates were 38% and 27%, similar to previous primary surgery studies. The authors concluded that overall morbidity rates were not significantly affected by the use of induction therapy. They reported an operative mortality rate of 24% for patients undergoing right pneumonectomy following induction therapy. This number was higher than previous mortality rates seen in trials where patients did not have induction therapy. The authors recommended that right pneumonectomy after induction therapy can be performed very selectively and only when no alternative resection is possible.

Neoadjuvant carboplatin and paclitaxel increased the perioperative severe complications in a cohort of 34 patients compared with a similar cohort of 67 patients operated

by the same surgeons [44]. The most common complication was the failure to respond to antibiotics given for pneumonia. Investigators in France reviewed 114 patients who underwent thoracotomy following induction chemotherapy [45]. In this series, there was only 1 death following pneumonectomy in 55 patients.
Overall morbidity rate was 29%, similar to other surgical series. The authors concluded that preoperative chemotherapy did not increase postoperative morbidity and mortality.
A German cooperative group compared preoperative chemotherapy and concomitant chemoradiation and observed a doubling of the mortality rate (4.5 versus 9.2%) with the latter [34]. Another French group reported a 30-day mortality of 6.7% in a series of 60 patients undergoing pneumonectomy after induction chemotherapy [46]. A Canadian group reported a 27% overall mortality after 27 pneumonectomies and even a 50% for complex pneumonectomies. Causes of death were adult respiratory distress syndrome and postoperative hemorrhage [47].
Although the abovementioned series give conflicting results, most experts agree that after induction treatment, a pneumonectomy should be avoided, and that the use of concomitant chemoradiotherapy further increases the operative mortality, even in experienced centers.
Based on the observed improvement, neoadjuvant chemotherapy followed by surgery quickly became the new standard of care for clinical stage IIIA NSCLC and prospective series and studies in homogenous N2-subgroups confirmed the earlier results with even better outcome, albeit selection and stage migration biases cannot be excluded and the results look less favourable when analysed on an intention- to- treat basis than on per-protocol basis [48-50]. Whether chemotherapy should hence precede or follow resection is likely to require a large randomized trial. Taking into account the heterogeneity of trials and the limited intertrial comparability between neoadjuvant and adjuvant populations, both induction and adjuvant chemotherapy seem to result in a benefit of the same magnitude in stage IIIA-N2 patients and such a trial will probably show equivalence of the approaches [20].

(Post-induction) radiotherapy and chemoradiotherapy

A full review of this topic is beyond the scoop of this manuscript. The interested reader is referred to a number of recent in-depth reviews [6,51]. The issue is further blurred by the lack of discrimination between stages IIIA and B in the studies reported. The following landmark findings are however evidence-based by meta-analyses (Table 6):

Table 6: Individual patient meta-analyses of outcome of stage IIIA patients treated with chemoradiotherapy

Comparison	Reference	Arms	N pts with IIIA	Hazard ratio 95% CI
Radiotherapy versus radiotherapy combined with platinum-based chemotherapy	Rolland et al [52]	Radiotherapy	449	0.91 (0.79-1.05)
		Platinum-based concomitant chemoradiotherapy	548	
Radiotherapy versus sequential chemoradiotherapy	Rolland et al [52]	Radiotherapy	723	0.87 (0.78-0.97)
		Sequential chemoradiotherapy	741	
Radiotherapy versus combined chemoradiotherapy at sensitizing dose	Aupérin et al [53]	Radiotherapy	490	0.81 (0.71-0.92)
		Concomitant chemoradiotherapy	592	
Sequential versus concomitant approach at systemic doses of chemotherapy	Aupérin et al [55]	Sequential chemoradiotherapy	190	0.72 (0.58-0.90)
		Concomitant chemoradiotherapy	188	

1. Adding platinum-containing chemotherapy either at systemic doses preceding or at low radiosensitizing dose concomitant with chest radiotherapy in good performance patients significantly improves the outcome as compared to single modality chest radiotherapy with traditional dose and fractionation schedules (1.8-2.0 Gray (Gy) per fraction per day to 60 to 70 Gy in 6-7 weeks), which yields in poor survival rates and patterns of failure which are both locoregional and distant [52,53]. Although the evidence was already observed in a previous meta-analysis, the latter did not specifically analyse for stage IIIA and for the sequence in which both modalities were administered [54].
2. Concomitant chemoradiotherapy at systemic doses results in superior outcome as sequential chemoradiotherapy, at the cost of a moderately increased toxic morbidity and is considered the present standard of care in selected patients [55]. Five year survival rates of 15% in a mixed population of selected stage III patients seem hence achievable and are comparable to unmatched series using a surgical approach.
3. In all meta-analyses, the effect was observed to be independent of patient and tumour characteristics, substage (IIIA vs. IIIB) and time period in which the trials were conducted.

Definitive-dose thoracic radiotherapy should be no less than the biologic equivalent of 60 Gy, in 1.8-Gy to 2.0-Gy fractions to the planning target volume (PTV) [56]. Ideally, this requires 3-dimensional (3D) conformal radiotherapy, a technique characterized by beam outlines that match the shape of the PTV. Mapping of the PTV is improved when using information from FDG-PET/CT-scan and-whenever available- from the (minimally) invasive mediastinal staging techniques, to match the closest possible the actual 'involved field' (IF). PTV-tailored fields allow the administration of higher total radiation doses which have been associated with improved local control and better survival in retrospective series without concomitant

chemoradiotherapy [57]. However, due to the lack of randomized data the relationship between radiation dose, tumor volume and survival is still debated [58]. The field of (thoracic) radiotherapy is rapidly moving with dose-localization techniques aiming at irradiating the tumour with near surgical precision and at higher dosages, reducing the frequency of the radiation associated pneumonitis and esophagitis [59]. It is hence expected that local control of the tumour will further improve in the near future with less morbidity. Distant failure pattern will have to be addressed by more and better systemic therapy, either using cytotoxic or biological agents. However, adding more chemotherapy before or after a concomitant chemoradiotherapy regimen has not been associated with improved survival [60-62].
One small randomized trial has compared radiotherapy and neoadjuvant chemotherapy followed by surgery [64]. The trial was stopped prematurely and did not show any difference in outcome.

Neoadjuvant chemo(radio-) therapy followed by either radiotherapy or surgery

Adding a systemic treatment to either locoregional modalities-surgery or thoracic radiotherapy- was hence associated with an improved outcome in uncontrolled trials. With opinions differing with regard to the standard approach, investigators embarked on strategies comparing which local treatment modality is most effective. In a systematic review from 2006, 2 randomized trials were mentioned [65]. In one study, the inclusion criteria included the demonstration of pathological N2 disease [66] but the TNM status of participants was not well described in the other study [67]. These trials were diverse in terms of the interventions and populations and therefore not suitable for pooled analysis. In none of the studies was the surgical treatment arm found to be significantly superior to the nonsurgical group in terms of overall survival. A pooled analysis of the two studies comparing chemotherapy followed by surgery with chemotherapy followed by radiotherapy found a significant statistical heterogeneity between these studies, so a pooled analysis was not performed [65]. In one study there were two treatment related deaths in the chemotherapy/surgery group and one in the chemotherapy/ radiotherapy group [66]. Treatment related deaths were not described in the other trial [67]. Taylor et al. observed an equivalent outcome in patients randomized to either concurrent chemoradiation or induction chemotherapy followed by resection [68]. However, patients undergoing induction C/S often needed postoperative RT to achieve local control equivalent to that achieved with concurrent CRT.
The European Organization for Research and Treatment of Cancer (EORTC) performed a large multicenter randomized trial to compare surgery with radiotherapy in patients

with stage IIIA-N2 NSCLC who showed response to induction chemotherapy [69]. There was no significant difference in median survival (17.5 months in the radiotherapy arm versus 16.4 months in the surgery arm), 5-year overall survival (14% versus 16%) or progression-free survival (Table 7). Patients randomized to radiotherapy tended to relapse more frequently in the chest, whereas those randomized to surgery had more distant metastases. In a posthoc unplanned univariate subgroup analysis of the surgical arm, 5-year survival was longer if a radical resection was performed, nodal downstaging was present or if a lobectomy was performed. The authors concluded that, after a radiologic response to induction chemotherapy, surgery is not superior to radiotherapy, which remained the preferred treatment in view of its lower morbidity and mortality.

US investigators conducted the Intergroup (IG) trial 0139, wherein patients with T1-3 tissue proven N2M0 NSCLC and Performance Status of 0-1 were randomized between induction chemoradiotherapy followed by either surgery or consolidation radiotherapy to 61 Gy. PORT was optional in case of incomplete resection. Both arms received con-

Table 7: Randomized trials in stage IIIA-N2 NSCLC comparing surgery and radiotherapy as locoregional modalities after induction chemo(radio)-therapy

Study (reference)	EORTC 08941 [69]		Intergroup 0139 [70]	
Treatment arm	Induction chemotherapy + surgery	Induction chemotherapy + radiotherapy	Induction chemoradiotherapy + surgery	Chemoradiotherapy
Number of patients with IIIA-N2	167	166	202	194
Chemotherapy regimen	Platinum based	-	Cisplatin-etoposide	-
Radiotherapy total dose (Gray)	-	60	45	61
Rate of pneumonectomy/ (bi-)lobectomy/ exploratory thoracotomy (%)	47/ 38/ 14	-	27/ 49/ 4	-
R0 resection rate(%)	50	-	71	-
Treatment related mortality rate (%)	4	<1	8	2
Pathological nodal downstaging rate (%)	41 (pN0-1)	-	38 (pN0)	-
Pathological complete respons rate (%)	5	-	15	-
Median PFS (months)	9.0	11.3	12.8	10.5
Locoregional failure rate (%)	32	55	10	22
Median OS (months) with 95% CI	16.4 (13.3-19.0)	17.5 (15.8-23.2)	23	22.2
5 y SR (%) with 95% CI	15.7 (10-22)	14 (9-20)	27.2	20.3

PFS: progression free survival; OS: overall survival; R0: microscopically radical resection;

solidation chemotherapy with two cycles of cisplatin/etoposide. The results of this trial are only available as abstract [70]: progression-free survival was significantly better in the surgery group but overall survival did not differ, mainly because of the postoperative mortality (Table 7). Longer follow-up confirms the significantly improvement in progression-free survival but not in overall survival, when surgery follows induction chemoradiation. Three factors were found in multivariate analysis to be associated with improved outcome: lobectomy, pathological downstaging and completeness of resection. An unplanned exploratory analysis showed a significant better survival for patients who underwent lobectomy compared to matched irradiated patients.
An ongoing Danish trial compares consolidation radiotherapy versus surgery with postoperative radiotherapy, both following induction chemotherapy in stage IIIA-N2 NSCLC [71]. This trial started its accrual in 1998 and was expected to have its last patient enrolled in January 2008. Mature results are not to be expected before 2010 at the earliest.

DISCUSSION

Comparing the results of EORTC 08941 and IG 0139 , the following conclusions can be drawn:

1. Although both trials claim to target a population of patients with stage IIIA-N2, they are composed of other subgroups of patients: the EORTC study results are more representative of the IIIA-4 subgroup, while the Intergroup trial reflects IIIA-3 patients. This might already explain the observed absolute differences in outcome between both trials.
2. Both trial show equipoise in overall survival between surgery and thoracic radiotherapy. Although this does not mean that surgery is not feasible or inferior to radiotherapy, the results do not justify a presumption of efficacy of thoracic surgery, nor a defeatism against radiotherapy. In both trials, the operative morbidity and mortality is higher than with radiotherapy in both trials, suggesting that a preference is to be given to the safest approach, regardless of the III-A subgroup studied.
3. The rate of pathological nodal downstaging is low, confirming the low accuracy of radiological response assessment (see further) and a low activity of the induction regimens used. The rate of complete pathological remission with neoadjuvant chemotherapy is lower than with chemoradiotherapy, confirming the results of other aforementioned series [30-32].
4. In both trials local control with surgery is better than with radiotherapy, as the locoregional relaps rate in the EORTC study was higher with radiotherapy and

progression-free survival was better in the Intergroup trial. Although this observation can be credited to the surgical resection only, it cannot be excluded that the administration of PORT in the EORTC trial and an imbalance in the consolidation chemotherapy in the IG-trial are responsible for this finding, as both modalities have been shown to reduce local control [21, 23].

5. Exploratory subgroup analyses of both trials show an improved outcome in patients who are downstaged, and/or in whom a complete resection can be obtained with a lobectomy, as compared to either operated patients without these features, or compared to matched irradiated patients.

Arguments in favour of restricting surgery to certain predictive categories are of a circular kind, as these factors are derived from a multivariable analysis and are then used to categorize the same data. Similar to the procedure in prognostic genomic signatures first isolated by hierarchical clustering in a test set, the predictive validity of these factors should be proven by applying them to a new series, independent from the one from which they were derived. There is a flaw in the promulgation of those factors to select patients who are most likely to benefit from radical surgery, in that they were all defined postoperatively. Completeness of resection can only be defined post hoc, lymph node status is revised as part of pathological staging, and surgeons are not likely to be certain before the operation that a pneumonectomy will definitely not be necessary for an individual patient with stage III, even in one showing radiological evidence of response. This fact is illustrated by the rates of pneumonectomy averaging 25% in some of the best surgical series [48-50]. If physicians are to have a set of predictive criteria upon which to select or counsel their patients, these criteria must be available before surgery and be validated before they can be used.

Paulson defines surgical salvage as the difference between the 5-year survival and the operative mortality rate and considers surgery futile when this figure approaches zero [72]. In the IKA PLUS study [73], the primary outcome measure was the number of futile thoracotomies, defined as the presence after resection of either benign lung lesion; pathologically proven mediastinal lymph-node involvement (stage IIIA–N2) other than minimal N2-disease; stage IIIB disease; explorative thoracotomy for any other reason; or of recurrence or death within one year after randomisation. Similarly to these definitions, one might define a thoracotomy in stage III NSCLC as futile whenever the difference between the 5 year survival rate and the sum of (i) persisting pN2/3 rate (ii) exploratory thoracotomy and (iii) the rate of recurrence or death from any cause within 1 year, approaches zero. In the absence of data, one might speculate about the futility of surgery in both abovementioned randomized trials.

Areas of uncertainty and further research

The optimal treatment of patients presenting with stage IIIA-N2 disease is a moving target, as clinicians are constantly challenged with improvements in staging and therapy, resulting in evolving patterns of approach. This reflects in a number of areas of ongoing or planned research.

The vast majority of IIIA-N2 patients will have their mediastinal lymph node involvement clinically suspected and demonstrated. Crucial to patient selection will be a thoroughfull mediastinal staging, in order to exclude those patients with false positive or negative imaging studies. Minimally invasive techniques using fine needle aspiration via echo-endoscopic guidance through either esophagus (EUS) or bronchus (EBUS) allow access to mediastinal and hilar lymph nodes under conscious sedation. Both are considered complementary and are likely to supersede the more invasive surgical mediastinal procedures [74, 75]. An ongoing randomized trial is investigating this issue [76].

These techniques will result in an increase of the number of so-called 'minimal N2' patients, who would previously proceed to immediate surgery. These patients are more likely to be defined as 'resectable' by some but data from patients with head and neck cancer show that post-chemoradiotherapy nodal control rate is better with small volume lymph node disease as compared to a large volume one [77]. Although comparable data are lacking in NSCLC, their extrapolation might make modern concomitant chemoradiotherapy an attractive alternative to study in these patients.

Our present systemic induction treatment is still poor. Ongoing Korean and Swiss trials compare the optimal intensity of induction treatment [36,37]. It is unclear whether new cytotoxic drugs will result in an improved outcome, as most third generation drug containing induction combinations seem to have a similar activity in locally advanced disease. Many's expectations are turned towards an incremental effect of adding a targeted biological agents to the standard induction treatment, either during or following radiotherapy. The latter approach was not successfull in a trial conducted by SWOG, wherein patients with stage III were treated with consolidation docetaxel after chemoradiotherapy and then randomized between gefitinib, a small molecule oral inhibitor of the Epidermal Growth Factor Receptor (EGFR) and placebo. A detrimental effect of gefitinib was observed [81]. Early data on the concomitant use of chemoradiotherapy and cetuximab and bevacizumab are promising [82,83] and need randomized confirmation [91].

As mentioned earlier, consolidation chemotherapy after chemoradiotherapy was also shown not to improve outcome and is currently not advocated [62].

As only downstaged patients seem to benefit from multimodality treatment, mediastinal restaging by both imaging and endoscopic techniques will increasingly become of interest. The correlation between Ct-response and pathological downstaging in the

mediastinum has been shown to be low and even patients with stable disease can have pathological complete responses [81]. Opinions differ whether PET-Ct scan is currently enough accurate to confidently predict mediastinal downstaging. Whereas several authors have shown that a decrease in glucose uptake in the primary tumour –as measured by SUVmax- is predictive for survival and pathological response in the primary tumour, the sensitivity, specificity and accuracy of PET-Ct in predicting mediastinal downstaging in patients with proven N2 involvement was lower than in initial staging [82-84]. De Leyn et al. prospectively demonstrated that integrated PET-Ct scan was significantly more accurate for the restaging of the mediastinal lymph nodes than either Ct scan, PET-CT scan or remediastinoscopy but reached still only 83% [85]. This compares poorly with the first reports on the use of EBUS or EUS for mediastinal restaging after induction therapy [86-87]. It is expected that the minimally invasive EBUS and EUS will change the spectrum of restaging of the mediastinum in the near future [88].

In order to address the question which locoregional therapy is to be preferred after mediastinal downstaging, a trial would be required randomizing patients with clinical substage IIIA 3 and perhaps 4 after adequately proven downstaging by induction therapy, between resection and radiotherapy. The current heterogeneity of the (re-)staging procedures and the large required sample size are two important hurdles for such a study.

Local recurrence remains an important challenge, certainly with chemoradiotherapy. One way to circumvent this is by escalating the total dose of irradiation given. Whether this is feasible will be explored by an upcoming US Intergroup trial, in which stage III patients will be randomized between a conventional regimen of 63 Gy versus an conformal regimen of 74 Gy, both given along concomitant and consolidation chemotherapy [89]. Improvements in dose localization techniques such as Involved Field Radiotherapy (IFRT), Intensity Modulated Radiotherapy (IMRT), four dimensional radiotherapy (4D-RT), Image Guided Radiotherapy (IGRT), breathing-adapted radiation therapy, particle beam therapy or a combination of these will come of age and become standard, allowing high dose irradiation with near-surgical precision, in patients with low burden N2-involvement with sparing of normal lung tissue and other radiosensitive organs (myelum, esophagus, heart, liver, kidneys). IFRT has been shown to result in a low incidence of 'out of field' nodal failures. In a randomized trial comparing IFRT and elective nodal irradiation, comparable tumour control, reduced incidence of radiation pneumonitis and a superior 3 year survival were observed [90]. In a non-controlled series of patients treated with chemoradiation, IMRT resulted in significantly lower levels of severe radiopneumonitis and esophagitis compared with 3D-conventional radiotherapy [91, 92]. Clinical, dosimetric, and patient selection factors may have influenced the observed rate of radiation pneumonitis. The target volume can further be reduced by including only the FDG-PET

avid volume. The early experience with IFRT using this so-called FDG-PET/Ct painting technique has been reported to result in low isolated nodal failure rates [93]. Others have not confirmed these preliminary data [94]. Data are still scarce regarding the use of respiratory gating in locally advanced NSCLC. The three-dimensional displacement of a nodal mass exceeded 10 mm in one series [95]. In a retrospective series, respiration-gated radiotherapy by 4D-RT reduced the risk of pulmonary toxicity in middle and lower lobe tumours [96]. Early results suggest that proton beam therapy permitted higher total doses with concomitant chemotherapy, yet were associated with reduced esophageal reactions compared with 3-dimensional conformal photon therapy [97].

Guidelines

Several societies have issued guidelines with regard to the treatment of stage IIIA3-4 NSCLC [6, 56, 98-100]. However, some of these guidelines do not specifically address the issue of N2-disease in its various subcategories.

A recommendation for the routine use of adjuvant cisplatin-based chemotherapy in case of pN2 (IIIA1 and 2) is unanimously given by most oncological societies. In patients with completely resected stage IIIA NSCLC, PORT is controversial and not recommended for routine use by US and Canadian oncological societies because of the lack of prospective, randomized clinical trial data evaluating its efficacy [98].

The British National Collaborating Centre for Acute Care guidance recommends chemotherapy and radical radiotherapy as first choice for eligible patients with stage IIIA, surgery with or without PORT or adjuvant chemotherapy as suitable for some patients and does not recommend preoperative chemotherapy except within a clinical trial [99]. This guidance does however not specifically address the issue of N2- disease.

The ESMO recommends preoperative cisplatin-based combination chemotherapy in patients with stage IIIA N2 disease [100]. For restaging, a CT scan of the chest and upper abdomen should be performed and minimally invasive techniques providing mediastinal cytohistological diagnosis may be considered. Surgery is considered questionable in those patients with persistent N2 disease after chemotherapy. This guidance does however not specifically address the role of definitive chemoradiation and is vague with regard to the evidence provided and its weighting.

The American College of Chest Physicians (ACCP) provides the most thoroughly documented, updated and evidence-based guidelines with regard to the treatment of stage IIIA NSCLC [6]. The ACCP recommends that in NSCLC patients with stage IIIA-N2 disease identified preoperatively, induction therapy followed by surgery is not recommended except as part of a clinical trial. Furthermore, although the use of any induction chemo-

therapy followed by surgery in stage IIIA lung cancer appears feasible, published data do not support this treatment as the standard of care in the community.
The US National Comprehensive Cancer Network (NCCN) practice guidelines in Oncology allocate a category 1 evidence to definite concomitant chemoradiation for patients with clinical T1-3N2 NSCLC and a category 2B evidence to surgery in case of non-progression after an induction with either chemotherapy or chemoradiation for clinical T1-2N2 NSCLC [101].
Taken together, these guidelines suggest a limited role for immediate surgery in patients with stage IIIA that is preoperatively documented, recommend a combined approach with a systemic induction treatment combined or followed by a locoregional intervention with definite radiotherapy or resection, the latter in highly selected cases.

Recommendations

Concomitant chemoradiation is increasingly becoming the standard of care in clinical stage IIIA3-4 in selected patients with a good risk profile: low co-morbidity, good performance and pulmonary function and adequately staged as described earlier. In the absence of any comparative data, a combination of cisplatin and etoposide, both at systemic doses as used in IG 0139, is considered appropriate. Conventional daily 1.8-2.0 Gy fractionation remains the standard after 2 randomized trials show no significant benefit for hyperfractionation [60-61]. Total dose can be escalated from the present 60-63 Gy till 66-70 Gy with an acceptable increase in radiation esophagitis and pneumonitis, provided the volume of healthy lung and the relative esophageal volume receiving more than 20 Gy (V20max) remains acceptable (<35%) and/or the mean lung dose is inferior to 20 Gy [90,91].
For those patients with stage IIIA3-4 not qualifying for adequate concomitant chemoradiation as described above, a sequential approach with either post-induction surgery or radiotherapy might be indicated. Post-induction surgery should be performed by an experienced team and avoid pneumonectomy. Post-induction radiotherapy should aim at the same total dose and fractionation as described earlier, whenever necessary restricting the irradiated volume to the post-chemotherapy involved field by excluding downstaged mediastinal nodes with appropriate imaging or endoscopic techniques. In both instances, the post-induction treatment should preferably not be delayed beyond 30-40 days after the last cycle of induction chemotherapy to avoid accelerated repopulation [102].
Figure 1 shows the treatment algorithm presently followed at the author's institution for the routine care of patients with stage IIIA -3, 4 NSCLC.

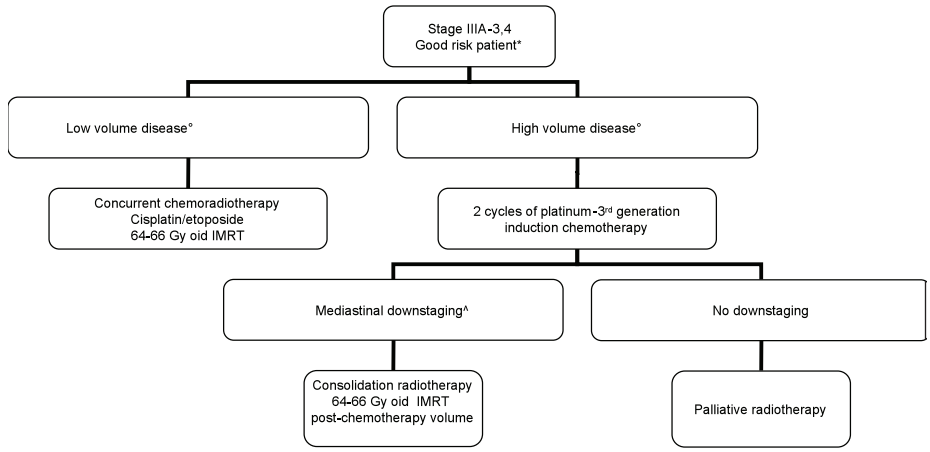

Figure 1: treatment algorithm for stage IIIA-3, 4 in the author's institution

CONCLUSIONS

More than 20 years have elapsed since the term stage IIIA was first coined by Mountain in 1986. Radically resected incidental pIIIA-1/2 should be followed by adjuvant chemotherapy, whenever appropriate. Surgical resection after induction treatment for cIIIA-3/4 can be radical but whether this approach is superior to modern thoracic radiotherapy remains unproven. Patients should be given a balanced view of both treatment options, taking into account the availability of local expertise and resources and treatment complications. This gradual shift of treatment has been made possible by the collaboration of many investigators and patients and has known the growth pains of the oncological specialty, continuously balancing between improving techniques and the need to constantly validate their promising results in endpoints relevant for the patient: survival and his/her quality of life. The way ahead looks promising, albeit not less difficult, with a plethora of novel techniques and drugs waiting to be tested before being implemented. We ought it to our patients to guide them through these challenges with dedication and professionalism.

Conflict of Interest Statement

None declared

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CHAPTER 6

A randomized phase II study comparing two schedules of the 21-day regimen of Gemcitabine and Carboplatin in advanced NSCLC.

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ABSTRACT

Purpose : Carboplatin area under the curve (AUC) 5 ml/min d1 with gemcitabine 1250 mg/m^2 d1, 8 is a widely used regimen in advanced NSCLC. Grade 3-4 thrombocytopenia and neutropenia is frequent.

The aim of this study is to investigate, whether toxicity of gemcitabine/carboplatin could be reduced by administering carboplatin on day 8 instead of day 1 without decrease in response rate. (RR)

Methods: Patients received gemcitabine 1250 mg/m^2 on days 1 and 8, carboplatin AUC 5 on day 1 (arm A) or day 8 (arm B). Drugs were administered over a 21-day cycle. Toxicity and RR were evaluated weekly and every second cycle, respectively.

Results: 71 patients were enrolled. We found 79 % (95% confidence interval (CI) 61-91%) grade 3-4 toxicity (neutropenia and thrombocytopenia) in arm A and 50% (95% CI 32-68%) in arm B; 66% grade 3-4 thrombocytopenia in arm A and 26% in arm B. We observed 30% grade 4 hematological toxicity in arm A and 3% in arm B. RR was similar in both arms.

Conclusions: Although the study was prematurely closed , we believe that the current data remain of interest. The schedule with carboplatin on day 8 is associated with less grade 3-4 neutropenia and thrombocytopenia with comparable dose intensity.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in many countries. Approximately 40% of patients with non-small cell lung cancer (NSCLC) have metastatic disease at the time of diagnosis. The primary role of chemotherapy in patients with advanced NSCLC is palliative and safeguarding patients' quality of life (QOL) is an important issue. So, for the choice of treatment, side-effects have to be taken into account. Platinum-based chemotherapy remains the standard palliative chemotherapy regimen in metastatic non-small cell lung cancer [1]. In an attempt to avoid cisplatin-induced toxicities, carboplatin was substituted to cisplatin as its administration results in less severe neurotoxicity, nephrotoxicity, nausea and vomiting [2]. In patients with advanced NSCLC, carboplatin-based chemotherapy has been extensively investigated [3-10]. In a recent meta-analysis carboplatin-based chemotherapy regimens were considered equivalent to cisplatin-based chemotherapy regimens in patients with advanced NSCLC [11]. The combination of a platinum and gemcitabine is among the current standard regimens in Europe for the treatment of advanced NSCLC [12]. In comparative studies the gemcitabine/carboplatin combination had a similar outcome as the gemcitabine/cisplatin combination in terms of overall response rate, median time to progression, response duration and survival [6,13]. Non-hematological toxicity was however lower in the gemcitabine/carboplatin treated patients.

The dose limiting toxicity in the gemcitabine/carboplatin chemotherapy regimen is haematological [14,15] In the currently-used 3-weekly dose regimen in which gemcitabine and carboplatin are both administered on day 1 and gemcitabine again on day 8, thombocytopenia grade 3-4 was found in more than 40% of cases, neutropenia grade 3-4 in 20% [16].

The hypothesis of the present study was that the administration of carboplatin on day 8 instead of day 1 would result in less hematological toxicity of the gemcitabine/carboplatin combination without compromising the activity of the gemcitabine/carboplatin combination.

METHODS

Patient selection

Patients with histologically or cytologically proven stage IV or IIIB NSCLC with malignant pleural effusion and/or supraclavicular lymph nodes were eligible. Other selection

criteria were: measurable disease according to the RECIST criteria [17]; age older than18 years; WHO performance status less than 2; adequate bone marrow reserve (hemoglobine > 6.0 mmol/l or 9.66 g/dl; absolute neutrophil count ≥ 1.5 x 10^9 /L, platelet count ≥ 100 x 10^9/L) and a calculated creatinin clearance rate of at least 50 ml/min. Exclusion criteria were weight loss of more than 10% of body weight in the month prior to registration, the presence of other malignancies (previous or present), except adequately treated *in situ* carcinoma of the cervix or basal cell carcinoma of the skin and a previous malignancy more than 5-years ago without evidence of recurrence. No prior therapy for NSCLC was allowed. Patients were registered and randomized at the Unit Trials and Statistics of the Erasmus Medical Center Rotterdam, prior to start of treatment and after verification of the eligibility criteria. The study was approved by the ethical committee of the Erasmus MC and all participating hospitals. Patients were included after written informed consent.

Treatment Plan

Patients in arm A were treated with gemcitabine (1250 mg/m^2 days 1,8) and carboplatin (AUC 5 ml/min day 1). Patients in arm B were treated with gemcitabine (1250 mg/m^2 days 1,8) and carboplatin (AUC 5 ml/min day 8). Both drugs were administered as a 21-day cycle, on an outpatient basis. Treatment was given until progression of the disease with a maximum of 4 courses, or unless unacceptable toxicity occurred or the patient refused further treatment. Patients with a complete response after 4 cycles could receive 2 additional cycles to a maximum of 6. Tumor response was assessed after every second cycle. Post-study therapy was permitted at the discretion of the investigator. The dose of gemcitabine was reduced to 1000 mg/m^2 and the dose of carboplatin to AUC 4 in subsequent cycles if the nadir of the absolute neutrophile count (ANC) was < 0.5 X 10^9/L and/or the nadir of the platelets was < 50 X 10^9/L or in case of febrile neutropenia or severe bleeding (grade 4). If on day 21 the white blood count (WBC) was < 3 X 10^9/L, ANC < 1.5 X 10^9/L and the platelets < 100 X 10^9/L, treatment was delayed until these criteria were met. In case of more than two weeks of delay, the patient went off-treatment. In case the platelets were ≤ 50 X 10^9/L and/or the WBC ≤ 1 X 10^9/L and/or the ANC ≤ 0.5 X 10^9/L on day 8 no carboplatin or gemcitabine was given. In all other cases no dose reduction for carboplatin on day 8 was allowed. Dose adjustments for gemcitabine on day 8 are summarised in Table 1.

Table 1 Per Protocol Dose adjustments Gemcitabine day 8

Gemcitabine dose level	WBC ($x10^9$/L)	ANC ($x10^9$/L)	Platelets ($x10^9$/L)
100%	≥ 2	≥ 1	≥ 100
75%	≥ 1 ≤ 2	≥ 0.5 ≤ 1	50-99
0%	≤ 1	≤ 0.5	≤ 50

Abbreviations:
WBC: white blood count
ANC: absolute neutrophile count

Efficacy and tolerability assessments

Study assessments including physical examination, complete blood count and electrocardiogram had to be performed within 2 weeks before the start of treatment, chest-upper abdomen computed tomography scan (CT), bone scan or PET-scan within 3 weeks before the start of treatment. Routine blood tests for blood chemistry and haematological toxicity were performed before each chemotherapy administration. Response assessments by CT were performed after every two cycles using RECIST criteria.
Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2 (NCI-CTC) and assessed on day 1, 8, 15 and 21 of each cycle by physical examination, direct questioning and appropriate hematological and biochemical values. Hematological toxicity rate is defined as the rate of any grade 3-4 thrombocytopenia and/or neutropenia during chemotherapy.

Study design, statistical considerations and analysis

The study was an open multicenter randomized phase II trial. Eligible patients were randomized in a 1:1 fashion by computer list. All participants were stratified by institution, disease stage, WHO performance status, gender and age. A Bryant and Day design was used to simultaneously assess response rate and hematological toxicity as co-primary endpoints [18]. Secondary endpoints were overall survival and 1-year survival.
Based on predefined expectations that arm A (carbo/gem day 1) is associated with a grade 3-4 toxicity (thrombopenia and neutropenia) in 30% of cases with a response rate of 45% and that arm B (carbo/gem day 8) is associated with 15% grade 3-4 toxicity and a respons rate of 45%, we designed the study as follows. Considering P_0 = 30% (unacceptable response rate) and P_1 = 50% (acceptable response rate) and T_0 = 30% (unacceptable toxicity rate) and T_1 = 15% (acceptable toxicity rate), with an alpha of 0.10 and a power of 90%, the sample size was estimated to be 67 patients in each arm. A first stage analysis was planned after the inclusion of the first 54 patients (2x 27). For both arms the following rule was applied: if 8 or less patients showed a response and/or 8 or more patients

developed grade 3-4 thrombocytopenia and/or neutropenia, closure of the arm was necessary. Patients who did not receive any treatment, were excluded from the toxicity analysis and patients for whom response was not assessed due to early death or early discontinuation were excluded from the activity analysis.
Response and toxicity rates, including 95% confidence intervals, were reported. Survival was estimated according to Kaplan Meier.

RESULTS

Patients and disease characteristics

A total of 71 patients (34 in arm A and 37 in arm B) were enrolled in the study between April 2004 and March 2006, before the planned first stage analysis. 71 patients were included in our study instead of 54 because not all patients were evaluable for response and results of the first stage analysis were not immediately available.
As the previous described stopping rule was achieved for both arms, the investigators decided to close the study accrual prematurely.
Two of the patients were ineligible (one because of WHO 2 at baseline and one patient with a simultaneous oesophageal carcinoma).
Patient and disease characteristics at baseline for the 69 eligible patients were well balanced between both arms and are summarized in Table 2.

Table 2. Patient and disease characteristics

	overall	Arm A	Arm B
Number of patients	69	34	35
Gender			
male	52 (75%)	25	27
female	17 (25%)	9	8
Age			
median	61	61	61
range	39-77	41-77	39-74
ECOG Performance			
0	11 (16%)	6	5
1	58 (84%)	28	30
Stage of disease			
IIIB	13 (19%)	6	7
IV	56 (81%)	28	28
Histology			
squamous	14 (20%)	8	6
adenocarcinoma	33 (48%)	17	16
other	22 (32%)	9	13

Dose administration and intensity

The total and median number of cycles administered were well balanced between the treatment groups (117 and 4 cycles in arm A, versus 113 and 4 cycles in arm B). Median dose intensity for gemcitabine in arm A is 708 mg/m^2/week (range 189-847) and in arm B 804 mg/m^2/week (range 314-849). Relative Dose Intensity is 85% in arm A, 96% in arm B. The median total carboplatin dose in arm A is 1830 mg versus 2090 mg in arm B. The main reason for dose adjustments was hematological toxicity. Gemcitabine day 1 dose reductions occurred in 9% of cycles in arm A and in 3% in arm B. For gemcitabine day 8, dose adjustments occurred in 11% of cycles in arm A and in 5% in arm B. Carboplatin doses were reduced in 9% of cycles in arm A and in only 1% in arm B.

Toxicity

Four patients were excluded from the toxicity analysis as they received no chemotherapy. The frequency of the toxicity check was weekly and balanced between the two arms, with in arm A 7% missing values for ANC and/or platelets compared to 6% in arm B.

The most frequently observed toxicities were neutropenia and thrombocytopenia. There were no treatment-related deaths on either arm. Table 3 shows the grade 3-4 toxicity (neutropenia and thrombocytopenia) in arm A: 79% (95% confidence intervals (CI) 61-91%) and in arm B: 50% (95% CI 32-68%) Grade 3-4 thrombocytopenia occurred in 66% of patients in arm A and in 26% in arm B. Platelet transfusions were required in

Table 3. Hematological toxicities and Response

Toxicity	Arm A (n=33)	Arm B (n= 34)
platelets/ANC gr 3-4	26 (79%)	17 (50%)
platelets/ ANC gr 4	10 (30%)	1 (3%)
platelets gr 3-4	22 (67%)	9 (26%)
ANC gr 3-4	18 (55%)	12 (35%)
ANC gr 4	10 (30%)	1 (3%)
Platelets gr 4	1 (3%)	0 (0%)
Response		
CR	0	1
PR	6	5
SD	21	19
PD	3	9
Overall RR (%)	20%	18%

Abbreviations:
CR: complete response
PR: partial response
SD: stable disease
PD: progressive disease

14% of patients in arm A and in 0% in arm B. Only one patient (arm A) developed febrile neutropenia.
The observed differences between arm A and B are even more pronounced when only grade 4 hematological toxicity is analysed. (see Table 3).
Grade 4 non-hematological toxicity was mild: only one patient (arm A) developed grade 4 skin-rash. Among grade 3 non-hematological toxicities the most frequent were lethargy (4 patients: 2 arm A, 2 arm B), elevated transaminases (2 patients, 1 arm A, 1 arm B), febrile neutropenia (1 patient, arm A), constipation (1 patient, arm B), dehydration (1 patient, arm B) and diarrhea (1 patient, arm B).

Response and outcome

Five out of 69 patients were considered unassessable for response evaluation as they did not receive at least 2 cycles of therapy: 1 patient died before the first response evaluation (due to pneumonia) and in 4 patients early discontinuation was necessary (2 patient's withdrawal, 1 patient's best interest, 1 patient grade 3 liver toxicity and grade 4 skin rash). In the remaining 64 patients we observed 1 complete response and 11 partial responses; 40 patients remained stable and 12 progressed under treatment, either radiologically and/or clinically.
In arm A an overall response rate of 20% (95% CI 7.7-38.6%) was seen, 18.2% (95% CI 7-35.5%) in arm B.
The median survival time for all patients was 7.3 months, with a 1-year survival rate of 28%. Median survival for arm A was 9.4 months, for arm B 6.8 months .

DISCUSSION

With carboplatin-gemcitabine being widely used as a standard regimen in advanced NSCLC, we wanted to investigate whether administration of carboplatin on day 8 instead of day 1 could reduce its haematological toxicity without a loss of activity. Based on the early stopping rule, the study was prematurely closed as response rates in both arms were lower and toxicities higher than expected in the statistical design. According to earlier data showing response rates varying between 20-40%, we set the lower threshold of activity for this phase II trial below which a regimen would not be of interest for further study, at 30%. Although the patients' demographics seem quite similar to these of other studies, the standard arm in the present study did not reach the expected threshold response rate and its overall survival is also lower than reported probably due

to a high percentage of patients (81%) with stage IV disease. Compared to other trials, grade 3-4 hematological toxicity in the present study is high. This probably reflects the weekly sampling instead of sampling at retreatment or at clinical toxicities only. Another reason for the premature closure could be that the cut-off value for acceptable/unacceptable response and toxicity in the standard arm was too optimistic.

Although the study was prematurely closed, data obtained for the two treatment groups are interesting. Response rates were found to be similar but we observed a considerably lower rate of hematological toxicity by administering carboplatin on day 8 instead of day 1 with preservation of the dose intensity.

Gemcitabine/cisplatin combination is one of the most widely used regimens in Europe for first-line treatment in patients with advanced NSCLC. Problems with cisplatin administration in this palliative setting include a significant non-hematologic toxicity and the need for in hospital hydration. Carboplatin constitutes a reasonable alternative to cisplatin in this combination as it is easier to use in outpatient setting and is associated with fewer non-hematological side-effects.

Since several studies demonstrated that a carboplatin-based two drug combination is effective with a favourable safety profile and is well tolerated, gemcitabine and carboplatin is a widely used combination for the treatment of advanced non-small-cell lung cancer [13, 19,20]. In the advised 3-weekly schedule with gemcitabine (1250 mg/m^2) and carboplatin (AUC 5), both administered on day 1, the treatment is well tolerated, but clinicians frequently have to deal with grade 3-4 neutropenia and especially grade 3-4 thrombocytopenia. Even though severe bleeding problems are infrequently seen, physicians feel uncomfortable especially about this thrombocytopenia because it necessitates more attention, repeated platelets count controls, dose reductions and platelets transfusions [21] In the present study, the high incidence of grade 3-4 thombocytopenia in arm A led to frequent platelet transfusions.

The Norwegian Lung Cancer Study Group, recently report a grade 3 thrombocytopenia of 25% and grade 4 thrombocytopenia of 19% in the carboplatin day 1-gemcitabine regimen resulting in more frequent transfusions and higher costs [22]. The high frequency of thrombocytopenia in the gemcitabine/carboplatin treatment is thought to be due to a synergistic thrombocytopenic effect of both agents. Gemcitabine single agent therapy was studied earlier in advanced non-small cell lung cancer and was associated with a low frequency of thrombocytopenia of 2% [23]. In advanced non-small cell lung cancer, carboplatin has been studied as single agent and is known to have a thrombocytopenic effect, but carboplatin has been studied as single agent and is known to have a thrombocytopenic effect in other malignancies also in other malignancies. Furthermore, as this dose limiting toxicity is less frequently found in gemcitabine combinations with

cisplatin, it can be postulated that this toxicity is increased by the association of carboplatin to gemcitabine. The high incidence of thrombocytopenia on day 15 in arm A can be explained by the fact that gemcitabine on day 8 is administered at the time platelets are already lowering. On day 8, the thrombocyte count in most patients is - although lower than on day 1,- still high enough to administer the planned dose of gemcitabine. In arm B gemcitabine is given as single agent on day 1 which will have a minor effect on platelets on day 8, the day when carboplatin is administered. The same reasoning applies for the incidence of neutropenia. Similar effects are reported for the cisplatin/gemcitabine regimen [24,25,26]. In a randomized phase III study comparing two different schedules of administration of cisplatin in combination with gemcitabine, the regimen with cisplatin on day 15 was associated with significant less thrombocytopenia compared to the arm with cisplatin on day 2 [24]. The difference in toxicity in our study cannot be explained by a difference in missing data of ANC and platelets in the two arms.

In a randomized phase II study, gemcitabine (1100 mg/m^2 days 1,8) and carboplatin (AUC 5, day 8) every 4 weeks was compared to gemcitabine (1000mg/m^2 days 1,8) and carboplatin (AUC 5, day 1) every 3 weeks [27]. The treatment with carboplatin on day 8 showed a more favourable toxicity profile. Although the 28-day regimen appeared to be associated with less preferable outcomes (response rate and median time to progression), differences between treatment groups were not statistically significant. Median progression-free survival and response rates were 3.8 months and 22.9%, respectively, with the 28-day regimen, and 4.9 months and 40.4%, respectively, with the 21-day regimen. Differences in progression-free survival, response rate and overall survival were not statistically significant. We believe that the reported decrease in response is due to an asymmetry in rescheduling: 4 weeks in the carboplatin-day 8 regimen vs 3 in the carboplatin day 1 regimen. In contrast with this study we report no difference in response rate when both regimens are rescheduled every 3 weeks.

A limitation of our study is that the sample size is too small to reasonably consider any comparisons between the two arms in terms of survival. In the Ricci study, patients treated in the arm with cisplatin on day 15 experienced a significantly more prolonged progression free survival and overall survival [24].

CONCLUSION

In conclusion, this study was designed to investigate the possibility of lowering toxicity of the standard chemotherapy regimen carboplatin- gemcitabine in patients with

advanced NSCLC. Although the study was prematurely stopped, we believe that the current data remain of interest. With comparable dose intensity, the schedule with carboplatin day 8 is associated with less grade 3-4 neutropenia and thrombocytopenia.

Conflict of Interest Statement

None declared

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CHAPTER 7

Non-Cross Resistant, sequential single agent chemotherapy in first line advanced Non-Small Cell Lung Cancer Patients: Results of a phase II study

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ABSTRACT

Background: The rationale of sequential chemotherapy is to maintain dose intensity and to preclude cumulative toxicity by increasing drug diversity.

Purpose: to investigate the toxicity and efficacy of the sequential single agent regimen of gemcitabine followed by paclitaxel in first line stage IIIB/ IV non-small cell lung cancer (NSCLC) patients with good performance status (PS).

Patients and methods: In this non-randomized phase II trial gemcitabine 1250 mg/m^2 was administered on day 1 and 8 of course 1 and 2; Paclitaxel 150 mg/m^2 on day 1 and 8 of course 3 and 4. Primary endpoint was response rate (RR), secondary endpoints toxicity and time to progression (TTP).

Results: Of the 21 patients (median age 56, range 38-80 years; 62 % males, 38 % females) 10% (2/21) had stage IIIB, 90% (19/21) stage IV, 15% PS 0, 85% PS 1. No dose reductions were needed. Of the 20 evaluable patients 20% had a partial response, 30% stable disease, 50% progressive disease. Median TTP was 12 weeks (range 6-52 weeks), median overall survival (OS) 8 months (range 1-27 months) and the 1-year survival was 33%. One patient had grade 3 hematological toxicity, 2 patients a grade 3 peripheral neuropathy.

Conclusions: the sequential administration of single agent gemcitabine followed by paclitaxel in first line treatment of advanced NSCLC had a favourable toxicity profile, a median TTP and OS comparable with other sequential trials reported and might, therefore, be a treatment option for NSCLC patients with high ERCC1 expression.

INTRODUCTION

Even with the use of novel chemotherapeutic agents, the prognosis of patients with advanced NSCLC remains poor. Platinum based chemotherapy combined with either gemcitabine, vinorelbine, paclitaxel or docetaxel is currently the mainstay in the treatment of advanced NSCLC (1-5). Standard therapy for advanced NSCLC results in response rates of 20 to 40%, a median survival between 8-10 months and 1-year survival rates between 30-50% (1-3).

Chemotherapy may lead to the selection of chemo-resistant tumor clones. Frequent exposure to different cytotoxic agents with brief intervals may inhibit tumor re-growth and limit the emergence of drug resistant cell lines (6,7). Sequential chemotherapy administration offers the possibility to increase drug diversity while maintaining dose intensity, potentially leading to less dose reductions, an optimal dose intensity and prolonged treatment duration and disease control (6,7).

In order to investigate the validity of this approach, we decided to conduct a non-randomized phase II study, to investigate the toxicity and efficacy in terms of time to progression and response rate of a sequential single agent regimen consisting of gemcitabine followed by paclitaxel in the first line treatment of patients with stage IIIB/ IV NSCLC.

PATIENTS AND METHODS

In this multi-center trial patients with stage IIIB (malignant pleural effusion or N3 due to supraclavicular lymph node involvement) and stage IV have been enrolled between 2003-2006. The study was approved by the ethical committees of the Erasmus MC and 4 other hospitals. Patients were included after written informed consent. Other selection criteria were: measurable disease according to the RECIST criteria (8), age over 18 years, WHO performance status less than 2, adequate bone marrow reserve (absolute neutrophil count $\geq 2.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L), adequate hepatic function (total bilirubin $\leq$ 1.5 x upper normal limit, ASAT and ALAT $\leq$ 3.0 x upper normal limit, alkaline phosphatase $\leq$ 2.5 x upper normal limit, total billirubin 1.5 - 2.5 x upper normal limit and ASAT or ALAT 3-5 x upper normal limit in case of liver metastases).

Exclusion criteria were prior treatment with chemotherapy and the presence of other malignancies (previous or present), except adequately treated *in situ* carcinoma of the cervix or basal cell carcinoma of the skin and a previous malignancy more than 5-years

ago without evidence of recurrence (except for malignant melanoma, hypernephroma or breast cancer).

Treatment

Gemcitabine 1250 mg/m^2 was administered intravenously on day 1 and 8 of course 1 and 2 as a 30-minutes infusion. Paclitaxel 150 mg/m^2 was administered intravenously on day 1 and 8 of course 3 and 4 as a 3-hours infusion. One course was defined as two weekly doses of chemotherapy followed by one week of rest and one cycle as 2 courses of gemcitabine followed by 2 courses of paclitaxel (Fig. 1). At least 1 cycle was administered unless patient refusal or excessive toxicity precluded further therapy. If there was no PD after 1 cycle the same treatment schedule could be repeated up to a maximum of 2 cycles. If PD was observed at the end of the first or second cycle, further treatment was according to local policy.

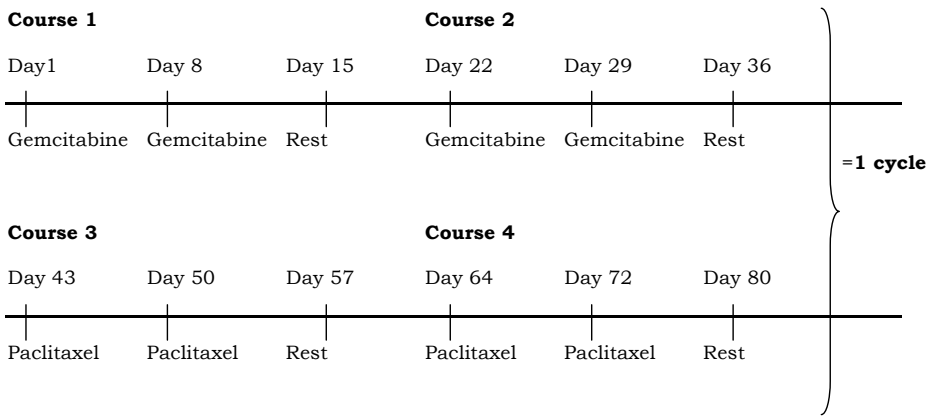

Figure 1. Treatment schedule

Efficacy and tolerability assessments

Study assessments included physical examination, complete blood count, electrocardiogram, tumor measurements (chest X-ray and chest-upper abdomen computed tomography scan), within 4 weeks before start of the treatment. Routine blood test for blood chemistry and haematological toxicity were performed before each chemotherapy administration. Response evaluation by CT took place after every 2 courses by RECIST criteria (8). Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3

(NCI-CTC) and was assessed every 3 weeks by physical examination, direct questioning and haematological and biochemical parameters.

Statistical considerations

It was hypothesized that if the sequential regimen had an efficacy lower than 25%, it was unlikely to be of interest and would not result in further investigation. According to Fleming's single stage procedure P0 was set at 0.20. The response percentage that would certainly warrant further investigation (P1) was set at 0.40. With a power of 0.93 and an α of 0.06 this implies that 35 patients had to be enrolled. For the power calculation the best response during the first cycle has been used. P values < 0.05 were considered significant.

RESULTS

Twenty-one patients have been enrolled in this trial over a 3-years period due to competing trials in the participating centres. Median age was 56 years (range 38-80 years), 62 % (13/21) was male, 38 % (8/21) female, 10% (2/21) had stage IIIB, 90% (19/21) stage IV, 15 % (2/21) ECOG performance status 0, 85% (18/21) ECOG 1. Ten (47.5%) patients had an adenocarcinoma, 3 (14.5%) squamous cell carcinoma and 8 (38%) had large cell carcinoma. (Table 1)

Tabel 1 Patient characteristics

Number of patients	21
Gender	
male	13 (62%)
female	8 (38%)
Age	
median	59
range	38-80
ECOG Performance	
0	2 (10%)
1	19 (90%)
Stage of disease	
IIIB	2 (10%)
IV	19 (90%)
Histology	
squamous	3 (14.5%)
adenocarcinoma	10 (47.5%)
large cell	8 (38%)

One non-evaluable patient died one week after the first gemcitabine dose administration due to a cerebral vascular accident. At that time the platelet count was normal. Of the 20 evaluable patients 20% (4/20) achieved a partial response (PR), 30% (6/20) stable disease (SD) and 50% (10/20) progressive disease (PD). (Table 2) Five patients (25%) progressed after 2 courses of gemcitabine, all of them had an adenocarcinoma. Median time to progression (TTP) was 12 weeks (range 6-52 weeks), the median overall survival (OS) 8 months (range 1-27 months) and the 1-year survival rate 33%. Toxicity was mild: only one patient developed grade 3 hematological toxicity, in two others there was grade 3 peripheral neuropathy occurring at the second cycle. There were no treatment-related deaths. No dose reductions were needed.

Tabel 2 Results of the 20 evaluable patients

Response	Number of patients
PR	4
SD	6
PD	10

DISCUSSION

In this non-randomized phase II study, the sequential administration of single agent gemcitabine followed by paclitaxel in the first line treatment of advanced NSCLC had a favourable toxicity profile, a median TTP and OS comparable with other sequential trials reported in the literature (Table 3) (9-20).

When we designed our study (2002-2003) Vansteenkiste et al. reported that treatment of patients with symptomatic advanced NSCLC with single agent gemcitabine, resulted in a superior clinical-benefit response rate compared to cisplatin-based combination chemotherapy. Gemcitabine was equally effective in controlling 'disease-specific' symptoms, but superior in controlling 'constitutional' symptoms (21). Therefore, single agent gemcitabine in first line treatment of stage IIIB/IV NSCLC was at that time a valid therapeutic choice and we decided to investigate the sequential administration of two single agent non-cross resistant chemotherapeutic drugs, gemcitabine and paclitaxel. In the present study, paclitaxel was selected as sequential agent because taxanes do not require the presence of an intact p53 pathway for apoptosis induction in contrast to DNA-damaging agents like gemcitabine (22). The dose of paclitaxel of 150 mg/m^2 was based on the results of phase I and II trials (23-25). Akerley et. al reported on a phase I trial of weekly paclitaxel administered over 3 hours for 6 consecutive weeks followed by 2 weeks of rest. From this study the recommended phase II dose was 175mg/m^2/week

Table 3. Overview of the sequential studies reported in the literature (Continu on next page)

Study	Phase	N=	Regimen	RR (%)	PD (%)	MS (m)	1year OS (%)	PFS (m)	Major grade 3-4 toxicity (%)
Doublet→ Doublet									
Gebbia (9)	III	400	G + IFO (2)→CDDP + VNR (2) versus	19	59	NR	NR	3.1[a]	Neutropenia 57/67/26/21
			CDDP + VNR (2)→G + IFO (2) versus	32	33	NR	NR	5	Thrombo 32/35/17[b]/41
			CDDP + VNR (up to 6 cycles) versus	44[a]	25	9	24	4.1	Vomiting 13/15/21/23
			CDDP + G (up to 6 cycles)	34	37	8.2	20	4	Asthenia 29/35/35[c]/50
Doublet → SA									
Edelman (10)	III	204	CBDCA + G (3)→PTX(3) versus	21	29	9	34	4	Neutropenia 47[a]/70 Anemia 19/14
			CDDP + VNR (3)→DOC(3)	28	22	9	36	4	Thrombocytopenia 37/2[a] Fatigue 7[a]/18 Emesis 5[a]/24 Toxic deaths 3/3
Clark (11)	II	18	CDDP (2) + VNR(2)→DOC (4)	31	44	9.5	44	NR	Leukopenia 45[d] Emesis 26[d] Toxic deaths 3
Grossi (12)	II	51	CDDP + PTX (2)→VNR(2) →G (2)	43	25	14	53	6.8	Neutropenia 41 Toxic deaths 1
Kubota (13)	III	401	CBDCA + PTX (up to 6) versus	36[a]	10	13.8	55.5	6	Neutropenia 54/30[a] Neuropathia 21/2[a]
			VNR + G (3)→DOC (3)	23	16	13.1	55.6	5.9	Toxic deaths 0/2
SA → doublet or triplet									
Feliu (14)	II	52	PTX (6)→CDDP + GEM + VNR (up to 6)	56	31	NR	56	9	Neutropenia 20 Neuropathy 12 Emesis 10
Rixe (15)	II	32	DOC (4)→CDDP + VDS (4)	17	27	11	47	4.4	Neutropenia (gr 4) 71 Febrile neutropenia 14 Neuropathy 24
SA→SA									
Present study	II	21	G →PTX	20%	**50**	8	33	3	Neutropenia 4 Neuropathy 9
Manegold (16)	II-III	338	G +DOC (6) versus	33[a]	NR	7.3	27	6.3[a]	Neutropenia 36/27 Infection 17/13
			G (3) "DOC (3)	22	NR	7.4	25	4.9	Dyspnoe 21/20 Asthenia 12/11
Martoni (17)	II	52	G(3)→VNR (until PD)	23	23	10	42	6	Neutropenia 22[e] Constipation 3[e]

Study	Phase	N=	Regimen	RR (%)	PD (%)	MS (m)	1year OS (%)	PFS (m)	Major grade 3-4 toxicity (%)
Poon (18)	II	23	G (3) → CDDP (4)	21	52	14.6	63	3.3	Neutropenia 13 Anemia 13
Hirsch (19)	II	42	VNR (2) → G	38	36	8	29	3.5	No grade 3-4 tox.
Tibaldi (20)	II	56	G (3)→ DOC (3)	16	43	8	34	4.8	Neutropenia 5.4 Thrombopenia 3.6 Mucositis 3.6 Diarrhea 3.6 Asthenia 9

a: statistically significant

b: difference in thrombocytopenia incidence between CT arms was statistically significant (p=0.0001)

c: asthenia more frequent in the GC arm than VC arm (50% vs 35%, p=0.015)

d: toxicity evaluated per cycle

e: worst toxicity per step

Abbreviations: G: gemcitabine, IFO: ifosfamide; CDDP: cisplatin; VNR: vinorelbine; CBDCA: carboplatin; PTX: paclitaxel; DOC: docetaxel; RR: response rate; MS: median survival; MPFS: median progression- free survival; NR: not reported; OS: overall survival; PD: progressive disease; SA: single agent

NR: not reported

(23). In the subsequent phase II trial this dose-dense regimen led to a high proportion of grade 3-4 neutropenia and grade 2-3 peripheral neuropathy (32%) (24). Therefore, in the CALGB study 9713, weekly paclitaxel at a reduced dose of 150 mg/m^2/week for 6 consecutive weeks was used followed by 2 weeks of rest. They demonstrated that this dose-dense regimen could be administered safely (25).

Because 50% of the participants in our trial had disease progression and because disease progression occurred already after 2 courses of single agent gemcitabine, we decide to close our study prematurely. At that time, it had also become evident from the literature that single agent gemcitabine in first line treatment of stage IIIB/IV NSCLC was inferior compared to platinum-based doublets (26,27).

Even though our study has been closed prematurely, our data add to our current understanding on the treatment of NSCLC because they contribute to the concept of maintenance therapy with non-cross resistant drugs. In a recent randomized phase III trial of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care, PFS was 4 months in the pemetrexed arm versus 2 months in the placebo arm with an hazard ratio (HR) of 0.6 (p< 0.00001) and the OS was 13.4 months versus 10.6 months, respectively (HR 0.79, p=0.012) (28). The phase III trial of immediate versus delayed docetaxel after first line chemotherapy in advanced NSCLC showed also a superior progression free survival (statistically significant) and greater median overall survival (not statistically significant) for the arm with immediate docetaxel (29). These trials support the rationale of using a non-cross-resistant third generation agents before

disease progression has occurred. We also believe that a single agent non-platinum approach could be of value in ERCC1 positive patients, especially in the perspective of individualized treatment. Patients with completely resected NSCLC and ERCC1-negative tumors appeared to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors did not (30). A prospective trial of 366 patients, in which patients with low ERCC1 were selected for platinum-based therapy (docetaxel, cisplatin), while those with high ERCC1 expression were directed to alternate non-platinum therapy (docetaxel, gemcitabine), demonstrated a significantly higher overall response rate in the genotypic arm compared to the non-selected control arm (31). The response rate in the low ERCC1 group receiving platinum chemotherapy was 53%, but the RR in the high ERCC1 non-platinum arm was 47%, compared to 39% for the non-selected group receiving platinum therapy. A prospective phase II feasibility trial in which patient's therapy was selected based on ERCC1 expression showed that the low ERCC1 group treated with gemcitabine/carboplatin and the high ERCC1 group treated with gemcitabine/docetaxel had a similar median survival of 13 months and response rates of 44% (32).

Our data also confirm that gemcitabine is less active in adenocarcinoma's than in squamous cell carcinoma's (1) because all patients in our trial who progressed after 2 courses of gemcitabine had an adencocarcinoma.

In conclusion, although this non-randomized phase II study failed to meet the primary efficacy endpoint, the sequential administration of single agent gemcitabine followed by paclitaxel in first line treatment of advanced NSCLC had a favourable toxicity profile, a median TTP and OS comparable with other sequential trials reported in the literature and might, therefore, be a treatment option for NSCLC patients with high ERCC1 expression.

Conflict of Interest Statement

None declared

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CHAPTER 8

Oral UFT, leucovorin and etoposide in recurrent non-small cell lung cancer: a non-randomized phase II study

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ABSTRACT

Background: Oral treatment regimens with few side-effects are appealing in the 2nd or 3rd line treatment of non-small cell lung cancer (NSCLC) patients.

Purpose: The aim was to investigate the efficacy and toxicity of the oral combination etoposide, Uracil-Tegafur (UFT) and leucovorin in 2nd or 3rd line in Caucasian patients with advanced NSCLC.

Methods: Etoposide 50 m g/m^2, UFT 250 mg/m^2 and leucovorin 90 mg (fixed dose) were dosed in 3 gifts approximately 8 hours apart for 14 days followed by one week rest every 3 weeks until progressive disease (PD). Primary endpoint was response rate (RR), secondary endpoints toxicity and time to progression (TTP).

Results: The median number of cycles was 3.5 (95%CI 2-5); 9 patients received ≥ 6 cycles, 4 >10 cycles. The median dose intensities for etoposide and UFT were 223 mg/m^2/week (95% CI 213-232) and 1092 mg/m^2/week (95% CI 1032-1167), the relative dose intensities 92% and 90 %, respectively. Grade 3/4 neutropenia was observed in 12% (4/32), grade 3/4 thrombocytopenia in 15 % (5/32), without febrile neutropenia. Non-hematological toxicity grade 3 included hepatic toxicity (6%), lethargy (15%), diarrhea (3%) and nausea (3%). One patient developed grade 4 arterial ischemia. Fourteen percent (95% CI 4-33%) (4/28) had a confirmed partial response , 57 % (95% CI 44-81%) (16/28) stable disease and 28% (95% CI 19-56%) (8/28) progressive disease. The median TTP was 3 months (95% CI 1.3-4.4), the median overall survival 6.7 months (95% CI 4.0-9.3).

Conclusion: The combination of UFT, etoposide and leucovorin is active in 2nd or 3rd line therapy of Caucasian NSCLC patients and because of its favourable toxicity profile this treatment warrants further investigation.

INTRODUCTION

Lung cancer is world-wide the leading cause of cancer-related deaths. Approximately 40% of all patients with non-small cell lung cancer (NSCLC) have metastatic disease at the time of diagnosis. Platinum-based chemotherapy remains the standard of care for the first line therapy of patients with metastatic NSCLC and good performance status. Since several years 2nd and even 3rd line therapy has become part of our therapeutic arsenal (1-4). Several agents including docetaxel, pemetrexed and the epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) erlotinib are available for 2nd line treatment, but it is yet unknown what the preferred drug or drug combination is for this setting (5-9). A direct comparison between pemetrexed and docetaxel in a non-inferiority randomized phase III study showed similar activity but less toxicity for the pemetrexed arm (7).

Oral agents with few side effects are appealing in 2nd or 3rd line setting when patients are usually in a less favourable condition. The combination of the oral agents Tegafur and Uracil (UFT) appeared to be effective in adjuvant setting in Asian NSCLC populations (10,11) with few side effects even after prolonged administration. Tegafur is the pro-drug of 5-Fluor Uracil (5-FU) and Uracil inhibits the rate-limiting catabolic enzyme for 5-FU, dihydropyrimidine dehydrogenase. Leucovorin enhances the cytotoxicity of 5FU by one of its metabolites 5,10-methylenetetrahydrofolate. The FdUMP/thymidylate synthase complex that forms after 5-FU administration depends on the presence of adequate concentrations of reduced folate (12,13). Leucovorin is a derivative of tetrahydrofolic acid, the reduced form of folic acid, which increases intracellular concentration of reduced folates, thus stabilizing the FdUMP/ thymidylate synthase complex (13).

The efficacy of single agent UFT in advanced NSCLC appeared to be modest, with response rates of only 9% (14). In 1st line treatment of advanced NSCLC doublets have proven to be more effective in terms of response rate and overall survival than single agents (15). A recent meta-analysis showed that in 2nd line both platinum and non-platinum based doublets significantly increased the response rate compared with single agents, but without improvement in overall survival and with an increase in toxicity (16). In contrast, Smit et al. recently reported that the combination of carboplatin and pemetrexed was superior with regard of time to progression (TTP) compared with pemetrexed alone in 2nd line without increase in toxicity (17). UFT with cisplatin, but without leucovorin, has been investigated in 1st line Japanese NSCLC patients, with response rates ranging from 28-47% and acceptable toxicity (18,19). However, the same combination led to low response rates and high toxicity in Caucasians, which precluded further studies (20).

Despite the fact that etoposide has well known activity in NSCLC (21,22), there are no reports on the single-agent activity of oral etoposide in refractory NSCLC except one retrospective study which showed no activity (23). In vitro data show synergism between UFT and etoposide in mouse Lewis lung carcinoma cell lines (24). Despite the fact oral etoposide is known to have variable absorption and hence disposition, and the lack of pharmacokinetic data on the interaction of oral etoposide with UFT, the combination of oral UFT and etoposide was well tolerated and appeared to be active in first line gastric cancer (25) and in pre-treated breast cancer and head and neck tumors (26-27).
Purpose of our study was to investigate the efficacy and toxicity of the non-cross resistant oral drug combination UFT, etoposide and leucovorin in 2nd or 3rd line in Caucasian patients with advanced NSCLC.

METHODS

Selection criteria

Patients with histologically or cytologically proven stage IIIB with malignant pleural effusions and / or supraclavicular lymph nodes or stage IV NSCLC treated with at least one prior platinum-based 3rd generation drug combination have been selected. They had to have measurable disease (28), age >18 years, WHO performance status < 3, adequate bone marrow reserve (white blood count ≥ 3 x 10^9/L, absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L) and a calculated creatinin clearance rate of >50 ml/min. Exclusion criteria were a recent (< 6 months) myocardial infarction, signs of cardiac failure or rhythm disturbances requiring medication, a history of another malignancy, except *in situ* carcinoma of the cervix or basal cell carcinoma of the skin and a previous malignancy more than 5-years ago without evidence of disease. Patients with symptomatic brain metastases were ineligible.

Evaluation and Treatment

Baseline evaluation included a physical examination, complete blood count, electrocardiogram and a computed tomography (CT) of the chest and upper abdomen < 4 weeks before start of the treatment. Treatment consisted of oral etoposide 50 mg/m^2 , oral Uracil-Tegafur 250 mg/m^2 and oral leucovorin 90 mg (fixed dose) in 3 gifts approximately 8 hours apart for 14 days followed by one week rest. Courses were repeated every 3 weeks. All drugs had to be taken while fasting (no meal from one hour before until one

hour after taking the study medication). Three dosing groups were defined according to body surface area (< 1.6 m^2, 1.60-1.8 m^2 and > 1.8 m^2). Tumor response evaluation took place after every 2 courses according to the RECIST criteria. (28) Evaluable were those who received at least 2 chemotherapy courses. Treatment was stopped in case of severe toxicity, disease progression or when it was considered in the best interest of the patient. Haematological and non-hematological toxicity was assessed before start of each cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.

Statistics

This is a non-randomized open label phase II study. The minimum response rate below which treatment is considered of no interest is set at 5%. Responses rates of 20% or higher are clearly of interest and should be detected with a power of 80 %. The hypothesis that the response rate is at most 5% should be rejected with a type I error of 5% (alpha = 0.05) According to the 2-phase Simon design (29) 10 patients are needed for the first part of the trial. If one response is observed, the UFT-etoposide-leucovorin combination is of potential interest and another 19 patients could be enrolled. If at the end of the trial 3 or fewer responses are observed, a minimum response rate of 20% can be rejected. Overall survival and TTP were estimated according to the log rank test and plotted according to Kaplan- Meier (30).

RESULTS

Patients

Over a 18-months period 35 Caucasian patients from 2 institutions have been enrolled in 2005-2006. In the first part of the trial 15 patients instead of 10 because 1 patient was ineligible (symptomatic brain metastases) and 4 were excluded from interim-analysis because of protocol violations (n=2) or because they received < 2 cycles of chemotherapy (one patient experienced extreme fatigue and another died after a non-study drug related myocardial infarction). In the 2nd part of the trial 20 patients have been enrolled, 2 patients were not evaluable for response. The characteristics of the 34 eligible patients are summarized in Table 1. 53% (18/34) of patients received 2nd line and 47% (16/34) 3rd line therapy.

Tabel 1. Patient characteristics

	N (%)
Eligible patients	34
Males	19 (56)
Females	15 (44)
ECOG Performance	
0	9 (27)
1	24 (71)
2	1 (3)
Stage of disease	
IIIB	11 (32)
IV	23 (68)
Previous treatment	
1	18 (53)
2	16 (47)
Treatment in first line:	
Platinum-based doublet	33 (97)
Non-platinum-based doublet	1 (3)
Treatment in second line:	
Single agent Taxanes (docetaxel, paclitaxel)	10 (62)
Platinum-based doublets	6 (38)

Dose intensity and toxicity

The median number of cycles was 3 (range 0-34); 9 patients received ≥ 6 cycles, 4 of them even > 10 cycles. The median dose intensities for etoposide and UFT were 223 mg/m^2/week (95% CI 213-232) and 1092 mg/m^2/week (95%CI 1032-1167) and the relative dose intensities 92% and 90 %, respectively. The most frequently observed grade ¾ hematological toxicities were neutropenia in 12 % (4/32) and thrombocytopenia in 15% (5/32), without febrile neutropenia (Table 2). Grade 3 non-hematological toxicity included elevated transaminases in 6% (2/32), lethargy in 15% (5/32), diarrhea in 3% (1/32) and nausea in 3% (1/32). One patient developed treatment related grade 4 peripheral arterial ischemia. Admissions for adverse events occurred in 38 % (13/34) of which 26% was related to disease progression and 13% treatment related.

Effect evaluation

28 patients were evaluable for response. Fourteen percent (95% CI 4-33%) (4/28) had a confirmed partial reponse , 57% (95%CI 44-81%) (16/28) stable disease and 28% (95% CI 19-56%) (8/28) progressive disease. The overall disease control rate was 71 % (20/28). The median TTP for all eligible patients was 3 months (95% CI 1.3-4.4) , for those treated in 2nd line 3.3 months (95% CI 1.4-5.2) and for 3rd line treatment 2 months (95% CI 0.8-4.4) (Fig 1). The median overall survival time was 6.7 months (95% CI 4.0-9.3) (Fig 2).

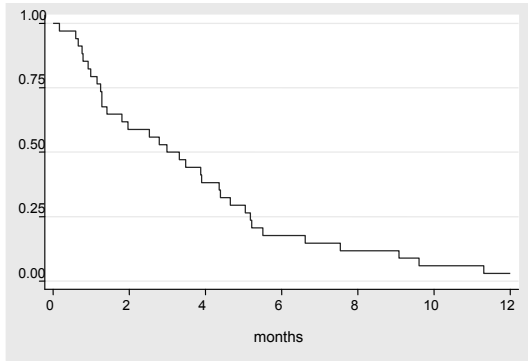

Fig 1. Kaplan-Meier curve of the time to progression of non-small cell lung cancer patients after treatment with UFT-etoposide-leucovorin in 2nd and 3rd line.

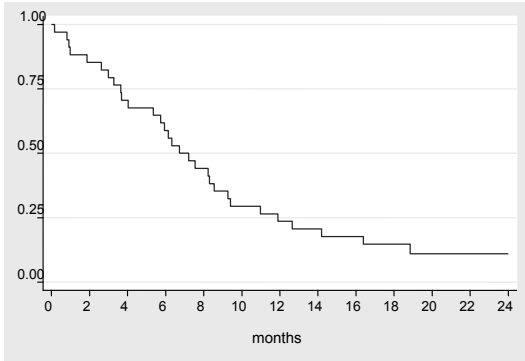

Fig 2. Kaplan-Meier curve of the overall survival of non-small cell lung cancer patients after treatment with UFT-etoposide-leucovorin in 2nd and 3rd line.

Costs

According to the Institution rates list 2007 of the Dutch Healthcare Authority (Tarieflijst Medisch Specialistische Behandeling Instellingen 2007 van de Nederlandse Zorgautoriteit) one 3-week cycle of UFT-etoposide-leucovorin costs 826 euros. In comparison, the costs for one 3-week cycle docetaxel, pemetrexed, erlotinb and topotecan are 1300, 3200, 1528 and 1410 euros, respectively (Table 2).

DISCUSSION

This study shows that the combination of UFT, etoposide and leucovorin is active in 2nd or 3rd line therapy of NSCLC patients with a favourable toxicity profile even after prolonged treatment and with relatively low costs in comparison with other 2nd line therapies.

Table 2. Comparison of UFT-etoposide with the historical series of the registered 2nd line agents docetaxel, pemetrexed and erlotinib.

	Docetaxel	Pemetrexed	Erlotinib	UFT-etoposide	Oral Topotecan
Grade 3/4 neutropenia (%)	40.2	5.3	0	12.5	50
Grade 3/4 thrombopenia (%)	0.4	1.9	0	15.6	26
Febrile neutropenia (%)	12.7	1.9	0	0	26
Hospitalisation drug related AE (%)	10.5	6.4	NR	13	NR
Alopecia (any grade) (%)	37.7	6.4	0	57.1	20
Rash (grade 3/4) (%)	0.7	0.8	9	0	NR
Diarrhea (grade 3/4) (%)	2.5	0.4	6	3	4
Nausea (grade 3/4) (%)	1.8	2.6	3	3	4
ORR (%)	8.8	9.1	8.9	12.5	5
TTP (median, months)	2.9	2.9	2.2	3	2.75
MS (months)	9.1	9.4	6.7	6.7	7
Costs for one cycle (euros)	1300	3200	1528	826	1410

Definition of abbreviations: AE: adverse event; ORR: objective response rate; TTP: time to progression; NR: not reported; MS: median overall survival.

Although no formal comparisons can be made with historical series, they suggest that the response rate and TTP of our UFT-etoposide combination is comparable with those of the established 2nd line agents docetaxel, pemetrexed and erlotinib (Table 2). Median overall survival time seems to be lower than for pemetrexed and docetaxel, but comparable with erlotinib which could be explained by the fact almost half of our patients was treated in 3rd line. A phase III trial comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced NSCLC, demonstrated that also oral topotecan provides activity. The results in terms of ORR and TTP are comparable with our UFT-etoposide trial. However hematological toxicity for oral topotecan is high; grade 3-4 neutropenia in the oral topotecan arm was 50%, grade 3-4 anemia 26% and grade 3-4 thrombopenia 26% (31).

With a similar range of efficacy, the toxicity of the UFT–etoposide combination is much lower than for the other 2nd line agents. Although costs have not been evaluated in our study, a cost estimation for UFT-etoposide seems lower than for the other 2nd line agents. Given the incurable nature of advanced NSCLC and the only limited survival advantage that can be achieved by 2nd or 3rd line treatment, treatment convenience and toxicity of the regimen are of great importance in the choice of treatment. Dubey et al. performed a survey of 464 lung cancer patients registered in the Alliance for Lung Cancer Advocacy Support and Education about their treatment preference and concerns about toxicity (32). In that survey 73% of the responders reported that they would choose a chemotherapy regimen because of its side-effect profile, assuming that outcome was equivalent. Most important side effect were considered nausea and vomiting (48%), followed

by infection risk (20%) and fatigue (13%). Hair loss (9%) was of minor concern. Therefore, we believe that the UFT-etoposide combination deserves further investigation in 2nd or 3rd line treatment in a randomized fashion.

UFT activity might be correlated with thymidylate synthase (TS) expression. TS is an enzyme that plays an important role in DNA biosynthesis, catalyzing the methylation of fluorodeoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). It is the target enzyme for anti-metabolites such as 5-FU and UFT. Several studies clearly show a correlation between intra-tumoral TS mRNA expression and the response to 5-FU (33,34). TS protein expression levels appear to be negatively associated with prognosis in different tumor types due to a higher proliferative activity of the NSCLC cells (34,35). Miyoshi et al. showed that adjuvant treatment for stage I NSCLC patients with a TS negative expression led to a significant better survival compared to those who were TS positive (36). Ceppi et al. recently found higher TS levels in squamous cell and highly differentiated carcinomas (37). TS expression could, therefore, be used as a predictive marker for treatment of NSCLC patients with TS-inhibiting agents such as pemetrexed, UFT or 5-FU.

Another mechanism involved in the activity of UFT could be the anti-angiogenetic properties of its metabolites gamma-hydroxybutylic acid (GHB) and gamma-butyrolactone (GBL) (38,39). Therefore, a combination of UFT with other anti-angiogenetic agents like bevazucimab would be worth of investigation.

In conclusion, the combination of UFT, etoposide and leucovorin is active in 2nd or 3rd line therapy of Caucasian NSCLC patients and because of its favourable toxicity profile warrants further investigation.

Conflict of Interest Statement

None declared

Merck-Serono had no involvement in the study design, collection, analysis and interpretation of the data and in writing the manuscript.

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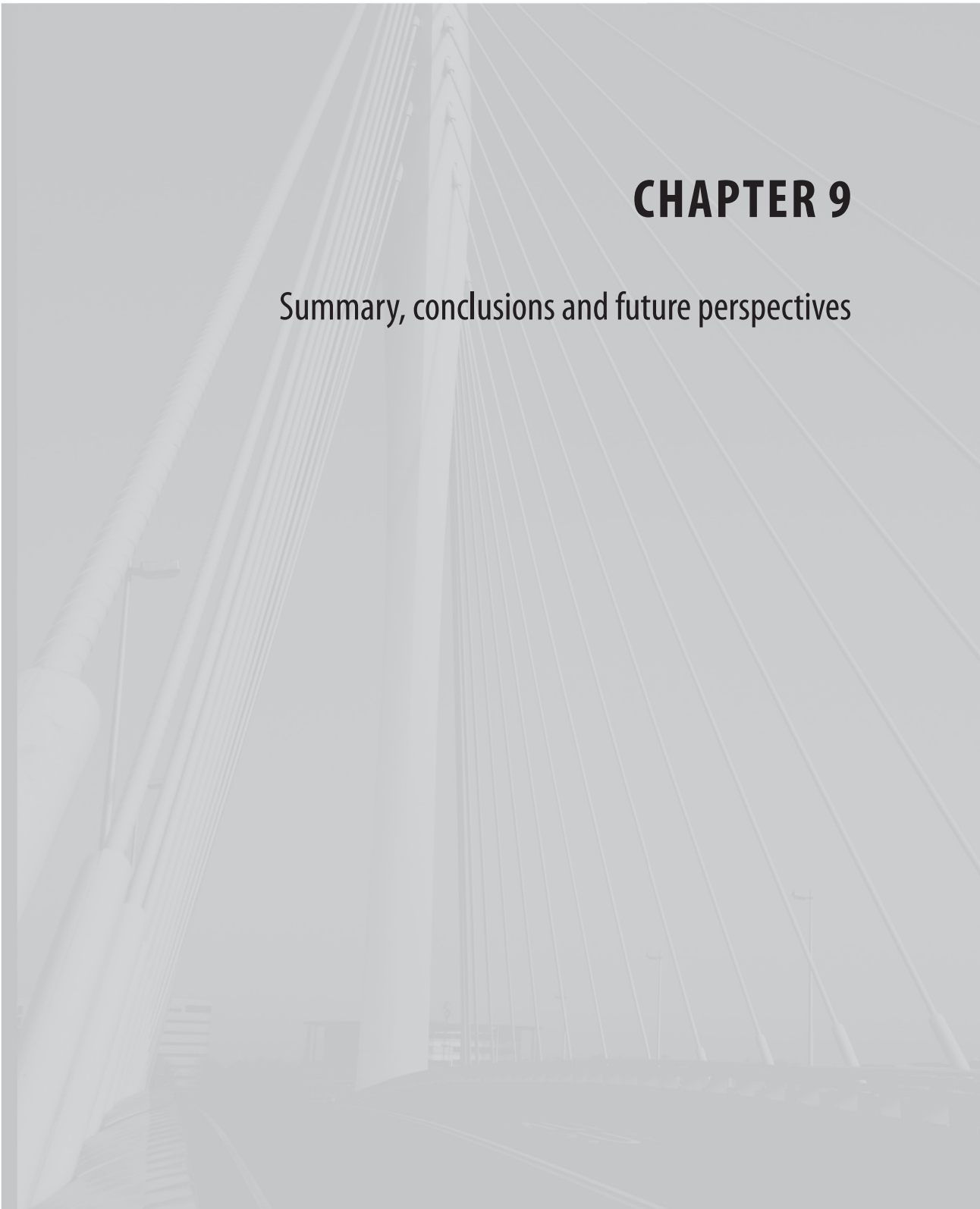

CHAPTER 9

Summary, conclusions and future perspectives

SUMMARY AND CONCLUSIONS

Lung cancer is the leading cause of cancer mortality in the United States and Europe. Approximately 85% of the patients with lung cancer have non–small cell lung cancer (NSCLC), which can be classified into squamous, adeno, large cell and not otherwise specified (NOS) histologies. Two third of the patients have locally advanced or metastatic disease at the time of diagnosis.
Both for stage IIIA and IIIB disease, the advantages of a combined modality approach including chemotherapy, radiation therapy with or without surgery are well documented for selected subsets of patients.
Although concurrent chemoradiotherapy is superior to sequential therapy, in a number of patients the sequential approach remains the treatment of choice. Approximately one third of our NSCLC patients have contraindications for cisplatin, such as inability to receive hyperhydration (cardiac dysfunction, renal failure) or pre-existing peripheral neuropathy or hearing loss. Patients with severe comorbidities are no good candidates for the concurrent chemoradiotherapy approach and for cisplatin-based chemotherapy.

In **chapter 2** we discussed in a phase II study the toxicity and effectivity of the induction chemotherapy regimen of carboplatin and gemcitabine in 41 patients with stage IIIA and IIIB NSCLC. The induction treatment was active and well tolerated. In this phase II study an overall response rate of 51% was achieved and toxicity was mild. Thrombocytopenia grade 3 and 4 was present in 35% of cases, neutropenia grade 3 and 4 in 41%. There was no febrile neutropenia and non-hematological toxicity was mild. Relative dose intensity equaled 99% for carboplatin and 91% for gemcitabine. 89% of patients completed treatment and underwent sequential radiotherapy. Although response rate was lower than in the induction regimens with cisplatin, gemcitabine and carboplatin administered according to a 3-week schedule is an active and safe induction regimen and a reasonable alternative especially for patients in whom cisplatin-based chemotherapy is contraindicated.

For well selected patients with stage III unresectable NSCLC, concurrent chemoradiotherapy is the treatment of choice (1-5).
In **chapter 3** we present the results of 2 phase I trials with pemetrexed and cisplatin with concurrent thoracic radiotherapy. The first trial was performed in patients with unresectable stage III NSCLC with a good performance status, the second trial in patients with limited disease SCLC.
This is the first report on the acute and late toxicity of this new combined modality treatment. Although both studies were prematurely closed without reaching the MTD, we

have demonstrated that the combination of full doses of cisplatin (75-80 mg/m^2) and pemetrexed 500 mg/m^2 with concurrent radiotherapy up to 50 Gy (25 x 2 Gy) is well tolerated. Hematological toxicity was mild, no febrile neutropenia or toxic deaths were observed. Grade 3 and 4 acute or late pulmonary toxicities have not been observed. Although one patient experienced a grade 3 acute esophageal toxicity, this patient was able to complete radiation therapy. In the stage III NSCLC study, two patients achieved a partial response, 1 patient had a complete response. One patient died with progressive disease at 21 months (local failure), the other patients are still alive after 3 years of follow-up. Because in boths studies, 2 out of 13 patients (15%) developed late grade 2 pulmonary toxicity, close follow-up for late pulmonary toxicity is recommended, especially in studies with higher radiation dosages. Currently, a randomized phase III study in unresectable non-squamous locally advanced stage III NSCLC with full dose pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2 and radiotherapy 66 Gy in 33 fractions followed by consolidation pemetrexed compared to cisplatin-etoposide with concurrent radiotherapy followed by consolidation chemotherapy is ungoing. (6)

Although this new combined modality treatment seems promising, this treatment appears to be suitable for highly selected patients. Our study in stage III NSCLC was conducted in 2 academic centers and only 4 patients have been enrolled in 18 months. Twelve patients have been registered, but appeared to be ineligible. Among these screening failures, 6 appeared to be stage IV NSCLC, 5 patients were ineligible because of V20 > 36% and 1 patient because of exceeding esophageal RT constraints.

Chapter 4

Despite promising results, the role of a surgical resection after induction chemotherapy (with or without radiation) in stage IIIA and IIIB NSCLC remains controversial.

The EORTC 08981 study in stage IIIB (T4-N3) was conducted to investigate whether an induction regimen with concurrent chemoradiotherapy followed by surgery after restaging by mediastinoscopy and/or FDG-PET was feasible in a multicenter setting. Unfortunately the study closed prematurely and illustrates that the conduct of a tri-modality approach across Europe was difficult at that time. One of the reasons was that in case of N2 or N3, re-mediastinoscopy after induction treatment was mandatory and it appeared to be a major threshold for patient enrolment. At that time, minimally invasive staging procedures such as endoscopic esophageal ultrasound (EUS) and endoscopic bronchial ultrasound (EBUS) were not widely available. As these techniques are now available in most centers, it can be expected that these techniques will change the spectrum of restaging of the mediastinum in the near future (7,8). It is very unlikely that a scenario with two mediastinoscopies (at baseline and post-induction) will be the best one in future

multimodality treatment. Upfront staging with minimally invasive endoscopic techniques has become very attractive; mediastinoscopy can then be performed in optimal conditions after induction treatment. Although the number of participants enrolled in our trial was low, the results are disappointing with a high rate of pneumonectomies and major complications after right-sided pneumonectomy. Subgroup analyses from both EORTC 08941 and the Intergroup Study 0139 (9,10) have shown an improved outcome in patients who are downstaged, and/or in whom a complete resection can be performed by lobectomy compared to matched irradiated patients.
From EORTC 08981 we have learned that minimally invasive new staging and restaging techniques are warranted and that a right-sided pneumonectomy after induction treatment should be avoided.
In general, in stage III-N2/3, the role of surgery compared with radical and adequate modern thoracic radiotherapy for local control after induction treatment is still a challenge. Further randomized controlled trials are needed to show superiority of neoadjuvant treatment followed by surgical resection for patients with stage III-N2/3 NSCLC. Two large randomized controlled trials are ongoing in stage IIIA-N2 (11) and IIIA/B NSCLC (ESPATÜ,12). There is no consensus on the intensity of the induction therapy. In patients receiving induction chemoradiation, early toxicities (e.g. esophagitis and hematotoxicity) are increased and in those undergoing surgery, postoperative mortality rate is higher especially when pneumonectomy is performed. Whether chemoradiation is superior to chemotherapy alone as induction therapy is currently investigated in a Swiss trial (13).

In **chapter 5** the treatment options for stage IIIA NSCLC are reviewed. Prospects on novel treatment modalities and future research opportunities are presented. Few issues are as controversial in NSCLC as the management of patients with stage IIIA-N2 NSCLC. The optimal treatment of patients presenting with stage IIIA-N2 disease is a moving target, as clinicians are constantly challenged with improvements in staging and changes in therapy, resulting in evolving patterns of approach. Incidental pIIIA-1/2 should be followed by adjuvant chemotherapy, whenever appropriate. Surgical resection after downstaging with induction treatment for cIIIA-3/4 can be radical and can result in long-term survival, but whether this approach is superior to modern radical thoracic radiotherapy remains unproven. In order to address this question a trial would be required randomising patients with clinical substage IIIA-3 and perhaps 4 after adequately proven downstaging by induction therapy between resection and radiotherapy. The current heterogeneity of the (re)staging procedures and the large required sample size are two important hurdles for such a study. Mediastinal restaging by both imaging and endoscopic techniques will increasingly become of interest. The minimally invasive

techniques, using fine needle aspiration via echo-endoscopic guidance through either esophagus (EUS) or bronchus (EBUS), are both considered complementary and are likely to be superior to the more invasive surgical mediastinal procedures (8). An ongoing randomized trial is investigating this issue (14).
Improvements in dose localization techniques such as Involved Field Radiotherapy (IFRT), Intensity Modulated Radiotherapy (IMRT), four dimensional radiotherapy (4D-RT), Image Guided Radiotherapy (IGRT), breathing-adapted radiation therapy (gating or tracking), particle beam therapy or a combination of these will become standard, allowing high dose irradiation with near-surgical precision. In summary, patients with locally advanced NSCLC encompass a heterogeneous group whose optimal management approach is dependent on multiple factors and remains to be defined for some patients. A combined modality approach with chemoradiotherapy with a platinum-based regimen has become the preferred treatment for the majority of patients with stage III disease detected clinically. The role of surgery in patients with pre-operatively detected but non-bulky mediastinal lymph node involvement who respond to chemotherapy or chemoradiotherapy remains unclear, but seems reasonable in those patients with down-staged nodal disease after induction therapy who do not require pneumonectomy.
Adjuvant platinum-based chemotherapy should be offered to those patients found to have stage III disease at the time of surgery.
A multidisciplinary approach to managing this diverse group of patients is recommended. In daily practice, it is important that we provide our patients with a balanced view of the different treatment options, taking into account the treatment complications and the availability of local expertise and resources.

The majority of patients diagnosed with NSCLC will eventually be treated with chemotherapy for metastatic disease. The current standard for this group of patients with a good performance status is cis- or carboplatin in combination with a 3rd generation agent, including paclitaxel, gemcitabine, vinorelbine or docetaxel and more recently pemetrexed for patients with non-squamous histology (15-18). However, as pointed out in the introduction, there is an ongoing debate about the choice of the platinum agent. Many North American physicians and Cooperative Groups prefer carboplatin-based therapies and also in Europe this regimen is frequently used. In **chapter 6** we studied two schedules of a 21-day regimen of carboplatin and gemcitabine in a randomized phase II study design. Although the study was prematurely stopped after first stage analysis, probably because of too optimistic predefined expectations, we believe that the current data remain of interest. The regimen in which carboplatin (AUC of 5) was administered on day 8 and gemcitabine 1250 mg/m^2 on day 1 and 8 (Arm B) was associated with less grade 3 and 4 neutropenia

and thrombocytopenia compared with the standard regimen in which gemcitabine was administered on day 1 and 8 and carboplatin on day 1 (Arm A). Seventy-nine percent (95% confidence interval (CI) 61-91%) grade 3-4 toxicity was observed (neutropenia and thrombocytopenia) in arm A and 50% (95% CI 32-68%) in arm B. Grade 3-4 thrombocytopenia occurred in 66% of cases in arm A and in 26% in arm B. The high incidence of grade 3-4 thombocytopenia in arm A led to frequent platelet transfusions. We observed 30% grade 4 hematological toxicity in arm A and 3% in arm B. The two regimens had comparable dose intensity. The regimen with carboplatin administered on day 8 will lead to less frequent blood count controls, dose reductions and platelets transfusions, which is important for the daily patient care.

The optimal duration of platinum-based therapies has been an area of investigation as well. Four trials (19-20) showed that with a maximum of 4 courses of chemotherapy overall survival was equivalent to more than 4 courses with similar (21-23) or less toxicity (20,21). Chemotherapy may lead to the selection of chemo-resistant tumour clones. Frequent exposure to different cytotoxic agents with brief intervals may inhibit tumor re-growth and limit the emergence of drug resistant cell lines (24,25). Sequential chemotherapy administration offers the possibility to increase drug diversity while maintaining dose intensity, potentially leading to less dose reductions, an optimal dose intensity and prolonged treatment duration and disease control (26,27).
In **chapter 7** we investigated the use of non-cross resistant sequential single agent chemotherapy in first line advanced NSCLC patients, at a time the inferiority of single agents to platinum-based doublets was not proven. In this non-randomized phase II study the sequential administration of single agent gemcitabine followed by paclitaxel in the first line treatment of advanced NSCLC has a favourable toxicity profile, a median time to progression and overall survival comparable with other sequential trials reported in the literature. However, it has become now evident from the literature that single agent gemcitabine in first line treatment of good performance status patients with stage IIIB/IV NSCLC is inferior compared to platinum-based doublets (27,28). Because of its favourable toxicity profile, our regimen with sequential single agents might be a viable option for elderly or poor performace status advanced NSCLC patients, as demonstrated in the study of Tibaldi et al (29).
The results of the sequential study add to the existing knowledge on the treatment of NSCLC. First, the data contribute to the concept of maintenance chemotherapy with non-cross resistant drugs. Recent trials support the rationale of using non-cross-resistant third generation agents before disease progression (26,27). Secondly, we strongly believe that our single agent non-platinum approach, might be of value in ERCC1

positive patients, especially if we move to a time of individualizing treatment (28). This hypothesis should be further tested in a clinical trial.
Our data confirm the results of recent trials, showing that gemcitabine is not as effective in adenocarcinoma as in squamous cell carcinoma (18). Recently, it has become clear that histology matters in the treatment of NSCLC and this is a big challenge especially for our pathologists.

Second-line systemic therapy is chemotherapy administered once disease progression has been demonstrated after completion of first-line therapy. Approximately 40 to 50% of patients enrolled in first-line trials have subsequently received second-line therapy (19). There are currently three agents approved by the FDA for second-line therapy; two cytotoxic chemotherapy agents, docetaxel and pemetrexed, and the EGFR TKI, erlotinib (30-32). Currently many physicians base their choice for the second-line agent on personal and patient preferences, the presence of co-morbidity, the specific toxicity profiles associated with these agents and treatment convenience. Oral agents with few side effects are appealing in 2nd or 3rd line setting when patients are usually in a less favourable condition. In **chapter 8**, we have demonstrated that oral UFT-etoposide is active and well tolerated in second and third line Caucasian NSCLC patients with advanced disease. This is the first report on the efficacy of UFT-etoposide in Caucasian patients. With a similar range of efficacy, the toxicity of the UFT–etoposide combination is much lower than for the other 2nd line agents. Although costs have not been evaluated in our study, a cost estimate for UFT-etoposide appeared to be lower than for the other 2nd line agents. This is important given the high pressure on health care budgets today.
Thymidylate synthase is an enzyme that plays an important role in DNA biosynthesis and it is the target enzyme for anti-metabolites such as 5-FU and UFT. Recently it has been shown that TS levels are higher in squamous cell and highly differentiated carcinomas (33). TS expression could, therefore, be used as a predictive marker for the treatment of NSCLC patients with TS-inhibiting agents such as pemetrexed, UFT or 5-FU. Because of its low toxicity profile and low costs, UFT is also of special interest in the area of maintenance chemotherapy.

Today it has become clear that the crucial 'flaw' in the existing treatment paradigm for non-small cell lung cancer is the 'one size fits all approach'. There is evidence now that we definitely have to change the "one size fits all approach" towards a personalized approach of treatment selection.

As a consequence, in the area of new targeted therapies, we have to realize that even conventional chemotherapy is "targeted therapy". The tools to begin appropriately "targeting" it are now available.

FUTURE PERSPECTIVES

Individualizing therapy for non-small cell lung cancer

In stage III NSCLC patients, integration of novel biological agents such as monoclonal antibodies and modern radiotherapy techniques as part of multimodality approach will further improve outcome. With the frequent occurrence of large tumour volumes and the central location in stage III NSCLC, high dose intensity may seem impractical. Several novel radiation techniques are likely to overcome this problem and to improve local control by delivery of higher radiation dose to smaller volumes, allowing for less toxicity. 4D radiotherapy and dose painting offer the prospect for stage III NSCLC of using dose-intensive schedules. Further implementation of these techniques needs well-designed clinical trials in appropriately selected patients.

Current practice for selection of therapy in patients with advanced stage NSCLC is largely empiric and based on patients characteristics such as age, performance status, weight loss. In general, in our decision-making process, four dimensions are considered: evidence from the literature, individual patient characteristics (age, sex, performance status), patient preference (longer life versus quality of life) and physician experience and preference. Although this empiric process serves most patients well, in 2009 a paradigm shift has begun. Our decision-making process moves from empiric to an "integrated approach". A variety of selection factors will make it possible to consider customizing therapy for the individual patient, by integrating clinical, histological and molecular factors.
For the first time, randomized clinical trials in NSCLC suggest that histologic subtyping can also be used for chemotherapy selection (17) and recent advances in treatment of lung cancer require greater accuracy in the subclassification of non-small-cell lung cancer (NSCLC). Interobserver variability and the lack of specific, standardized assays limit the current abilities to adequately stratify patients for such treatments. MicroRNA biomarkers for the identification of i.e. squamous cell carcinoma and standardized assays are warranted.
The importance of histology subtype rises a diagnostic issue. In clinical practice and particularly in patients with metastatic disease, diagnosis is frequently performed by

fine-needle biopsy, which produces a general cytological NSCLC finding. However, based on the previous statement, an optimal treatment calls for a specific diagnosis. Treatment of "unspecified" tumours with some agents may expose patients to unnecessary risks or deny them potentially effective treatment. Therefore, should we still use invasive approaches to obtain a tumour sample tissue for a subtype of histological diagnosis? Recent data on, for example the thymidylate synthase enzyme, suggest that histology is a crude method of molecular selection. In the future, the possibility of obtaining a molecular characterization of circulating tumor cells could probably help avoid an invasive strategy for diagnosis. Eventually, we hope to find markers that substitute for the significance of histologic subtype. As in the field of breast cancer management, where therapy is dictated by estrogen receptor, progesterone receptor, and HER2/neu expression, we anticipate that molecular predictors of response will eventually supplant the role of histology when making clinical treatment decisions in patients with NSCLC.

Technologies such as genomics, proteomics and biomarker development represent promising approaches with which to probe for predictive markers. Modern techniques have facilitated the identification of specific genetic factors that may play a role in disease progression and patient response to therapy, prompting research efforts to identify the clinical predictors of outcome for NSCLC. Recent evidence suggests that the application of a pharmacogenomic approach has the potential to greatly improve survival in certain subpopulations of patients with NSCLC, which could profoundly influence the decision-making process used in evolving treatment strategies for this malignancy.

The future success of targeted therapies will need a coordinated, multidisciplinary team approach. Clinical trials that investigate the activity of novel agents and incorporate patient selection, based on clinical and molecular factors, are required.

Future challenges will include ensuring that molecular determinants are identified as novel chemotherapeutic agents are being developed, enabling rationale therapeutics. Clinical trials will then enrich patients with the molecular determinants, potentially increasing response rates and survival in a specific group of patients who express this molecular determinant. It is hoped that these patient-specific 'individualized cocktails' will substantially improve response rates and survival. Integrated decision-making, incorporating clinical, histologic and molecular factors is a future goal.

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Samenvatting, conclusies en toekomstige ontwikkelingen

SAMENVATTING EN CONCLUSIES

Longkanker is de belangrijkste oorzaak van kankersterfte zowel in Amerika als Europa. Ongeveer 85% van de longkanker patiënten hebben een niet-kleincellig longcarcinoom en twee derde presenteert zich met locaal gevorderde (stadium IIIA of IIIB) of gemetastaseerde ziekte (stadium IV).
Voor zowel stadium IIIA en IIIB niet-kleincellig longcarcinoom zijn de voordelen van een combinatie behandeling, bestaande uit chemotherapie, radiotherapie en/of chirurgie, voor goed geselecteerde patiënten, duidelijk aangetoond.
Alhoewel chemotherapie toegediend gelijktijdig met bestraling leidt tot een betere overleving dan chemotherapie gevolgd door bestraling, blijft voor een grote groep patiënten de sequentiële behandeling de meest aangewezen behandeling. Ongeveer een derde van onze patiënten met niet-kleincellig longcarcinoom is niet geschikt voor een behandeling met cisplatine en dit omwille van cardiale problemen, nierfunctiestoornissen, neurologische- en gehoorsproblematiek. Ernstige comorbiditeit maakt een concomitante behandeling en toediening van cisplatine vaak onmogelijk.
In **hoofdstuk 2** wordt een fase II studie besproken waarin het effect en de bijwerkingen van inductiechemotherapie met carboplatine en gemcitabine, bij 41 patiënten met stadium IIIA of IIIB niet-kleincellig longcarcinoom, wordt beschreven. We hebben aangetoond dat het inductieschema werkzaam is en goed wordt verdragen. Het radiologisch responspercentage was 51% en de toxiciteit was vrij mild. In 35% van de patiënten werd een graad 3-4 thrombopenie vastgesteld en in 41% een graad 3-4 neutropenie. Febriele neutropenie werd niet gedocumenteerd en de niet-hematologische toxiciteit was laag. De relatieve dosisintensiteit voor carboplatine was 99%, voor gemcitabine 91%. 89% van de patiënten kon aansluitend worden behandeld met de geplande radiotherapie. De mediane overleving was 13 maanden, mediane tijd tot progressie 9 maanden.
Alhoewel de respons wat lager is dan in de inductiestudies met cisplatine, is de sequentiële behandeling met het drie wekelijks inductieschema met carboplatine en gemcitabine gevolgd door radiotherapie een goed alternatief, vooral voor patiënten die niet geschikt zijn voor cisplatine bevattende chemotherapie.

Voor een kleinere groep, goed geselecteerde patiënten met stadium III, is concomitante chemoradiotherapie de aangewezen behandeling.
In **hoofdstuk 3** stellen we de resultaten voor van 2 fase I studies met pemetrexed, cisplatine met concurrent thoracale radiotherapie. De eerste studie werd uitgevoerd bij patiënten met goede performance status met niet-resectabel stadium III niet-kleincellig

longcarcinoom, de tweede studie bij patiënten met limited-disease kleincellig longcarcinoom.
Dit is het eerste manuscript waarin zowel acute als late toxiciteit van deze nieuwe combinatie behandeling worden beschreven. Alhoewel beide studies vroegtijdig zijn afgesloten zonder bereiken van de MTD, hebben we kunnen aantonen dat de volledige dosis van cisplatine (75-80 mg/m^2) en pemetrexed 500 mg/m^2 kan gecombineerd worden met gelijktijdige thoracale radiotherapie tot een totale dosis van 50 Gy (25x2 Gy). Pemetrexed is het eerste, nieuwe derde generatie cytostaticum dat in volledige dosis kan gecombineerd worden met thoracale radiotherapie. Deze combinatie behandeling wordt goed verdragen. De hematologische toxiciteit was mild, er was geen febriele neutropenie en er waren geen toxische doden. We hebben geen graad 3 of 4 acute of late long toxiciteit vastgesteld. Eén patient had een graad 3 acute slokdarmtoxiciteit, maar dit leidde niet tot onderbreken van de radiotherapie. Dosis limiterende toxiciteit werd niet vastgesteld. Van de 4 patiënten met stadium III niet-kleincellig longcarcinoom had 1 patiënt een complete respons, 2 hadden een partiële respons, de vierde patiënt was niet evalueerbaar. Gezien in beide studies, 2 van de 13 patiënten (15%) graad 2 late pulmonale toxiciteit ontwikkelden, is een nauwkeurige follow-up aan te raden, zeker in studies waar een hogere radiotherapie dosis wordt toegediend. Een gerandomiseerde phase III studie bij patiënten met niet-squamous stadium III niet-kleincellig longcarcinoom, met cisplatine 75 mg/m^2 en pemetrexed 500 mg/m^2 met concurrent radiotherapie 66 Gy in 33 fracties gevolgd door consolidatie chemotherapie met pemetrexed, in vergelijking met cisplatine-etoposide met radiotherapie gevold door consolidatie chemotherapie naar keuze, is recent gestart in meerdere landen.
Alhoewel deze behandeling beloftevol lijkt, willen we toch benadrukken dat deze slechts voor een beperkte groep patiënten geschikt is. Onze fase I studie bij stadium III NSCLC werd uitgevoerd in 2 academische centra en slechts 4 patiënten werden geïncludeerd in een periode van 18 maanden. Twaalf patiënten werden geregistreerd maar bleken uiteindelijk niet geschikt voor inclusie; 6 omwille van stadium IV, 5 omwille van V20> 36% en 1 omwille van een te verwachten slokdarmtoxiciteit die niet acceptabel was.

Niet tegenstaande beloftevolle resultaten, blijft de rol van chirurgie na chemotherapie (met of zonder bestraling) bij stadium IIIA en IIIB niet-kleincellig longcarcinoom controversieel. In **hoofdstuk 4** beschrijven we de EORTC 08981 studie. Deze studie bij patiënten met stadium IIIB (T4-N3) niet-kleincellig longcarcinoom werd uitgevoerd om te onderzoeken of inductie chemoradiotherapie gevolgd door chirurgie na restagering door middel van re-mediastinoscopie en/of FDG-PET, haalbaar was in een multicenter setting. Helaas moest de studie worden gesloten en bleek deze tri-modality behande-

ling op dat ogenblik moeilijk uitvoerbaar in Europa. Eén van de redenen was dat, in geval van N2 of N3, na de inductie behandeling een re-mediastinoscopie moest worden uitgevoerd, wat voor een aantal centra toch een belangrijke hinderpaal bleek. Minimaal invasieve stageringsprocedures zoals EBUS en EUS waren toen niet beschikbaar. Het is te verwachten dat met het de komst van EBUS en EUS het restageren van het mediastinum nu veel gemakkelijker wordt. Het is weinig waarschijnlijk dat een scenario met mediastinoscopie baseline en na inductie nog zal worden uitgevoerd in toekomstige multimodality behandelingen. Upfront stagering met minimaal invasieve endoscopische technieken is te verkiezen; de mediastinoscopie kan dan worden uitgevoerd in optimale omstandigheden na inductie therapie.
De resultaten van de patiënten in onze studie waren eerder ontgoochelend met veel pneumonectomieën en toch majeure complicaties na rechtszijdige pneumonectomie. Exploratieve subgroep analyses van zowel EORTC 08941 als de Amerikaanse Intergroup studie 0139, hebben aangetoond dat enkel patiënten met downstaging en complete resectie met lobectomie een gunstiger overleving hebben, vergeleken met bestraalde patiënten.
Van EORTC 08981 hebben we geleerd dat nieuwe, minimaal invasieve stagerings en restagerings technieken nodig zijn en dat rechtzijdige pneumonectomie na inductie therapie moet vermeden worden.
De rol van chirurgie na inductie bij stadium III N2/N3 NSCLC blijft een punt van discussie. Gerandomiseerde, gecontrolleerde studies zijn nodig om de superioriteit van chirurgie na inductie tegenover radicale radiotherapie aan te tonen. Momenteel zijn twee dergelijke studies lopende in stadium IIA-N2 en IIIB niet-kleincellig longcarcinoom. Op dit moment is er nog geen consensus over de intensiteit van de inductie therapie. Of inductie chemoradiotherapie beter is dan inductie chemotherapie alleen, wordt nu onderzocht in een Zwitserse studie.

In **hoofdstuk 5** wordt een overzicht gegeven van de verschillende behandel mogelijkheden voor stadium IIIA niet-kleincellig longcarcinoom en de toekomstige ontwikkelingen worden besproken. De behandeling van patiënten met stadium IIIA-N2 niet-kleincellig longcarcinoom blijft een controversieel onderwerp. Bovendien is de optimale behandeling onderhevig aan verandering omdat we voortdurend te maken hebben met verbetering in stageringsprocedures en veranderingen in therapieën.
Patiënten met pIIIA-1/2 worden best behandeld met adjuvante chemotherapie zo mogelijk. Chirurgische resectie na downstaging met inductiebehandeling voor patiënten met stadium cIIIA-3/4 kan radicaal zijn en resulteren in langdurige overleving. Of deze benadering beter is dan combined modality met moderne radiotherapie blijft de vraag.

Om deze vraag te beantwoorden zouden in een trial, patiënten met stadium IIIA-3/4 na adequate downstaging, moeten geradomiseerd worden tussen chirurgie en radiotherapie. De heterogeniteit van de (re)stagering procedures en het groot aantal patiënten vereist voor dergelijke studie zijn een belemmerende factor.
Mediastinale (re)stagering door middel van nieuwere beeldvorming en minimaal invasieve endoscopische technieken zoals EUS en EBUS wordt steeds belangrijker. EUS en EBUS zijn complementair en zullen waarschijnlijk de meer invasieve mediastinoscopie overbodig maken. Een gerandomiseerde studie die deze vraagstelling onderzoekt wordt momenteel geanalyseerd. Verbeteringen in dosis localisatie technieken zoals Involved Field Radiotherapy (IFRT), Intensity Modulated Radiotherapy (IMRT), vier dimensionele radiotherapie (4D-RT), Image Guided Radiotherapy (IGRT), radiotherapie aangepast aan de ademhaling (gating or tracking), partikel beam therapy of een combinatie van deze technieken, zullen standaard worden en zullen hoge dosis radiotherapie met bijna chirurgische precisie mogelijk maken.
Samenvattend, patiënten met locaal gevorderd niet-kleincellig longcarcinoom zijn een zeer heterogene groep en de optimale behandeling is afhankelijk van veel verschillende factoren en moet zeker voor een aantal patiënten nog gedefiniëerd worden. Een combinatie behandeling met chemotherapie en radicale radiotherapie is voor de meeste stadium III patiënten aangewezen. De rol van chirurgie bij patiënten met preoperatief vastgstelde N2,N3 klieren, die reageren op chemotherapie of chemoradiotherapie, blijft controversieel. Chirurgie lijkt een te verdedigen optie bij patiënten bij wie downstaging is bereikt en bij wie de resectie kan beperkt blijven tot een lobectomie. Accurate mediastinale restagering is derhalve zeer belangrijk.
De behandeling van stadium III patiënten kan zeker nog verbeterd worden en een multidisciplinaire benadering van deze patiënten is cruciaal. In onze dagelijkse praktijk is het heel belangrijk dat we onze patiënten een zo volledig mogelijk beeld geven van de verschillende mogelijkheden, rekening houdend met complicaties van de diverse behandelingen, de locale beschikbare expertise en voortschrijdende onderzoeksontwikkelingen.

De meerderheid van onze longkanker patiënten zal vroeg of laat behandeld worden met chemotherapie voor gemetastaseerde ziekte.
De standaard behandeling voor deze patiënten met een goede performance status is cis-of carboplatine in combinatie met een derde generatie middel, paclitaxel, gemcitabine, vinorelbine of docetaxel en meer recent pemetrexed voor niet-squameuse histologie. Nog steeds verschillen de meningen over het gebruik van cis- of carboplatine. In Noord-Amerika wordt heel veel carboplatine gebruikt en ook in Europa gaat steeds

meer de voorkeur uit naar carboplatine bij patiënten met gemetastaseerde ziekte. In **hoofdstuk 6** vergelijken we in een gerandomiseerde fase II studie twee schema's van de 21-dagen kuur carboplatine en gemcitabine. Alhoewel de studie vroegtijdig moest worden gesloten, zijn we van mening dat de data van deze studie interessant zijn. Het schema met carboplatine (AUC 5) toegediend op dag 8 en gemcitabine 1250 mg/m^2 op dag 1 en 8 (arm B) vertoont minder graad 3-4 thrombopenie en neutropenie in vergelijking met het standaard schema met carboplatine op dag 1 en gemcitabine op dag 1 en 8 (arm A). We vonden 79% graad 3-4 toxiciteit (thrombopenie en neutropenie) in arm A en 50% in arm B. Graad 3-4 thrombopenie werd vastgesteld in 66% in arm A en 26% in arm B, graad 4 hematologische toxiciteit was 30% in arm A en 3% in arm B. De effectiviteit van beide schema's lijkt vergelijkbaar. Het schema met carboplatine op dag 8 kan in de dagelijkse praktijk zorgen voor minder bloedcontroles, minder dosisreducties en minder bloedplaatjes transfusies.

De optimale duur van platinum bevattende chemotherapie is reeds in verschillende studies onderzocht en er is aangetoond dat de overleving niet beter is wanneer meer dan 4 cycli chemotherapie worden gegeven. Meer dan 4 cycli platinum bevattende chemotherapie leidt tot meer toxiciteit en verminderde kwaliteit van leven.
Sequentiële chemotherapie is een benadering die het mogelijk maakt om verschillende drugs toe te dienen, dosis intensiteit te behouden en langduriger te behandelen met als gevolg langere ziektecontrole.
In **hoofdstuk 7** onderzoeken we niet-cross resistente sequentiële single agent chemotherapie als eerst lijns behandeling voor patiënten met gevorderd niet-kleincellig longcarcinoom. In deze niet-gerandomiseerde fase II studie hebben we aangetoond dat de sequentiële toediening van gemcitabine gevolgd door paclitaxel een behandeling is met een gunstig toxiciteitsprofiel en met een mediane tijd tot progressie en mediane overleving vergelijkbaar met de andere sequentiële studies uit de literatuur. Ondertussen is echter duidelijk geworden dat single agent gemcitabine als eerste lijn voor patiënten met goede performance status inferieur is aan een platinum gebaseerd doublet.
Ons schema met sequentieel single agents, gemcitabine en paclitaxel, zou wel kunnen gebruikt worden voor oudere patiënten of patiënten met minder goede conditie, zoals recent ook door andere auteurs is aangetoond. Het toedienen van sequentieel single agents past in het concept van maintenance chemotherapie met niet-cross resistente drugs. Zeer recente trials ondersteunen het gebruik van niet-cross resistente derde generatie drugs vóór het optreden van ziekteprogressie.

We zijn van mening dat het sequentiële single agent non-platinum schema uit onze studie waardevol zou kunnen zijn voor patiënten die ERCC1 positief zijn en derhalve geen baat hebben bij platinum bevattende chemotherapie. Deze hypothese zou moeten getest worden in een klinische studie. Tot slot bevestigen onze resultaten de gegevens van recent onderzoek, waaruit blijkt dat gemcitabine minder actief is bij het niet-squameus carcinoom. Het wordt dus meer en meer duidelijk dat histologie van belang is bij de behandeling van het niet-kleincellig longcarcinoom en dat is een mooie uitdaging voor onze pathologen.

Tweede lijns chemotherapie is chemotherapie die toegediend wordt als ziekteprogressie wordt vastgsteld na het beëindigen van de eerste lijns behandeling. Momenteel zijn 3 middelen geregistreerd voor 2e lijns behandeling van het niet-kleincellig longcarcinoom: docetaxel, pemetrexed en de EGFR TKI erlotinib. Voor behandeling in 2e of 3e lijn zijn orale middelen met weinig bijwerkingen te verkiezen, zeker omdat een aantal patiënten toch in een minder goede algmene toestand zijn. In **hoofdstuk 8** hebben we in een fase II studie aangetoond dat oraal Uracil-Tegafur (UFT) met etoposide actief is en goed wordt verdragen in 2e en 3e lijn bij Caucasische patiënten met gevorderd niet-kleincellig longcarcinoom. Dit is het eerste artikel dat de effectiviteit van UFT-etoposide aantoont bij Caucasische patiënten. De effectiviteit in termen van tijd tot progressie en mediane overleving is vergelijkbaar met de andere 2e lijns middelen en de toxiciteit is beduidend minder. Een kostenschatting voor UFT-etoposide lijkt veel lager dan voor de andere 2e lijns middelen, wat van belang is gezien de enorme druk op de gezondheidsbudgetten.
Thymidylate synthase is een enzyme dat een rol speelt in de DNA biosynthese en een target enzyme voor anti-metabolieten zoals 5-FU, pemetrexed en UFT. TS expressie zou kunnen gebruikt worden als predictieve marker voor behandeling met middelen als pemetrexed, 5-FU en UFT.
Gezien zijn werking in 2e en 3e lijn, het gunstig bijwerkingsprofiel en lage kosten zou UFT-etoposide uitermate geschikt kunnen zijn voor maintenance behandeling na eerste lijns chemotherapie.

Het is nu duidelijk geworden dat de cruciale zwakte in de tot nu toe toegepaste behandelingen bij het niet-kleincellig longcarcinoom, de "one size fit all" benadering is.
Er is evidentie dat een geïndividualiseerde benadering en behandeling van de patiënt met een niet-kleincellig longcarcinoom nodig is.
In het tijdperk van de "targeted" therapieën moeten we ons realiseren dat conventionele chemotherapie eveneens "targeted" therapie is geworden en de middelen om adequaat te "targeten" zullen in de toekomst meer en meer beschikbaar zijn.

TOEKOMSTIGE ONTWIKKELINGEN

Integratie van nieuwe biologicals, zoals monoclonale antibodies en moderne radiotherapie technieken als onderdeel van multimodality behandeling, zal hopelijk de overleving verbeteren van onze patiënten met stadium III NSCLC.
Er is momenteel veel beweging in het domein van de radiotherapie. Nieuwere radiotherapie technieken zullen het mogelijk maken locale controle te verbeteren door toediening van hoge dosis radiotherapie op kleinere volumes met minder toxiciteit. 4D radiotherapie en "dose painting" met IMRT zullen toelaten bij stadium III NSCLC individuele, dosis-intensieve schema's toe te passen. Verdere implementatie van deze technieken zal mogelijk worden door goed opgezette studies bij goed geselecteerde patiënten.

Tot op heden gebeurde de keuze van therapie bij patiënten met gevorderd stadium longkanker vooral empirisch en gebaseerd op patiënten eigenschappen zoals leeftijd, gewicht en performance status. Verder baseren we ons op evidentie uit de literatuur, eigen voorkeur en ervaring.
In 2009 is er toch een duidelijke verandering merkbaar. Onze benadering verschuift van een empirische naar een meer geïntegreerde approach. Het zal mogelijk worden een gepersonaliseerde behandeling te bieden, rekening houden met klinische, moleculaire en histologische factoren. Voor het eerst in de geschiedenis hebben gerandomiseerde studies bij het niet-kleincellig longcarcinoom aangetoond dat histologie kan gebruikt worden als selectie voor chemotherapie. Accurate subclassificatie van het niet-kleincellig longcarcinoom wordt daarom zeer belangrijk. Zogenaamde "unspecified tumours" houden het risico in dat we patiënten onnodig blootstellen aan toxicteit van bepaalde therapieën, terwijl we sommige patiënten goede behandelingen onthouden. De variabliteit tussen de waarnemers en het gebrek aan gestandardiseerde testen maakt accurate subclassificatie moeilijk; een bijkomend probleem is dat we vaak de diagnose van longkanker stellen op cytologie. Micro-RNA biomarkers die adenocarcinoom en spinocellulair carcinoom kunnen onderscheiden zijn daarom momenteel onderwerp van onderzoek.
Moleculaire karakterisatie van circulerende tumorcellen en identificatie van biomarkers zullen misschien het probleem van histologie subtype oplossen. Recente data betreffende bijvoorbeeld thymidylaat synthase tonen aan dat histologie eigenlijk een uiting is van moleculaire selectie.
Proteomics, genomics en de ontwikkeling van verschillende biomarkers zijn beloftevol. Het succesvol zijn van de targeted therapieën zal een gecoördineerde, multidisciplinaire aanpak vereisen. Studies die de activiteit van nieuwe middelen nagaan, gecombineerd met patiëntenselectie op basis van klinische en moleculaire factoren, zijn wenselijk. Ho-

pelijk zullen deze “patiënt-specifieke geïndividualiseerde cocktails” dan ook resulteren in een betere overleving van onze longkanker patiënten.

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CURRICULUM VITAE

Veerle Surmont is op 5 maart 1971 geboren te Izegem, België.
Zij volgde middelbaar onderwijs (Latijn-Wiskunde) aan het Bisschoppelijk Lyceum der Grauwe Zusters in Roeselare. In 1989 begon zij haar studies Geneeskunde aan de Katholieke Universiteit Leuven, waarna ze in 1996 het artsendiploma behaalde. Aan dezelfde universiteit volgde ze de opleiding interne geneeskunde (Prof. Dr. J. Févery) en aansluitend een opleiding tot longarts onder leiding van Prof Dr. M. Demedts. Zij volgde één jaar van haar opleiding longziekten in het Erasmus Medisch Centrum Rotterdam. Tijdens dat jaar was zij vooral werkzaam op de afdeling Thoracale Oncologie van de locatie Daniel den Hoed. In 2002 werd ze erkend als longarts. Hierna heeft ze vijf jaar gewerkt als staflid bij de dienst Longziekten (Prof. Dr. H.C. Hoogsteden) van het Erasmus Medisch Centrum Rotterdam, met als aandachtsgebied thoracale oncologie. Ze hield zich vooral bezig met klinische en poliklinische zorg, multidisciplinaire oncologische problematiek, klinische studies en patiëntgebonden wetenschappelijk onderzoek. In die periode zijn de studies beschreven in deze thesis tot stand gekomen.
Momenteel is de auteur werkzaam als staflid op de dienst Longziekten in het Universitair Ziekenhuis Gent, waar zij haar werkzaamheden in de thoracale oncologie verderzet. Zij is sinds maart 2009 secretaris van de EORTC Lung Group.

LIST OF PUBLICATIONS

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