Bulky disease is the most important prognostic factor in Hodgkin Lymphoma stage IIB

Ingrid Glimelius¹, Daniel Molin¹, Rose-Marie Amini¹, Anita Gustavsson², Bengt Glimelius¹, and Gunilla Enblad¹

¹Department of Oncology, Radiology, and Clinical Immunology, Rudbeck laboratory, Uppsala University Hospital, Uppsala; and ²the Department of Oncology, Lund University Hospital, Lund, Sweden.

Corresponding author: Gunilla Enblad, Department of Oncology, Radiology, and Clinical Immunology, Rudbeck laboratory, University Hospital, SE-75185 Uppsala Sweden. E-mail: gunilla.enblad@onkologi.uu.se

ABSTRACT

The aim of this study was to evaluate treatment results for HL patients younger than 60 years in stage IIB, treated according to the Swedish National Care Programme. The intention was also to identify specific subgroups depending on the number of negative prognostic factors the patients have, in order to optimise and differentiate future treatment. In total, 99 patients with HL stage IIB, diagnosed between 1985 and 1994, have been analysed. There were 47 men and 52 women and the median age was 33 years (range 17-59). Eighty-six patients presented with supradiaphragmatic disease and 13 with infradiaphragmatic. The HL specific and overall 10-year survival was 73% and 65%, respectively. The HL specific survival for patients in pathological stage IIB tended to be better, **although not statistically significant** than for clinical stage IIB, despite less chemotherapy ($p=0.1$). The patients in stage IIB who were selected for laparotomy were, however, younger and with fewer negative prognostic factors. The only significant negative prognostic factor was bulky disease ($p=0.001$). The following factors also tended to have a negative influence on the prognosis **although not statistically significant**: the International Prognostic Score, the number of involved lymph node stations, extranodal involvement, and leukocyte count $> 15 \times 10^9/L$. In conclusion, we suggest that bulky disease should be taken into account when treating patients with stage IIB HL.

INTRODUCTION

Patients with Hodgkin lymphoma (HL) generally have a favourable prognosis and at least 75% of all young patients are cured by radiotherapy (RT) and/or chemotherapy (Brandt *et al.*, 2001; Diehl & Josting, 2000; Hasenclever & Diehl, 1998). The treatment has, however, considerable early and late side effects. Modern principles for the treatment of HL aim at reducing toxicity and consolidating or improving the good results. In Sweden, all adult (>16 years) patients with HL in 5 out of 6 health care regions have been treated according to a National Care Programme since 1985. The programme describes principles for staging, treatment, and follow-up. The results have continuously been evaluated and modifications and changes have been introduced (Amini *et al.*, 2000; Glimelius *et al.*, 1996; Glimelius *et al.*, 1994; Kalkner *et al.*, 1997; Molin *et al.*, 2002).

We have recently evaluated the treatment results for patients below the age of 60 years in advanced stages (IIB-IV). Apart from stage IVB, patients in stage IIB had the worst prognosis (Amini *et al.*, 2000). When the treatment in relapsed patients was evaluated, patients in stage IIB, and especially those with bulky disease had the worst outcome (Amini *et al.*, 2002). Patients or subgroups of patients, in stage IIB are variably included among early and intermediate stages in some comparative group studies but not in others (EORTC, 1998; GHSG, 1998; NLG, 1999). Due to these rather contradictory approaches we decided to evaluate the treatment results of patients who presented with stage IIB in an unselected population-based material. The intention was also to identify subgroups of stage IIB, depending on the number of negative prognostic factors, to optimise and differentiate future treatment.

MATERIAL AND METHODS

Patients

Between 1985 and 1994, 1226 adult patients with newly diagnosed HL were registered in 5 out of 6 health care regions in Sweden. Out of those 764 (62%) patients were below the age of 60 years. In total 103 patients below the age of 60 were in stage IIB.

The age limit was chosen since the older patients have been treated according to a separate protocol (Enblad *et al.*, 1991; Glimelius *et al.*, 1996). Two patients were excluded because they had HL together with non-Hodgkin lymphoma (NHL) and in two patients no information about treatment and follow-up was available. Therefore 99 patients were studied. All diagnoses were made by the regional haematopathologist and defined according to the Rye-classification (Glimelius *et al.*, 1996; Lukes RJ, 1966).

Treatment recommendations for patients between 16 and 60 years, valid between 1985 and 1994, were, for patients in stage IIB, a full course, i.e. 6-8 cycles of chemotherapy, followed by involved field (IF) RT in case of initially bulky disease, slow tumour regression (30 Gy) or residual disease (40 Gy). The number of cycles was individualised according to treatment response. Patients who achieved complete remission (CR) after 2 cycles were treated with a total number of 6 cycles and all others with 8 cycles, provided there was no disease progression (Amini *et al.*, 2000). Recommended chemotherapy was MOPP/ABVD between 1985 and 1993 (in one region MOPP only was given during the first two years) and MOPP/ABV hybrid since January 1994. One MOPP/ABVD was counted as two cycles. The therapy could be reduced to 2 cycles of chemotherapy and mantle field RT, provided that the patient was pathologically staged (staging laparotomy with splenectomy performed) and that no disease was found in the abdomen (PS IIB). Median follow up for living patients was 6.7 years, range 0-13 years.

Staging

The patients were staged according to the Ann Arbor system (Carbone *et al.*, 1971). Initial staging included a clinical history, physical examination, chest x-ray, computed tomography scan of the chest, abdomen, and pelvis, ultrasound of the abdomen, and bone-marrow biopsy. The laboratory parameters leukocyte count, erythrocyte sedimentation rate (ESR), and blood haemoglobin (Hb) were all recorded before therapy was started. Unfortunately the blood chemistry values were not prospectively registered but collected retrospectively. Six or all 7 of the factors included in the International Prognostic Score (IPS) were possible to retrieve in 89 (90%) patients (Hasenclever & Diehl, 1998).

Bulky disease was defined as a mediastinal mass ratio greater than 0.33 of the thorax diameter at the Th. 5-6 level or a lymph node region with a diameter greater than 10 cm. Extreme bulky disease was defined as a ratio greater than 0.45. The number of lymph node regions with HL-engagement was also defined and varied between 2 and 9. Involvement of both hili and the mediastinum were defined as three locals. The patients were divided into groups with 2, 3, and 4 or more involved sites.

Statistical methods

The Chi² test was used to compare differences in proportions between groups. The survival curves were calculated according to the method of Kaplan and Meier. Log-rank test was used to compare survival in two groups. Cox proportional hazard regression model was used to test the laboratory parameters. Since some data are missing, the analyses are based on the patients with complete data sets relevant to the specific analyses performed.

Disease-free survival (DFS) was defined as the time from diagnosis to relapse or death from HL. The patients who never reached CR had a DFS of zero days. Patients that were disease-free at the last follow up and patients dead by other reasons than HL in CR were censored. HL-specific survival was defined as the time from diagnosis to death from or with HL.

RESULTS

The clinical characteristics of the 99 patients are given in tables 1 and 2. Eighty-six patients had supradiaphragmatic disease (table 1) and 13 had infradiaphragmatic disease (table 2). These two groups are presented separately because they often have different clinical presentations and natural history (Amini *et al.*, 2002; Kalkner *et al.*, 1997).

Supradiaphragmatic disease

The treatment results for patients with supradiaphragmatic disease are shown in table 3. In 16 patients staging laparotomy was performed. These patients were slightly younger than those in CS IIB (median age 27 versus 34 years). Six (38%) of these patients had bulky disease (compared to 49/70 (70%) for CS IIB, $p=0.01$), but none had extreme bulky disease. Only one patient had an

extranodal lesion and it was not noticed until after therapy had been started. All patients achieved a CR. Two patients received RT alone. One patient was initially evaluated as stage IB, achieved a CR and no chemotherapy was given. For the second patient there is no explanation of the choice of treatment and this patient later relapsed in a new local.

The two patients that relapsed out of the 14 treated with 2 cycles of chemotherapy + RT both had bulky disease. One of the relapses was at the border of the radiation field and the other one was a generalised relapse both inside and outside of the area treated with radiotherapy.

Seventy patients were in CS IIB and the treatment results are presented in table 2. The four patients who did not achieve a CR all had initially bulky disease and died of HL. Twenty-two (31%) patients have relapsed and 17 of them had bulky disease. Five of these 17 patients relapsed within previously irradiated areas. Relapse treatment was chemotherapy, mostly ABVD or MIME, followed by high-dose chemotherapy and autologous stem cell transplantation (ABMT) in 10 patients. Seven patients have experienced a new relapse and six died of HL. Additionally, one patient died from pneumonitis. The reasons for not treating 7 patients with ABMT were in two cases patient refusal, both subsequently died of HL; in one case rapid progression and death, in one death from acute myeloid leukemia, in one patient death from pneumocystis carinii infection, in one patient data is missing (dead of HL), and one patient was treated with chemotherapy alone and there is no explanation why ABMT was not performed. That patient is, however, in continuous CR (CCR).

Of the five relapsing patients with non-bulky disease at diagnosis two were treated with chemotherapy and RT and are in CCR, one died of urinary bladder carcinoma without HL and two were treated with chemotherapy and ABMT of which one is in CCR and one relapsed and died of HL.

Since the majority of patients who relapsed and subsequently died from HL initially had bulky disease, differences in clinical parameters between patients with and without bulky disease were analysed. Fifty-five (64%) patients with subradiaphragmatic presentation had bulky disease, 54 in the mediastinum and one in the neck. Nineteen (35%) of the patients with bulky disease have relapsed as compared to 6 (19%) with non-bulky disease ($p=0.07$). There was, however, no difference

between the two groups regarding age, sex, histopathology, number of B-symptoms or any of the laboratory parameters investigated. All but one patient received both chemotherapy and RT (one patient received chemotherapy alone) and was thus treated according to the recommendations.

Treatment results for the patients with infradiaphragmatic disease.

Eleven patients achieved CR and have remained disease-free. However, one of those died from a non-Hodgkin lymphoma. Two patients rapidly progressed and died during the treatment period. One patient, a 37 years old man who had a poor general state of health when diagnosed, with HL in both inguinae and in the spleen, and with bulky disease, died from acute peritonitis after one course of MOPP. The other patient, a 35 years old man, had HL in the spleen and in lymph nodes in the abdomen. He had residual tumour after 8 cycles of MOPP/ABVD and during RT the disease progressed to the liver.

Survival

The overall survival (OS) in all patients was 78% after 5 years and 65% after 10 years (Fig 1). The actuarial HL-specific 5-year survival was 81% and the 10-year survival 73%. The DFS was 74% after 5 years and 65% after 10 years. For the patients with infradiaphragmatic disease the OS, HL-specific survival, and DFS at 5 and 10 years all were 85%. For the patients with supradiaphragmatic disease the 5- and 10-year OS were 77% and 61%, respectively and the HL-specific survival was 81% after 5 years and 70% after 10 years. The DFS in those with supradiaphragmatic disease was 72% after 5 years and 61% after 10 years. Patients in stage IIB can be included among the intermediate stages in some European studies (EORTC, 1998; GHSG, 1998) if they have an erythrocyte sedimentation rate (ESR) below 30, less than 4 affected locals and non-bulky disease. Among the 9 patients that fulfilled all three criteria there have been no relapses. Four of these patients were treated with 2 courses of chemotherapy followed by RT, 4 with a full course of chemotherapy, and 1 with RT alone. If only ESR is tested among all patients, those with an ESR below 30 tended to have a better DFS than those with a higher ESR, although not statistically significant (p=0.09).

Secondary effects of treatment

In total, there were seven secondary malignancies, three acute myeloid leukemia, one non-Hodgkin lymphoma, two urinary bladder carcinoma, and one basal cell carcinoma. All but the patient with basal cell carcinoma died of their secondary malignancy. Three patients died for other reasons, one because of pneumocystis carinii infection, one from a perforated gastric ulcer, and the last patient died from interstitial pneumonia and pulmonary fibrosis after ABMT.

Prognostic factors for all patients

The following factors were included in univariate analyses for DFS and HL-specific survival: bulky disease, number of engaged stations, occurrence of extranodal lesion, number of B-symptoms, histological subgroup, sex, leukocyte count $> 15 \times 10^9 /l$, ESR > 30 mm, Hb < 105 g/l, and IPS 0-1 (n=55) versus ≥ 2 factors (n=34). All factors were investigated in all patients and in patients with supradiaphragmatic disease. Bulky disease was the only statistically significant prognostic factor, $p=0.001$ (Fig 2). Extreme bulk was not worse than more moderate bulky disease, $p=0.5$.

DISCUSSION

Patients with HL stage IIB do not constitute a uniform group of patients. The presentation may vary from two small lesions, a single B-symptom, and normal laboratory values to a large tumour burden, extranodal disease, extensive B-symptoms, and multiple deranged laboratory parameters. The Swedish National Care Programme for HL recommended chemotherapy + RT to all patients in CS IIB but less chemotherapy followed by RT to the patients who were selected to staging laparotomy, and became PS IIB. The reason was to minimise therapy to some patients, e.g. to be able to preserve fertility. The overall results of the present study imply that most stage IIB patients should be regarded as having an advanced stage HL. The HL-specific survival of 73% and the OS of 65%

after 10 years is worse than the survival seen in all patients in stages III-IV, diagnosed between 1985 and 1992 (Amini *et al.*, 2000) and is clearly below the above 90% in stage IA-PSIIIA:1, seen during the same time period (Molin *et al.*, 2002).

Our present results indicate, however, that the patients in stage IIB can be separated in prognostic subgroups, i.e. stage IIB is both an intermediate and an advanced stage. The results for patients in PS IIB appear better than those for CS IIB despite less chemotherapy. The patients chosen for laparotomy were, however, younger and with fewer negative prognostic factors. Maybe those potentially low risk patients could be identified without laparotomy as in the GHSG and EORTC trials, since laparotomy with splenectomy is associated with both morbidity and mortality and has now been abandoned. Because of the risk of secondary cancers it would be very valuable to identify these low risk patients. If 4-6 courses of chemotherapy and involved field radiotherapy as in the GHSG and EORTC trials is equally good as 2 courses of chemotherapy and mantle field RT, as used in this study, remains to be seen.

Why stage IIB has an outcome that is indeed poorer than the outcome in advanced stages other than IVB (Amini *et al.*, 2000) is not known. The remission rate was better in stage IIB than in the others, with the exception of stage IIIA (data not shown). However, it can be demonstrated that patients in stage IIB more often had bulky disease (56% as compared to 28% in IIIA, 34% in IIIB, 43% in IVA, and 36% in IVB) (Amini, personal communication).

The chemotherapy used in the present study was mainly MOPP/ABVD but some patients were treated with MOPP only or MOPP/ABV hybrid. It has been shown in a large study that MOPP/ABVD and ABVD is superior to MOPP alone (Canellos *et al.*, 1992). Although this result has been debated (Somers *et al.*, 1994), ABVD is currently considered to be the “golden standard” in treatment of advanced HL due to the increased incidence of myelodysplastic syndrome and acute leukemias with MOPP containing regimens (Duggan *et al.*, 2003). However, the choice of chemotherapy in this study cannot explain the inferior results seen in stage IIB.

Bulky disease was the only significant negative prognostic factor in this group of patients despite the fact that a majority of the patients with bulky disease received both a full course of chemotherapy

and RT. The patients with bulky disease did not otherwise have more negative prognostic factors than the non-bulky patients so this does not explain the poor outcome. Bulky disease is a well established risk factor for patients with early stage HL, especially when the patients are treated with RT only (Mauch *et al.*, 1978, Hoppe *et al.*, 1982). However, most studies using combined modality treatment could not show any difference in relapse rate or survival (Anderson *et al.*, 1989). Also the presence of constitutional symptoms in early stage HL is a well known prognostic factor. Most studies, however, have included both stages I and II disease and most studies are performed on pathologically staged patients. Very few studies have focused on clinically staged stage IIB patients who comprise the majority of the present study. However, patients with clinically staged stage IIB patients are included in the early stage studies in most large groups.

The presence of tumour bulk might constitute a high risk in stage IIB due to unknown tumourbiological characteristics since bulky disease has not been an equally important factor when stages I-IIA and stages IIB-IV have been analysed previously in the Swedish National Care Programme (Amini *et al.*, 2000; Molin *et al.*, 2002). Bulky disease is also not a prognostic factor in the International prognostic score (IPS) (Hasenclever & Diehl, 1998) developed for advanced disease. The reduced importance for tumour bulk in advanced disease might indicate that bulky disease in advanced stages is associated with other prognostic factors or is compensated for by more intensive treatment i.e. addition of RT after chemotherapy. Since all patients but one in the present study who were scheduled to receive radiotherapy also did this, and the design was not randomised, we can not evaluate whether RT after chemotherapy has a role in these patients.

The patients diagnosed with infradiaphragmatic compared to supradiaphragmatic disease are usually older, they are more likely to be men, and the histology is MC more often than NS (Amini *et al.*, 2002; Kalkner *et al.*, 1997). This was seen also in this study. It was also noted that more patients had two B-symptoms and loss of weight seems to be more frequent than night sweats for the ones with infradiaphragmatic disease compared to those with supradiaphragmatic disease. The treatment for the infradiaphragmatic patients according to the Swedish National Care Programme seems to be sufficient since all patients who reached a CR remain disease-free. The results for the patients with

infradiaphragmatic disease also support other studies (Kalkner *et al.*, 1997) showing that the prognosis is not worse than for the ones with supradiaphragmatic disease.

In this study we have described all patients in 5 out of 6 regions in Sweden diagnosed with stage IIB HL from 1985 to 1994. The results seem comparable to those seen at specialised centres treated during the same time period (Glick *et al.*, 1998, Haesenclaver & Diehl, 1998). Most of the patients must be regarded as having an advanced stage of HL and should be treated accordingly. Stage IIB patients are, however, frequently excluded from trials in advanced stages (e.g. the EORTC 20012 study, (EORTC, 2002)). However, a small proportion of the patients could probably be treated with less intensive therapy. Patients with stage II with bulky disease seem to have a particularly poor prognosis and are not identified by the IPS, especially female patients. The value of the more intensive regimens, e.g. BEACOPP (Diehl *et al.*, 1997) in this subgroup of patients has been investigated in the GHSG HD9 trial. The study was intended for advanced HL but patients with stage IIB, bulky disease were included. The patients were randomised between 4 COPP/ABVD, 8 BEACOPP baseline or 8 BEACOPP escalated followed by limited radiation. The study showed superiority for the BEACOPP and this concept is currently explored further in the HD12 study (Franklin & Diehl, 2002).

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Table 1: Clinical characteristics of patients with supradiaphragmatic disease.

Patients with supradiaphragmatic disease	N	%
Total	86	
CS/PS	70/16	81/19%
Median age (range)	33(17-59)	
Sex (Male / Female)	39/47	45/55%
Histology NS	73	85%
MC	10	12%
LD	2	2%
Unclassifiable	1	1%
Extranodal disease	9	10%
Number of B-symptoms 1/2/3	37/33/16	63/38/19%
type: night sweat / loss of weight / fever	79/34/40	81/38/47%
Number of stations 2	30	35%
3	24	28%
4+	32	37%
Bulky / Non-Bulky	55/31	64/36%

CS = clinical stage, PS = pathological stage, NS = nodular sclerosis,

MC = mixed cellularity, LD = lymphocyte depleted.

Table 2. Clinical characteristics of patients with infradiaphragmatic disease

Patients with infradiaphragmatic disease	N	%
Total	13	
CS / PS	7/6	54/46%
Median age (range)	39(28-59)	
Sex (Male / Female)	8/5	62/38%
Histology NS	6	46%
MC	6	46%
LD	1	8%
Number of B-symptoms 1/2/3	4/4/5	31/31/38%
type: night sweat / loss of weight / fever	9/11/6	69/87/46%
Bulky / Non-Bulky	8/5	62/38%
Extranodal disease	2	15%

Table 3: Treatment results for patients with supradiaphragmatic disease.

Stage	Bulk	N	CR	Relapse (%)	Dead from HL (%)	Dead without HL (%)
PS IIB	Bulky	6	6	2 (33)	1 (17)	0 (0)
	Non-bulky	10	10	1 (10)	0 (0)	1 (10)
CS IIB	Bulky	49	45	17 (35)	14 (29)	3 (6)
	Non-bulky	21	21	5 (24)	1 (5)	1 (5)
Total		86	82	25 (29)	16 (19)	5 (6)

CR = complete remission after treatment, HL = Hodgkin lymphoma,

CS = clinical stage, PS = pathological stage.

Figure legends

Figure 1: HL-specific and disease-free survival in all patients, N=99.

Figure 2: HL-specific survival in all patients with versus without bulky disease, N=99, $p=0.01$.

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