Prognostic factors, survival and late mortality of patients with hodgkin's lymphoma

Spronsen, Dick Johan van

SUMMARY

This thesis presents prognostic factors, survival and late mortality of patients with Hodgkin's lymphoma diagnosed in South-East Netherlands.

Chapter 1 consists of an overview of epidemiology, pathogenesis, clinical presentation, management and its complications of Hodgkin's lymphoma (HL). HL can be diagnosed based on its typical histological picture with pathognomonic multinucleated Reed-Sternberg (RS) cells and Hodgkin (H) cells, the mononuclear variants. Accumulating data suggest that these cells originate from germinal-center B cells and their descendants, which underwent a transforming event (EBV infection?), enabling them to escape apoptotic cell death. EBV-related proteins and mRNA have been detected in the H-RS cells of 25% to 50% of HL patients in the developed countries and up to 70% to 100% in the developing countries. EBV is known to be a highly potent transforming agent in B-lymphocytes, which is normally controlled by a cytotoxic T-lymphocyte mediated immune response, which fails in patients with HL. This failure may be due to several mechanisms including down regulation of MHC class I antigens on the H-RS-cells and the production of inhibiting cytokines, (IL-10 and TGF-β) by the H-RS cells. More than 95% of the cells in HL involved tissue consist of reactive cells and the majority of the infiltrating lymphocytes display a Th2-like immunophenotype. These Th2 cells are probably attracted by the chemokine TARC, produced by the H-RS cells. The Rye histological classification of HL as used in this thesis is based on the variation of the cellular infiltrate recognizing 4 subtypes: lymphocyte predominant, nodular sclerosis, mixed cellularity and lymphocyte depletion. The staging system is based on the biological behavior of contiguous spread, in which early stage disease is confined to lymph node involvement on one side of the diaphragm. If patients with HL are not treated they have a 5-year survival of less than 5%. Patients with early stage HL generally received radiotherapy, but recent studies indicate the benefit of (adjuvant) chemotherapy in defined patient-groups, in conjunction with lower radiation dose and smaller fields to minimize toxicity. Patients with advanced disease should receive chemotherapy and the role of adjuvant radiotherapy is controversial, except for patients presenting with a large mediastinal mass. Long term survivors have an increased incidence of several diseases of which second malignancies and cardiac diseases are the most feared. Cured HL patients suffer from an increased death-risk and therefore one of the major goals of new treatment strategies is to minimize toxicity with preservation of efficacy.

Although clinical trials are essential for the development of new treatment strategies, the application of those strategies in the general health care environment can give additional proof of their efficacy, safety and utility. This is of particular interest since the results of clinical trials, with their restrictive eligibility criteria, may be biased from those in the general population, which is likely to comprise more elderly and more patients with poor performance status and/or serious co-morbidity. **Chapter 3** describes the presentation,

treatment policy and results of all patients diagnosed with HL over a 20 year period in the region of the Eindhoven Cancer Registry, covering almost one million inhabitants. The study, in fact an audit study, was started in 1983, when doubt arose on the treatment approach. The crude incidence (1.9 per 100.000 person-years) remained stable over this period and is comparable with incidence rates in other developed countries. Likewise, the mean age (38-41 yr.) and the percentage of patients presenting with early stage disease (59%) remained stable over this period. After review of the histology 4% of the registered Hodgkin cases, diagnosed in the 1970s, were reclassified as non-Hodgkin's lymphoma. Patients were diagnosed and treated in 10 community hospitals and the regional Radiotherapy Department. From 1979 the staging and therapeutic policy was, in most cases, discussed in the regular regional multidisciplinary meetings. This study group participated in the clinical trials of the EORTC from 1983. Over the 20-year period the management of newly HL patients changed, following developing insights and in accordance with the treatment advocated by the EORTC trials. In general patients with stages IA and IIA received mantle-field or inverted Y-field irradiation, whereas patients with stages IB and IIB received more extensive irradiation with or without chemotherapy. Patients with advanced disease (stage III and IV) received chemotherapy, frequently followed by involved field irradiation. The percentage of patients receiving the extensive subtotal nodal irradiation (STNI) declined from 50% in the early 1970s towards 14% in the late 1980s. Likewise, the use of the MOPP-chemotherapy decreased from 50% towards 10% and was mainly replaced by MOPP/ABV. The percentage of patients achieving complete remission increased from 72% towards 89% and the 5-year survival rates improved significantly from 60% to 81%, with the greatest benefit in the elderly. At multivariate analysis advanced age, advanced stage and histology had independent adverse prognostic value. Period of diagnosis (1980s) was also of independent favourable prognostic value in the same analysis. Relative survival (the ratio of the crude to the expected survival in the general population) is an estimate of mortality attributable to the disease studied, provided that the study cohort does not differ from the general population, as is the case in this thesis. The relative survival of HL patients also improved significantly over the 20-year period studied, thus eliminating the confounding effect of competing death-risk and increasing life expectancy in the general population. The results at multivariate analysis and the improved relative survival indicate that the observed improvement in survival of HL patients in South-East Netherlands is independent of disease-related characteristics (stage, histology) and patient-related characteristics (age, gender) and therefore must be ascribed to the changed treatment-policy in this region.

The treatment results in the region equalled those obtained in referral centres, giving evidence that treatment of HL is feasible in community hospitals, provided that quality of care is guaranteed by a good multidisciplinary collaboration. Important components of such an approach are participation in clinical trials and the framework of a comprehensive cancer centre.

The increasing awareness of long-term treatment-related toxicity has led to application

of less aggressive therapy. In **chapter 4** this trend was also observed in the study-population, with a trend towards smaller radiation fields and a shift to lower dose (from 40 towards 20-24 Gray in involved fields). The use of chemotherapy shifted from MOPP towards the less myelotoxic and leukemogenic regimens, like ABVD and MOPP/ABVD. Patients being cured from HL in the 1970s suffered from an excess mortality of 16% compared with the general population. Although, the treatment policy appeared to be less toxic in the 1980s, the excess mortality declined only modestly towards 10%. The excess mortality in cured HL patients was mainly due to second malignancies and cardiac diseases. The 10-year cumulative risk of dying from a (second) malignancy declined from 7% for patients treated in the 1970s towards 4% for those treated in the 1980s and the relative risk, compared with mortality in the general population declining from 4.3 to 3.0. The 10-year cumulative incidence for second malignancies halved from 10% towards 5%. The vast majority of second solid tumours appeared in the field of previous irradiation. The 10-year risk of dying from cardiovascular disease barely changed from 6% towards 5%. However, this risk has declined significantly in the general population, ascribed to the increased preventive measurements and the improvement in cardiac care over the last decades. For this reason the relative risk of cardiac death after HL remained unchanged and was twice compared to the general population. Cardiac deaths were only found in those patients having received irradiation, again underscoring the role of radiotherapy in the development of cardiac disease. The preventive measurements and the improvements in cardiac care which appear to be effective for the general population, are probably less successful in radiation-induced coronary artery disease. After five years more than one third of survivors from HL suffer from one or more treatment-related diseases. Previous radiotherapy appeared to be associated with the majority of those sequels of which hypothyroidism was the far most prevalent. Secondary infertility was not evaluated in this study.

Although increasing awareness appeared to influence clinicians towards less toxic treatment in the 1980s, the late treatment-related toxicity remained substantial. Clinical trials of less damaging treatment are one of the major goals for improving the care for patients with HL.

Prognostic factors are an important tool for the prediction of treatment-outcome and subsequent patient-survival. Many prognostic factors reflect the biology of the tumour and can therefore be seen as epiphenomena of its malignant behaviour, whereas patient-related prognostic factors, such as age, reflect the fitness of the patient, including the ability to undergo anticancer treatment. The presence of co-morbidity appeared to be an important patient-related prognostic factor in several malignancies. **In chapter 5**, co-morbidity was prevalent in more than half of all unselected elderly lymphoma patients (60 years and over). The most common co-morbid conditions in HL patients were cardiovascular diseases, chronic obstructive lung diseases and hypertension. The presence of co-morbidity appeared to be an important contra-indication for chemotherapy, since the application of chemotherapy nearly halved in elderly HL patients when co-morbidity

was present. This was associated with a 15% lower overall survival in the first 4 months after diagnosis, a difference that is likely to increase after prolonged follow-up. The presence of co-morbidity apparently has a strong adverse impact on survival of HL patients, although longer follow-up is necessary for further proof. Besides being a contra-indication co-morbidity may interact negatively with chosen treatments. The complication-rate is likely to be higher, especially for infectious and cardiovascular complications. Moreover, the worse prognosis in the presence of co-morbidity may be due to the natural course of the co-morbid condition itself. The results of clinical trials may be biased for the effect of co-morbidity, caused by restrictive eligibility criteria, making their treatment results less applicable for the general health care environment. This was discussed at the fourth International Symposium on Hodgkin's Lymphoma following the presentation of the excellent results of new chemotherapy regimens. The Stanford V-protocol and escalated BEACOPP, both regimens with a high dose-intensity, obtained their results in patient-groups with a much lower mean age than found in the general population. For this reason those regimens are likely to be less applicable in the general population, especially in elderly patients with serious co-morbidity. The prevalence of co-morbidity in the general population will increase further in the near future caused by the ageing of the Dutch population and for this reason the effect of co-morbidity in clinical decision-making and survival-analysis of elderly HL patients will gain importance.

Whether the observed shift towards less frequent administration of chemotherapy in HL patients with co-morbidity is justified needs further investigation and choice and dose of treatment in patients with serious co-morbidity should be taken into account in prospective clinical trials.

Disease-related prognostic factors are an important tool for tailoring of treatment. In the presence of adverse prognostic factors patients are likely to profit from more intensive treatment. Moreover, in the absence of adverse prognostic factors a less intensive treatment may be justified, leading to a decline in late treatment-related mortality and morbidity. The NS subtype is by far the most frequent histological subtype and affects primarily young patients. For this reason prognostic sub-typing may have great impact. The British National Lymphoma Investigation (BLNI) group established a histological grading which appeared to be of prognostic significance in their large series. Essentially the sub-typing takes into account the presence of numerous malignant cells, the amount and quality of fibrosis and the amount of the cellular infiltrate. Grade II represents the more malignant variant, with worse prognosis and is found in 20-30% of cases with NS HL. Although several study-groups confirmed the prognostic relevance of this sub-typing, many other series did not and sub-typing according to the BNLI remains controversial. In **chapter 6** the results of a study on this sub-typing of patients diagnosed in the South- East Netherlands are presented. Grade II NS HL had a significant adverse prognostic impact for patients being treated in the 1970s, which was independent from other prognostic factors at multivariate analysis. For patients treated in the 1980s the

survival of grade II patients improved and equalled the survival of grade I patients. Likewise the prognostic value at multivariate analysis disappeared. Apparently, the more effective treatment policy in the 1980s has led to the disappearance of the prognostic value of sub-typing. This finding is in accordance with criticisms of this sub-classification that suggested that the use of optimal treatment strategies obviates the prognostic significance. In our study chemotherapy was more frequently applied in grade II patients in the 1980s compared to the 1970s. This is in accordance with the idea that grade II more frequently presents with occult abdominal disease, which will be treated with systemic chemotherapy but not by irradiation. Grade II NS HL is reported to present more frequently with constitutional B-symptoms and a raised ESR as was also found in this study. Both a raised ESR and B-symptoms are used in the prognostic score for the tailoring of treatment in early stage HL and are a reason for the use of systemic chemotherapy as they have been recognised as predictors for occult abdominal disease. For this reason the application of this tailored treatment in the 1980s, advocated by the EORTC trials, has contributed to the disappearance of the prognostic significance of sub-classification of NS HL.

Sub-classification of NS HL according to the BNLI does not have prognostic value under contemporary treatment. However, sub-classification can, among other variables, be an important tool for tailoring treatment, since it reflects the malignant biology of the tumour.

Although treatment is successful for the vast majority of HL patients, a subset will fail to achieve complete remission upon treatment with chemotherapy and subsequently have a poor survival. Attempts at identification of these patients using histological criteria have not been successful. In **chapter 7** a higher frequency of Bcl-2 expression in H-RS cells was found in the tumours of patients with NS HL who failed to achieve complete remission upon primary chemotherapy when comparing with patients who did achieve complete remission. No difference was found in Bax-expression and proliferative activity between both patient groups. Bcl-2 expression plays an important role in the sensitivity to chemotherapy drugs, apart from its role in the pathogenesis of certain malignancies. One of the functions of Bcl-2 is its capacity to block cell death by binding to and neutralising the pro-apoptotic effects of Bax, a promoter of apoptosis. In diffuse large cell non-Hodgkin Lymphoma Bcl-2 is frequently expressed and was found to be an independent predictor for shorter disease-free survival. Likewise, the H-RS cells in HL have been reported to express the Bcl-2 protein and it has been suggested that over-expression is related to clinical drug resistance. Bcl-2 is known to inhibit killing by cytotoxic T-cells by several pathways of which one is also used by certain cytotoxic drugs. The reported observation that many activated cytotoxic T cells in the vicinity of H-RS cells is associated with a poor prognosis can be explained by the increase of Bcl-2 levels in the H-RS. In the surrounding lymphocytes a distinct pattern of expression of Bcl-2 was observed. Lymphocytes immediately around the H-RS cells expressed Bcl-2 much less frequently than the more distant lymphocytes. This phenomenon was significantly

associated with clinical drug-resistance. The decreased expression of Bcl-2 in lymphocytes in the close vicinity of H-RS cells is most likely due to the disturbed network of cytokines and cellular activation. Its association with clinical drug resistance may therefore be a reflection of the severity of disturbance in the cytokine network and thus be an epiphenomenon of more aggressive biological behaviour. The low levels of Bcl-2 in conjunction with a frequent expression of the pro-apoptotic protein Bax suggests that many lymphocytes in the vicinity of H-RS cells will go into apoptosis. This is in accordance with the concept that tissues involved by HL are dependent on a constant influx of circulating T lymphocytes. Lymphocytopenia is indeed frequently observed in the peripheral blood of patients with active disease.

Although the apparent relationship between Bcl-2 expression and clinical drug resistance in HL in our study clearly fit in the biological concept, further investigations should be performed on its reliability and whether it can be used in clinical decision making.

GENERAL CONCLUSION AND PERSPECTIVES

In the past decades an important improvement in survival of HL patients has been observed in the population of South-East Netherlands. The treatment strategies, developed in clinical trials, appeared to be applicable for routine cases in the general health care environment, provided that quality of care is guaranteed by multidisciplinary collaboration. The quality of care, as assessed by its outcome, could be achieved in the presence of a good structure (facilities and equipment) and process (activities of health care providers and their collaboration).[1] Comprehensive Cancer Centres can offer the framework for such collaboration enabling treatment-results in community hospitals to approach results achieved in referral centres.

Of particular interest is the fact that elderly patients with HL profited the most from the improvement in treatment and elderly should be treated with curative intent. However, adoption of newly developed chemotherapy regimens with high dose intensity, like the Stanford V protocol or escalated BEACOPP, will be hampered by the presence of elderly with co-morbidity in the general health care environment.[2,3] Co-morbidity is present in more than 50% of unselected lymphoma of 60 years and older and clinicians frequently chose not to give chemotherapy in the presence of co-morbidity. The optimal policy in this group of patients will be of growing importance in the near future due to the ageing of the Dutch population. Guidelines can help to define the policy in individual cases with co-morbidity and, preferably, co-morbidity should be taken into account in future clinical trials.

Cured patients suffer from increased incidence of lethal treatment related diseases. The awareness of this problem has emerged since the 1970s and is an incentive to minimise toxicity of treatment. Despite the application of less aggressive treatment, late toxicity remains substantial. One of the challenges of future treatment strategies is further

refinement of risk-adapted treatment. Patients with a high risk for treatment-failure or relapse should receive more intensive initial treatment, whereas low-risk patients will benefit from less aggressive treatment to minimise late toxicity. For patients with stage IA Nodular Lymphocyte Predominant Hodgkin's Lymphoma, for example, a wait and see policy versus standard treatment is a suggested option. Since this is an infrequent disease, a global collaboration will be necessary to test which option is optimal.[4]

On the other hand, the identification of high-risk patients is difficult. The value of histological sub-classification/grading of the largest histological group with NS HL disappeared upon more effective treatment. The recently developed prognostic index for advanced HL patients may help define the poor risk patients.[5] The poor risk subgroup defined by this index however is small, thus requiring large prospective trials to find optimal treatment policy, which might include escalated or high-dose chemotherapy as initial treatment. Furthermore, the use of immunohistochemistry or molecular markers involved in multidrug resistance may help to define patients with clinical drug resistance. Since clinical drug resistance essentially resides in the resistance of cells to go into apoptosis, markers involved in this process are of interest. Indeed, the higher expression of the anti-apoptotic protein Bcl-2 in the H-RS cells appears to be associated with worse prognosis.[6,7] However, further study on the validity and usefulness as a prognostic tool is needed.

Of particular interest is the finding that clinical drug resistance is inversely related with Bcl-2 expression in the Th2 lymphocytes immediately surrounding the malignant RS cells, reflecting a more disturbed molecular microenvironment. Understanding the immune-escape of the malignant H-RS cells will give possibilities for the development of immune-therapeutic approaches. For example, systemic treatment with bispecific monoclonal antibodies with antigen-specificity against CD3 (on T-lymphocytes) and against CD30 (on Reed-Sternberg cells) are tested in phase I/II trials in refractory patients. The idea is to redirect cytotoxic T-lymphocytes to the H-RS cells and thus elicit an immune response.[8] Also, the use of autologous EBV-specific cytotoxic T-lymphocytes for adoptive transfer is under clinical evaluation in a group of patients with relapsed HL.[9] These and other immune-therapy approaches need to be further investigated for their efficacy and safety and might gain a place in either refractory patients as well as in low risk patients as adjuvant treatment in the context of a further minimised treatment-strategy