Survival Improvement of Young Patients, Aged 16-23, with Hodgkin Lymphoma (HL) during the Last Three Decades

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Abstract. *The prognostic factors, treatments and outcomes of 55 young adults (16-23 years old) with Hodgkin lymphoma (HL) treated in the Second Department of Internal Medicine Propaedeutic, Medical Oncology Unit, Athens University, over the past 25 years, are reviewed. Patients were treated with the chemotherapy regimens available at each time period which were MOPP (Group A; 1978-1987), MOPP/ABVD (Group B; 1988-1993) and BEACOPP or ABVD (Group C; 1994-2003). The eligible patients, received radiotherapy (RT) according to treatment consensus. Additionally, the patients were retrospectively divided according to risk factors (abnormal erythrocyte sedimentation rate (ESR), bulky mediastinal disease, >3 involved nodes and extranodal involvement) into low [stage I/II; five patients (9%)], intermediate [stage I/II with adverse prognostic factors; 18 patients (33%)] and high risk categories [stages IIB bulky and III/IV; 32 patients (58%)]. A total of 21 (38%) patients experienced relapse (three intermediate and 19 high risk). The 5-year survival and the 5-year event free survival (EFS) figures were Group A: 65% and 53%, Group B: 80% and 65%, Group C: 100% and 88.5%, respectively, the improvements between Group B and C were statistically significant ($p=0.04$ and $p=0.005$, respectively) among the three time periods. The overall survival (OS) and EFS differed significantly between intermediate and high risk categories (OS: $p=0.04$, EFS: $p=0.005$). The sequential use of RT did not influence OS and EFS but there was a trend of improvement with RT in the later periods. Survival of young patients with HL is significantly improving most probably due to improved chemotherapy treatment and understanding of the risk factors. Current controversial issues surrounding this disease, including the role of radiotherapy, positron emission tomography (PET), bone marrow biopsy and stem cell transplantation are discussed.*

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The development of curative combination chemotherapy for patients with Hodgkin lymphoma (HL) has been one of the major successes of cancer therapy during the past three decades.

Hodgkin lymphoma shows an age-related bimodal incidence. The first peak occurs in the third decade of life and a much smaller peak occurs after the age of 50 years. Single agent treatment with nitrogen mustard was the first chemotherapy treatment investigated by Goodman and Gilman in 1943 and showed an important, but not curative benefit. In 1964 the combination regimen MOPP was the first to show survival benefit (1). In the early 1970's the Milan Group reported on trials of ABVD which showed further improvement of the survival rates with an advantageous effect on fertility (2). In 1986 MOPP/ABV hybrid chemotherapy was developed by Canadian researchers and showed 5-year survival rates of 60-70% (3). In 1992 the German Hodgkin's Study Group designed the BEACOPP regimen that used a more intense drug regimen, in an attempt to increase efficacy (4). Further efforts were made by international groups to apply more effective scheduling of the active cytotoxic agents, such as Stanford V, ChlVPP/EVA and VAMP/COP reaching a higher dose intensity and/or dose frequency with similar results (5-7). Today ABVD and BEACOPP are the most studied regimens in large trials by HL study groups and are both considered as standard therapy, with similar toxicity in the short and long term, with the exception of fertility preservation in the ABVD group. In large series using these two drug combinations survival rates of 80-85% have been reported with cure achieved even in advanced stages of the disease (8, 9). In order to reduce acute and late toxicities, such as cardiopulmonary toxicity and secondary malignancies, the German Hodgkin Study Group proposed the optimization of treatment by tailoring chemotherapy according to the risk group of patients. Three risk groups

were identified, low risk patients: stages I and II without risk factors, intermediate risk: stages I and II with risk factors and advanced stages: IIB with large mediastinal mass (LMM) and extranodal disease, III and IV. Risk factors were: LMM, extranodal disease, high erythrocyte sedimentation rate ESR, and ≥3 lymph node (LN) areas (10). The use of radiotherapy has changed over the years from extended to involved field and from higher to lower dose, but its use remains controversial (11).

It was hypothesized that by improving chemotherapy regimens and examining the risk factors should improve both EFS and OS of young adults with HL. This study was conducted to review the prognostic factors, treatments and outcomes in young adults with HL over the past 28 years in the Second Department of Internal Medicine Propaedeutic, Medical Oncology Unit, Athens University.

Patients and Methods

The study population consisted of 55, previously untreated, patients with a lymph node biopsy-proven diagnosis of HL admitted to our unit between 1978 and 2003. Patients were divided according to the time period in which treatment was initiated into three groups: Group A (1978-1987; 17 patients), Group B (1988-1993; 20 patients) and Group C (1994-2003; 18 patients). The patients most often received the regimen available at each time period in our department such as MOPP (Group A, 1978-1987), MOPP/ABVD (Group B, 1988-1993), and ABVD or BEACOPP (Group C, 1994-2003). Exceptionally, three patients from Group A and one patient from Group B received COP and ChlVPP respectively. The treatment designs were approved by the national haematology group and the institute's research and ethics committees. All patients gave their verbal and, more recently, written informed consent, abiding by the rules of the appropriate internal review board and the tenet of the Helsinki protocol on human rights, prior to being enrolled. Following chemotherapy, selected patients received additional radiotherapy. Before 1992 extensive irradiation (either total or subtotal nodal radiotherapy according to disease presentation) was administered whereas after 1992 irradiation was limited to the nodal areas defined as bulky (mediastinal mass greater than 1/3 the thoracic diameter and/or nodal disease >5 cm).

Chemotherapy. The MOPP therapy was administered every four weeks (nitrogen mustard 6 mg/m^2, vincristine 1.4 mg/m^2 intravenously (*i.v.*) on days 1 and 8; procarbazine and prednisone orally at the dose of 100 and 40 mg/m^2, respectively, from day 1 to 14 of each treatment cycle as originally designed by the National Cancer Institute (1). The ABVD chemotherapy consisted of the *i.v.* administration of doxorubicin (25 mg/m^2), bleomycin (10 mg/m^2), dacarbazine (375 mg/m^2) and vinblastine (6 mg/m^2) on days 1 and 15, every 4 weeks as described by the Milan group (2). The sequential administration of MOPP and ABVD consisted of four full cycles of the MOPP regimen followed by ABVD every four weeks.

A modified BEACOPP regimen was delivered with *i.v.* cyclophosphamide 650 mg/m^2, adriamycin 25 mg/m^2 and vincristine 1.4 mg/m^2 on day 1 (maximum of 2 mg), procarbazine 100 mg/m^2 days 1-7 and prednisone 40 mg days 1-14 orally, bleomycin 10 mg/m^2 and etoposide administered *i.v.* on day 1 and orally at a dose of 100 mg/m^2, on days 2 and 3, as previously described (4, 12). The COP chemotherapy consisted of *i.v.* cyclophosphamide 600 mg/m^2 and vincristine 1.4 mg/m^2 on days 1 and 8 and procarbazine 100 mg/m^2 orally days 1-14 every 4 weeks (7). The ChlVPP chemotherapy was administered with chlorambucil 6 mg/m^2, prednisolone 50 mg and procarbazine 90 mg/m^2 orally days 1-7 and *i.v.* vincristine 1.4 mg/m^2 on day 1 (6). Relapsed patients were crossed over to second line chemotherapy treatment. Two patients with good performance status were offered high dose treatment with autologous stem cell transplantation.

Staging and follow up. The initial assessment of all patients consisted of a physical examination, full blood cell count, biochemical tests including albumin, erythrocyte sedimentation rate (ESR), chest X-ray, abdominal ultrasound and bone marrow core biopsy. Bipedal lymphangiography was performed until 1990. Computerized tomography (CT) and gallium scans were performed after 1990. For the purposes of this study all patients were classified into stages, using the Ann Arbor staging system, and into risk groups as recently described (10).

All patients had a physical examination and a full blood count before each drug administration. In the absence of suspicious findings, the physical examination, routine laboratory and imaging tests were repeated every three months during the first two years after completion of therapy, every six months during years three to five, and once a year thereafter. After the tenth year of follow-up, examinations were planned every 12-24 months, and when they were not performed in the outpatient clinic contacts were periodically maintained with the patients themselves and with their family doctors. In patients with suspicious or controversial findings, examinations were performed more frequently. The treatment response was assessed clinically and by repeating all studies that were abnormal at diagnosis. Annotations regarding fertility were not satisfactory and are not included in this study.

Statistical analysis. Statistical analysis was performed with SPSS 13.0 (SPSS, Inc, Chicago, IL, USA). Overall survival (OS) was measured from the day of treatment initiation until death due to any cause. Surviving patients were censored on the day of the last contact. Event free survival (EFS) was measured from treatment initiation until relapse of the disease. Time to event distributions were estimated using Kaplan-Meier curves (13) and compared using the log-rank-test (14). All statistical tests were two-sided and performed at a significance level of 0.05. The Cox proportional hazards models (backward selection procedure with removal criterion $p>0.10$) were used to assess the strength of association of OS and EFS with the following variables: albumin (≤4 *vs.* >4), WBC (≥15000 *vs.* <15000), lymphocytes (≤8% *vs.* >8%), haemoglobin (≥10.5 *vs.* <10.5) and ESR (normal *vs.* abnormal).

Results

A retrospective chart review of 55 young adults 16-23 years old (patient characteristics are shown in Table I), treated in our unit during 1978-2003, was conducted. Spleen involvement was present in 16 patients (29%) and B symptoms in 33 patients (60%). Thirty seven patients (67%)

Table I. *Patient characteristics.*

	Frequency (No of patients)	%
Age		
15-20	39	71
21-25	16	29
Gender		
Male	30	54.5
Female	25	45.5
Histology		
Nodular sclerosis	42	76
Mixed cellularity	10	18
Lymphocyte Predominant	3	5.5
Stage		
IA	2	4
IB	12	22
IIB	17	31
IIIA	8	14.5
IIIB	13	24
IVB	3	5.5
Prognostic group		
Low risk	5	9
Intermediate risk	18	33
High risk	32	58
Patients by time period		
1978-1987	17	31
1988-1993	20	36
1994-2003	18	33
Chemotherapy		
MOPP	13	24
ABVD	7	13
MOPP/ABVD	21	38
BEACOPP	10	18
OTHER (CLVPP, COP)	4	7
Radiotherapy		
Delivered	30	54.5

Table II. *Treatment type and outcome according to risk group by time period.*

	1978-1987 Group A	1988-1993 Group B	1994-2003 Group C	Total
Chemotherapy				
MOPP	13 (76.5%)	0 (0%)	0 (0%)	13 (24%)
MOPP/ABVD	1 (6%)	17 (85%)	3 (17%)	21 (38%)
ABVD	0 (0%)	1 (5%)	6 (33%)	7 (13%)
BEACOPP	0 (0%)	1 (5%)	9 (50%)	10 (18%)
Other (COP, ChlVPP)	3 (18%)	1 (5%)	0 (0%)	4 (7%)
Total	17 (100%)	20 (100%)	18 (100%)	55 (100%)
Outcome				
Low risk (n=5)				
Relapse	0/1 (0%)	0/1 (0%)	0/3 (0%)	0/5 (0%)
Death	0/1 (0%)	0/1 (0%)	0/3 (0%)	0/5 (0%)
Intermediate risk (n=18)				
Relapse	2/4 (50%)	1/7 (14%)	0/7 (0%)	3/18 (17%)
Death	2/4 (50%)	1/4 (14%)	0/7 (0%)	3/18 (17%)
High risk (n=32)				
Relapse	10/12 (83%)	7/12 (58%)	2/8 (25%)	19/32 (59%)
Death	10/12 (83%)	5/12 (42%)	0/8 (0%)	15/32 (47%)

		Frequency	%
Response to first treatment	CR	47	85.5
	PR	1	1.8
	PD	7	12.7

had mediastinal involvement (16 patients with bulky disease). One patient was found to have bone marrow involvement, already classified as Stage IV due to liver metastases and rapidly progressed shortly after treatment.

With respect to blood tests, from the evaluable patients, 43 (78%) had abnormal ESR, nine (16%) albumin <4 g/dl, five (9%) hemoglobin <10.5, nine (16%) white blood cell count (WBC)>15000 and eight (14.5%) had a lymphocyte count less than 8%. The Cox multivariate regression analysis for OS revealed that the hazard of death was significantly higher for patients with lower levels of albumin [≤4 *vs.* >4: hazard ratio (HR)=5.2, p=0.09] and lower levels of lymphocytes (≤8% *vs.* >8%: HR=8.7, p=0.02). Results of the Cox regression analysis for EFS revealed that lower levels of albumin (≤4 *vs.* >4: HR=14.7, p=0.03), lower levels of lymphocytes (≤8% *vs.* >8%: HR=16.2, p=0.02) and abnormal ESR (abnormal *vs.* normal: HR=9.1, p=0.10) were related to significantly worse EFS.

The distribution of patients according to the three time periods and chemotherapy regimens are shown in Table II. All patients completed treatment with manageable acute toxicities recorded. The responses are shown in Table II. A total of 30 patients additionally received radiotherapy treatment (54.5%).

After a median follow up of 138 months (range: 3.97-313.67+), 18 (33%) out of the 22 relapsed patients (40%) had died (Table II). Interestingly, the vast majority of patients relapsed within the first three years of diagnosis (range 3-70 months).

Although the follow up periods were not equal between the three treatment groups, there was an improvement of the 5-year survival and 5-year EFS over the years (Table III). Median OS and EFS times have not been reached yet, but differed significantly between the three time periods (OS: p=0.001, EFS: p=0.02) (Figure 1). OS and EFS differed significantly between intermediate and high risk categories (OS: p=0.04, EFS: p=0.005) (Figure 2). Overall survival and EFS did not differ significantly between those

Table III. *Overall survival (OS) and event free survival (EFS) by treatment period.*

	Time period		
	1978-1987 Group A	1988-1993 Group B	1994-2003 Group C
Overall survival			
Events	12/17	6/20	0/18
Range (months)	3.97-313.7+	6.72-201.97+	9.44-129.70+
Median (months)	68.75	NRY	NRY
95% CI	56.5 - 81.0	-	-
1-year survival rate	88.2%	85%	100%
3-year survival rate	88.2%	80%	100%
5-year survival rate	65%	80%	100%
Event-free survival			
Events	12/17	8/20	2/18
Range (months)	3.11-313.7+	4.19-201.97+	8.88-129.70+
Median	61.2	NRY	NRY
95% CI	19.79-102.57	-	-
1-year EFS*	76.5%	80%	94%
3-year EFS*	59%	65%	88.5%
5-year EFS*	53%	65%	88.5%

NRY: Median OS or TTP times have not been reached yet. *The probability of being without progression beyond the first, third and fifth year.

Table IV. *Effect of radiotherapy on overall survival (OS) and event free survival (EFS).*

	Radiotherapy	
	No	Yes
Overall survival		
Events	11/25	7/30
Range (months)	3.97-313.67+	8.79-231.18+
Median (months)	NRY	NRY
95% CI	-	-
1-year survival rate	84%	97%
3-year survival rate	80%	97%
5-year survival rate	64%	97%
Event-free survival		
Events	11/25	11/30
Range (months)	+	5.08-231.18+
Median	NRY	159.31
95% CI	-	-**
1-year EFS *	72%	93%
3-year EFS*	56%	82%
5-year EFS*	56%	78%

NRY: Not been reached yet. *The probability of being without progression beyond the first, third and fifth year. **There are not enough relapses for the calculation of confidence interval.

patients who had received and those who had not received RT (OS: $p=0.145$, EFS: $p=0.47$) (Table IV) but there was a trend towards improvement following treatment with RT in later periods (Group A: 1978-1987: 41%, Group B: 1988-1993: 45%, Group C: 1994-2003: 78%, $p=0.06$). There was no difference observed in the OS and EFS between gender or between the two age subgroups (15-20, 21-25).

All five patients in the low risk group were event free and are alive. Three out of the 18 patients in the intermediate and 19 out of the 32 patients in the high risk groups have relapsed. Relapsed patients were offered second-line chemotherapy with poor results. Two relapsed patients in group B were offered autologous stem cell transplantation (ASCT); one is alive without evidence of disease.

One patient in Group A developed haemoptysis and died of pulmonary fibrosis most probably due to extensive mediastinal radiation treatment. In the same group a second primary (acute non-lymphocytic leukaemia) was observed after six years of follow up.

Discussion

The treatment of patients with HL has shown significant improvement over the last decades and is reflected in our results from analysing 55 young adults, 16-23 years of age treated in our unit between 1978 and 2003. The male to female ratio, frequency of histological subtypes and mediastinal involvement were similar to those previously reported in this age subgroup (15).

Although the median times for OS and EFS have not been reached yet in our study, the OS and the probability of being without relapse at five years differed significantly between the three treatment groups of young adults. Similar gradual improvements have been previously reported by other groups in the OS of young adults and children (15) and in the OS and EFS rates in adult HL (3, 4, 16). Our results showing a gradually improvement of the five year survival rate are in agreement with those of Pearce *et al.* (17). There were no acute toxicity-related deaths or chemotherapy dose reductions in our study most probably because of the excellent performance status of young patients. In contrast to younger patients the prognosis of elderly patients with advanced HL has not improved substantially over the last 20 years mainly because of the acute toxicities due to chemotherapy treatment and the high relapse rates (18).

One of the major obstacles to curing HL has been the often fatal acute and late haematological and cardio-pulmonary toxicities together with secondary leukemias, myelodysplastic syndrome and solid malignancies, the later amounting to an annual rate of more than 1% of the deaths due to HL unrelated causes still unresolved after 20 years. One of our patients developed pulmonary fibrosis and one secondary acute non-lymphocytic

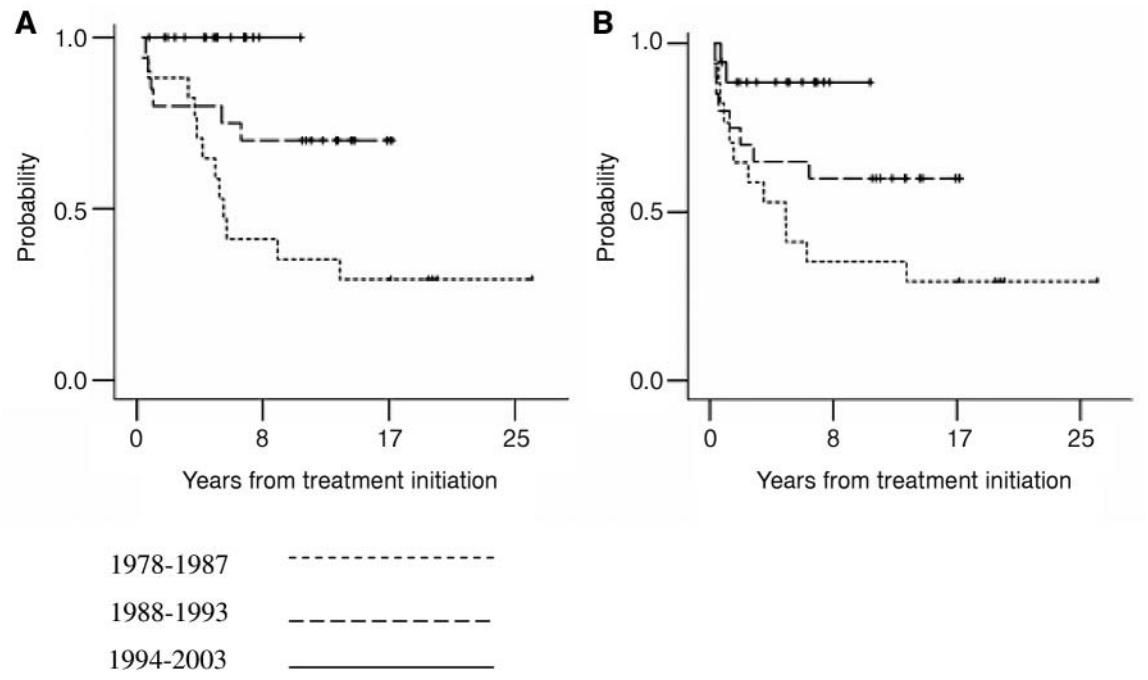

Figure 1. *Effect of treatment period on OS (A; p=0.001) and EFS (B; p=0.02).*

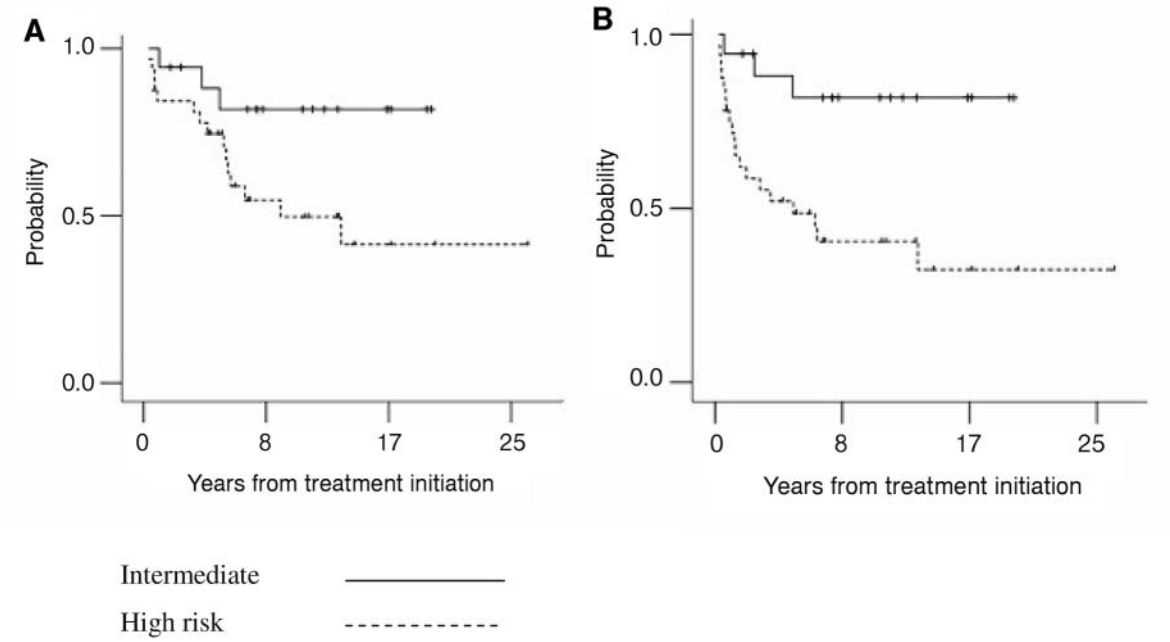

Figure 2. *Effect of risk category (intermediate vs. high) on OS (A; p=0.04) and EFS (B; p=0.005).*

leukaemia. Due to the small number of patients in our series and the short follow up period of the third treatment group, definitive conclusions on the incidence of secondary malignancies in young adults could not be extracted. From a large Italian series, 25 years of follow up revealed a 22.2% risk of developing secondary leukaemia or myelodysplastic syndrome (16). Furthermore, the incidence was lower after ABVD (1.7%)

than after either MOPP (6.2%) or MOPP alternated with ABVD (5.0%). Additionally and in agreement with another large series (19) a variety of secondary solid tumours (mainly lung, gastrointestinal and female breast cancer) were documented at an annual rate of 1% rising steadily after the first ten years with a total risk of 17.7% at 25 years. Moreover, the 25-year risk of solid tumours was higher after ABVD (22.1%) than after either MOPP (13.2%) or MOPP alternated with ABVD (14.3%).

The introduction of prognostic factors maybe one of the best strategies for maintaining the high standard of cure rates over all stages of HL. With such information those at low risk might be assigned a less intense chemotherapy protocol while high risk patients should receive an intensive one, sometimes followed by adjuvant radiotherapy. The retrospective classification of our patients into the risk categories proposed by the German Hodgkin Study Group (10) confirmed that OS and EFS differed significantly between risk groups. In our study albumin <4 g/dl and a lymphocyte count <8% were highly significant prognostic factors regardless of the treatment group and further studies are planned for their evaluation in the classification of young patients into risk groups. Although the use of bone marrow biopsies (BMB) is controversial (20), it could prove useful for patients with stage II disease, as valuable prognostic information may be obtained. PET (response adaptation), biological-risk factors and pharmacogenomics as a means of defining risk groups as well as de-escalating chemotherapy reduced radiotherapy and molecular targeted therapy are currently under investigation (10). Promising data for the predictive role of FDG-PET have been presented, but larger patient populations and longer follow-ups are necessary for confirmation (21).

Radiotherapy has been proposed for selected patients such as those with bulky disease and those achieving partial response to chemotherapy (10, 13). In the present study a trend towards improvement with RT was evident in the later periods and if appropriate risk groups could be identified this might reach significance. However, prospective randomized trials according to risk group together with newer drug combinations are required.

In all our treatment groups, the risk of lymphoma relapse was higher during the first three years from the start of chemotherapy and declined thereafter which is in agreement with the results of Diehl *et al.* (10). Relapsed and refractory HL patients can achieve complete response rates with second line chemotherapy but this outcome is usually short term. Attempts have been made to improve survival with high-dose chemotherapy (HDCT) and ASCT, particularly in children and young adults. The results of early studies in patients with relapsed HL have supported the use of stem cell transplantation (22, 23). Newest data, though, has indicated that the use of HDCT/ASCT is limited by the high rate of transplant-induced mortality (24). Comparison of a conventional regimen and reduced intensity allogeneic stem cell transplantation has shown a reduced transplant related mortality, but unfortunately graft-*vs.*-host disease, relapse rates and survival have not substantially changed (25). The outcome for patients with relapsed disease undergoing HDCT/ASCT depends on a number of prognostic factors, the strongest of which is the time interval between first remission and relapse (26). Patients with a late first relapse (>12 months after first complete remission) achieve a reasonable time to treatment failure and OS as compared to those who relapse in less than 12 months and do significantly worse (25).

The survival of young patients with HL has been significantly improving over the last 25 years most probably due to the excellent performance status of this group of patients, better understanding of risk factors, and improved treatment schedules, including HDCT/ASCT. Tailoring treatment by the use of novel molecular and imaging technology is expected to refine treatment strategies further and improve long term survival while at the same time decreasing long term sequels. It is proposed that this goal should be addressed by the use of case specific adjusted chemotherapy and radiotherapy taking account of further refinement of the risk groups using PET-CT, molecular markers and pharmacogenomics.

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