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ORIGINAL ARTICLE

The role of high-dose therapy and autologous stem cell transplantation in patients with primary refractory Hodgkin's lymphoma: a report from the Gruppo Italiano per lo Studio dei Linfomi (GISL)

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GISL recently conducted an exhaustive survey of 1078 patients with Hodgkin's Lymphoma (HL) enrolled between 1988 and 2002 in different prospective trials. Treatment failure was observed in 82 out of 1078 patients; of these 82 patients with refractory HL, complete information was available for 72, who form the evaluable population of the present study. After the initial therapy failure, 51 patients were treated with conventional salvage chemotherapy (CC) ($n = 24$) or high-dose chemotherapy (HDC) ($n = 27$); 4-year overall survival (OS) was 81% in the HDC group versus 38% in the CC group ($P = 0.019$). The remaining 21 patients had rapidly progressive disease and died. After a median follow-up of 2.8 years, the projected OS for all 72 patients is 58 and 49% at 3 and 5 years, respectively. Age <45 years, the absence of systemic symptoms and a PS <1 predicted a significantly longer OS. Interestingly, the majority of patients with two or three negative prognostic factors did not receive potentially curative therapy. In conclusion, HDC seems to be a reasonable option for selected patients with refractory HL, although the majority of them did not receive a transplant. Finally, patients with a high-risk score had little chance of receiving potentially curative treatment.

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Introduction

The outcome of Hodgkin's lymphoma (HL) has improved dramatically over the past decades and this lymphoma is now ranked among the most curable neoplastic diseases.[1] This is mainly due to the use of risk-adapted therapies able to achieve a high percentage of durable remissions.[1,2] However, despite the overall improvement in HL survival,[1–3] roughly 10% of patients fail to respond to an induction therapy and an additional 15–20% of cases will relapse after a complete remission has been achieved. Relapses after radiation therapy can be successfully treated with chemotherapy (CC),[4] and, conversely, selected patients with local recurrence after CC can be rescued with radiation therapy.[4] However, patients who are refractory to induction therapy with combination CC generally have a poor long-term prognosis; these patients are usually treated with salvage therapies, but it is estimated that only 25–35% obtain a further durable remission.[1–4]

A number of salvage treatments, followed by autologous stem cell transplantation (ASCT), have been proposed to improve the outcome of patients with refractory HL. Five-year event-free survival rates of more than 30% have been reported using regimens such as ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone),[5] DHAP (dexamethasone, cisplatin, cytarabine),[6] mini-BEAM (carmustine, etoposide, cytarabine, and melphalan),[7] and IGEV (ifosfamide, vinorelbine and gemcitabine)[8] followed by ASCT.

Nevertheless, despite the apparently better results achieved with high-dose chemotherapy (HDC) than with CC, the question of whether HDC should be offered to patients not responding to initial therapy is still under debate. The *Gruppo Italiano per lo Studio dei Linfomi* (GISL) recently conducted an exhaustive survey of patients with HL enrolled between 1988 and 2002 in different prospective trials of first-line therapy. The primary objective of this study was focused on refractory patients

to compare HDC to standard dose CC as first salvage treatment.

Patients and methods

Patients

Between January 1988 and December 2002, 1151 patients with HL were enrolled in several GISL trials, specifically designed according to a risk-tailored treatment strategy. Patients with a low-risk were treated with a VBM (vinblastine, bleomycin, methotrexate)-based CC plus involved-field radiotherapy (IF-RT).[9] Patients with an intermediate-risk were treated with four courses of an adriamycin-including regimen, that is, ABVD[10] or EVE (etoposide, vincristine, epidoxorubicin), a variant of the EVA (etoposide, vincristine, adriamycin) regimen[11] plus IF-RT. Finally, patients with a high-risk were treated with six courses of ABVD, MOPPEBVCAD (mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, bleomycin),[12] BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone),[13] or 12 weeks of Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone)[14] plus RT to residual masses or to sites of previously bulky disease. Out of 1151 cases initially registered, complete information on response to initial treatment was available for 1078 cases. One hundred and ninety-nine patients (18%) were grouped as low risk, 331 (31%) as intermediate risk and 548 (51%) as high risk.

Patients with HL who did not respond to an induction CC, whether they had progressive, stable or only minimally responsive disease were considered to have primary refractory HL. Out of the 1078 HL patients, 82 cases failed (7.6%). However, 72 cases with available data on salvage treatment and outcome constitute the present study population.

Salvage therapy

Information on salvage therapy, including type of salvage regimen, response to therapy and subsequent outcome, was retrieved. Twenty-seven patients underwent HDC. No grafts were manipulated *in vitro*. The conditioning regimens were melphalan plus thiotepa (1 case), mitoxantrone plus melphalan (five cases) and BEAM (21 cases). Twenty-four patients were treated with standard dose CC. The remaining 21 cases were treated with a palliative approach.

Statistical analysis

All calculations were performed using the statistical software SPSS for Windows, release 11.0, 2001. The following clinical features were analysed as potential prognostic factors: age, sex, performance status (PS), B symptoms, initial risk (L, I, H), disease stage, lactic acid dehydrogenase (LDH), albumin (ALB) and hemoglobin (Hb) levels, white blood cell (WBC) and lymphocyte (Ly) count, bulky disease. Age, Hb and LDH levels were transformed into binary variables, as appropriate. Statistical comparisons for binary variables were performed using two-way tables for Fisher's exact test and multiway tables for Pearson's χ^2 test. Logistic regression analysis was used for multivariate analysis, since the dependent variable was restricted to two categories (complete response (CR) versus not CR). The nonparametric Kruskal–Wallis and Mann–Whitney *U*-tests were employed to examine the differences between two or more groups. Overall survival (OS) was analysed by calculating the time interval between date of diagnosis and death from any cause, or date of the last follow-up for surviving patients. Prognostic groups were evaluated using univariate analysis by the log-rank test, and the relative influence on the survival of the different variables, significant at $P \leqslant 0.1$. Multivariate analyses were performed using a Cox proportional hazards technique. A value of $P \leqslant 0.05$ was considered significant for all statistical calculations.

Results

A total of 82 patients with primary refractory HL were identified. Ten patients were excluded from the final analysis because of incomplete information on salvage treatment or outcome. Thus, 72 patients were available for the final analysis. The characteristics of these patients are listed in Table 1. The median age of the patients was 39 years and approximately half the patients were male. The most commonly used first-line therapies were ABVD and MOPPEBVCAD, since the majority of patients had advanced disease.

After assessing initial therapy failure, 51 patients were treated with salvage therapy (24 with CC and 27 with HDC) and successfully concluded their therapeutic program. The distribution pattern of sex, disease stage, PS, systemic symptoms, bulky disease, LDH, ALB and Hb levels, WBC and Ly counts was not significantly different between cases treated with CC and those treated with HDC (Table 2). However, a significantly higher proportion of older patients ($P = 0.029$) was observed in the CC group, while fewer early favorable cases and more advanced cases were identified in the HDC group ($P = 0.007$) (Table 2).

The remaining 21 patients either rapidly progressed and died or were not treated with potentially curative therapy. Notably, patients in this latter group were older than those cases treated with curative intent, with a significantly lower proportion of 45-years-old younger subjects (33 versus 71%, $P = 0.007$) and, accordingly, a significantly higher number of cases with worse PS (8/21 versus 1/51, $P < 0.0001$) in the group of patients who received inappropriate or no salvage therapy.

Achievement of complete response by second line therapy

Overall, a CR was achieved in 26 cases. The CR rate was 40% among all 72 patients, but was 51% if only those treated with a curative intent were considered. Univariate analysis revealed no significant relationship between CR achievement and good PS, absence of systemic symptoms, age and all the remaining variables analysed in this study. However, when analysing cases on the basis of the type of

Table 1 Patient characteristics at diagnosis

Characteristic	*Number (%)*
No. of patients	72 (100)
Sex	
Male	35 (48.6)
Female	37 (51.4)
Age, median (range), years	38.9 (15–86)
Histology	
Nodular sclerosis	48 (66.7)
Mixed cellularity	15 (20.8)
Lymphocyte depletion	4 (5.6)
Lymphocyte predominant	5 (6.9)
Ann Arbor stage	
I	3 (4.2)
II	28 (38.9)
IIE	5 (6.9)
III	12 (16.7)
IIIE	2 (2.8)
IIIES	1 (1.4)
IV	17 (23.6)
Bulky disease	
No	48 (66.7)
Yes	24 (33.3)
Systemic symptoms	
Absent	35 (48.6)
Present	37 (51.4)
Performance status	
0–1	63 (87.5)
2–4	9 (12.5)
LDH	
Abnormal	20 (29.9)
Normal	47 (70.1)
Albumin (g/l), median (range)	36 (20–76)
Hb (g/dl), median (range)	11.6 (7–15.2)
White blood cells ($\times 10^9$/l), median (range)	8.2 (2.1–27)
Lymphocytes ($\times 10^9$/l), median (range)	1.5 (0.13–69.9)
Risk-adapted groups	
Early-favourable	10 (13.9)
Early-unfavourable	21 (29.2)
Advanced	41 (56.9)
First line therapy	
ABVD	20 (27.8)
MOPPEBVCAD	17 (23.6)
VBM	13 (18.1)
EVE	4 (5.6)
Stanford V	7 (9.7)
BEACOPP	3 (4.2)
Other	8 (11.1)

salvage therapy, the proportion of patients achieving CR was significantly higher in the HDC group than in the CC group (18/27 versus 8/24, $P = 0.025$).

Analysis of survival

At a median follow-up of 37 months (range 2–179 months), 37 patients died. The projected OS for all 72 patients was 58 and 49% at 3 and 5 years, respectively.

As expected, patients with rapidly progressive disease or those not treated with potentially curative therapy had a statistically significant shorter OS than the patients treated with potentially curative salvage therapy; indeed, the 3-year OS was 68% among patients who received salvage treatment and only 23% in those managed with palliative treatment (Figure 1).

At 4 years, 81 and 38% of patients are still alive among the HDC and CC groups, respectively ($P = 0.019$, Figure 2a). However, achievement of a CR guaranteed prolonged survival in all cases, regardless of the therapeutic approach (Figure 2b).

With the aim of reducing, at least in part, the bias of the retrospective nature of this study, a multivariate analysis for survival was performed on the 51 treated patients including as variables, age, B-symptoms, PS and type of treatment (CC vs HDT). As expected, the type of treatment remained the only variable, which significantly predicted survival on multivariate analysis. In particular, HDC reduced death risk of 67% ($P = 0.01$).

Discussion

Overall, our data confirm that the outcome of patients with refractory HL is dismal, particularly for patients receiving standard dose salvage CC.[15–17] Our results are comparable to those of Longo *et al*.[16] who found that no HL patient refractory to MOPP CC was alive after 8 years. Similarly, Bonfante *et al*.[17] showed that the 8-year survival rate was 8% among the 39 patients in whom MOPP-ABVD induction treatment was considered to have failed. However, several encouraging reports suggest that HDC can improve outcome in patients with primary refractory HL.[18–22]

Current clinical trials in HL are seeking to define the amounts of treatment that produce the optimum therapeutic results. Currently, the three-level scheme of division into early favourable, early unfavourable and advanced disease cases remains a suitable instrument for tailoring risk-adapted therapy. In 1988, GISL started to stratify patients with HL on the basis of major prognostic factors and to treat them with a risk-adapted therapy. A total of 1078 patients were included in these trials and 82 of them (7.6%) showed primary refractoriness to therapy. This finding is compatible with a recent German Hodgkin's Lymphoma Study Group (GHLSG) report of 6.3% of progressive cases recruited from trials for intermediate and advanced stages HL.[18] On the other hand, the Groupe d'Etudes des Lymphomes de l'Adulte reported an induction failure rate of 12.6% in the H 89 Trial on advanced HL.[19]

The first important finding emerging from our analysis was the noteworthy proportion of patients who failed to receive a potentially curative second-line treatment; this lack of treatment was significantly associated with an older age and with a worse PS. These patients, predictably, had a very poor clinical outcome, with a remarkable 72% death rate after a median follow-up of roughly half a year.

Conversely, 71% of the whole cohort received potentially curative treatment. In this regard, a second interesting consideration is the number of cases who received HDC in

Table 2 High-dose (HDC), conventional dose (CC) chemotherapy or palliative treatment, at the time of disease onset

Variable	*HDC (%)*	*CC (%)*	*Palliative (%)*	P#	P*	P§
Age, ⩾45 years	15	46	62	0.003	0.034	NS
Sex, male	48	62	43	NS	NS	NS
Stage, IV	26	17	40	NS	NS	NS
PS, WHO ⩾2	0	4	33	<0.001	NS	0.017
B symptoms, yes	56	46	52	NS	NS	NS
Bulky disease, yes	37	29	33	NS	NS	NS
LDH, abnormal	37	30	26	NS	NS	NS
Hb <10.5 g/dl	30	29	19	NS	NS	NS
Albumin <4 g/dl	59	82	89	0.055	NS	NS
WBC ⩾15°10^9/l	22	38	5	0.029	NS	0.012
Lymph. <0.6 × 10^9/l	12	4	5	NS	NS	NS
Risk-adapted groups						
Early-favourable	0	25	14			
Early-unfavourable	18	33	33	0.014	0.005	NS
Advanced	82	42	53			

P # = *P*-value between all groups.
*P** = *P*-value CC versus HDC.
P§ = *P*-value palliative versus CC.
Fisher's exact test or χ^2 test, two-sided.

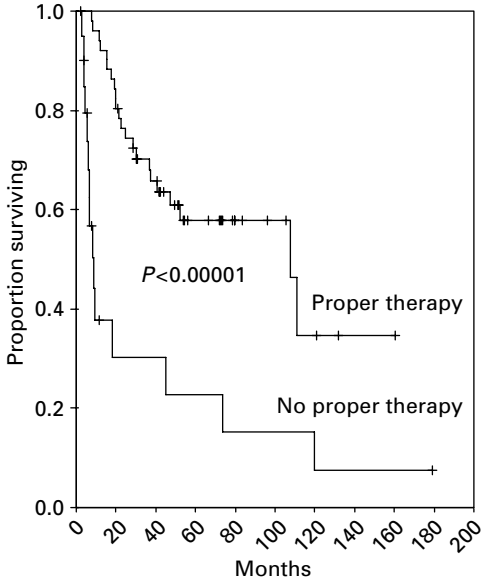

Figure 1 Kaplan–Meier estimates of OS for patients with rapidly progressive disease or those not treated with potentially curative therapy (no proper therapy) as compared with those treated with potentially curative salvage therapy (proper therapy).

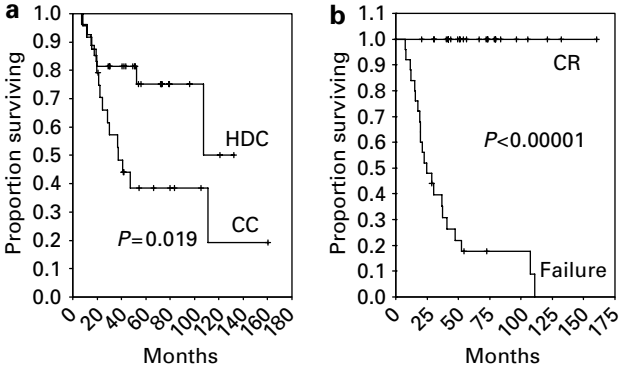

Figure 2 Kaplan–Meier estimates of OS for patients according to therapy (**a**) and to the achievement of CR regardless of the therapeutic approach (**b**).

our cohort analysis (33%, 27 out of the initial 82 refractory cases), which is in line with the 34% of patients who effectively underwent a transplant program reported in the database of the GHLSG,[18] while 43 out of 67 (64%) induction-failure cases were transplanted in French study.[19] Josting *et al*.[18] showed that the majority of patients with primary resistant disease receiving salvage therapy were excluded from high-dose programs because of progressive disease, life-threatening severe toxicity of conventional treatment or age above 60 years. In our series, 21 patients were unable to receive any potentially curative treatment. Moreover, despite the unbalanced distribution of age between the HDC and CC groups, we could not completely exclude that the therapeutic decisions were independent of the patients' status. This consideration could represent a potential bias for a comparison of clinical outcome. In this respect, we tried to avoid the influence of this bias by performing a multivariate analysis on the 51 properly treated patients. As expected, the type of treatment remained the only variable that significantly predicted survival.

We found that 67% of patients treated with HDC achieved a CR, whereas only 33% of those treated with CC did so. Czyz *et al*.[20] recently reported a 54% CR rate after second-line HDC in primary refractory HL. Subsequently, the same authors demonstrated, in a retrospective match-paired analysis comparing HDC versus CC, a CR rate of 41% in the transplanted cases versus 30% in the standard chemotherapy group.[21] None of them were in CR at the time of transplantation. Overall, literature data demonstrated that the HDC strategy is able to generate a reliable rate (29–58%) of complete responders in primary refrac-

tory HL;[22–31] however, it cannot be stated that this approach is definitively superior to conventional-dose salvage therapy. Notably, the achievement of a CR with a potentially curative treatment guaranteed prolonged survival in patients belonging to our series, regardless of the therapeutic approach. However, a longer follow-up is needed to confirm this finding. Moreover, those patients who failed to respond to both CC and HDC had a median overall survival of 24.6 months, with 35% of cases still alive at 3 years.

In our study, after a median follow-up of 2.8 years, the projected OS for the entire cohort of patients is 58.2 and 48.7% at 3 and 5 years, respectively. After a median follow-up of 42 months, patients who did receive potentially curative therapy had a median OS of 107.5 months. Notably, the only predictive factor for survival was the type of therapy. In particular, after 4 years, 81 and 38% of patients were still alive in the HDC and CC groups, respectively. The outcome of HDC group seems better than that usually reported. The actuarial OS for 70 patients treated with HDC was 43% in the German group,[18] 50% at 3 years in a group of 122 HL patients reported by Lazarus *et al*.,[31] about 25% at 5 years in the GEL/TAMO Cooperative Group study[22] and, finally, in the EBMT study dealing with 175 patients with primary induction failure, the actuarial 5-year OS was 36%; however, patients transplanted without further attempts to induce remission with CC had a longer OS comparing with patients who were transplanted after failing to respond to a second-line treatment.[23] Furthermore, Andrè *et al*.[24] reported a higher, although not statistically significant, 6-year OS rate for the autografted patients (38%) versus those cases treated with conventional therapy (29%) ($P = 0.058$). In a first Polish study, the actuarial 3-year OS was 55% for patients with primary refractory HL who were transplanted.[20] More recently, Czyz *et al*. showed no difference in survival between treatment groups, with 5-year OS rates of 33.7% in the grafted group and 35.6% in the CC group. Overall, these data showed no clear demonstration that HDC is not superior to standard CC for the treatment of patients with primary refractory HL.[21]

In conclusion, our study confirms that autologous hematopoietic stem cell transplantation can result in durable long-term complete remissions in a significant proportion of patients with primary refractory HL otherwise deemed incurable with conventional CC. However, the benefit of HDC can be overestimated due to selection bias. In this context, prospective randomised trials including early lymphoma restaging with more accurate criteria for the assessment of residual disease are warranted. Newer imaging techniques, such as positron emission tomography (PET) scanning[32] should improve the evaluation of disease status and consequently the timing and intensity of treatment to the individual patient. Finally, patients with early relapse after a more recent first-line CC, as well as patients with primary progressive disease, could be candidates for innovative approaches including non-myeloablative stem cell transplantation[33] and cytotoxic T lymphocyte therapy against Epstein–Barr virus.[34]

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