Hodgkin's Disease

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# Dose intensification with autologous stem cell transplantation in relapsed and resistant Hodgkin's disease

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*Background and Objectives.* Patients affected by Hodgkin's disease (HD) resistant to induction therapy or who have a brief duration of first remission have a poor outcome.

*Design and Methods.* We retrospectively reviewed the clinical data of 28 patients affected by Hodgkin's disease who relapsed 6 to 24 months from completion of treatment (14 patients) or who were refractory to first-line therapy or relapsed very early (14 patients). All the 28 patients were treated with salvage chemotherapy plus a conditioning regimen followed by peripheral blood stem cell transplant (PBCST) or autologous bone marrow transplant (ABMT).

*Results.* At a median follow-up of 35.5 months (range 14-119), of the 14 patients responding to first-line therapy but who relapsed > 6 months off therapy, 10 (72%) are alive, well and in complete remission (CR), 2 (14%) are alive with disease at 39 and 83 months from transplant, and 2 (14%) died 26 and 63 months after their transplant from acute myeloid leukemia and HD, respectively. At a median follow-up of 39 months, the overall survival (OS) is 68% and the event-free survival (EFS) is 56%. At a median follow-up of 30 months (1-98), of the 14 patients refractory to first-line therapy or who relapsed very early, 9 (64%) are alive in CR, 1 (7%) is alive with disease and 4 (29%) have died of their disease (3 patients) or myelodysplastic syndrome (1 patient). The OS is 58% and the EFS is 52%. There are no statistically significant differences in terms of OS and EFS between the two groups of patients.

*Interpretation and Conclusions.* Our study shows that salvage chemotherapy followed by a conditioning regimen and autotransplant is an effective, feasible and well-tolerated scheme of therapy not only for patients with HD who relapse after first-line treatment, but also for those resistant to first-line treatment.



Key words: autotransplant, IEV regimen, resistant Hodgkin's disease, salvage chemotherapy.

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Hodgkin's disease (HD) is a neoplasia with an overall survival (OS) exceeding 70% at 10 years. Despite the favorable results achieved, patients who fail to benefit from induction therapy or have a brief duration of first remission have a poor outcome.[1] However some studies suggest that the prognosis of these patients may be improved if they are treated with high-dose therapy and a bone marrow autograft.[2] This strategy has been claimed to significantly improve OS and event-free survival (EFS).[3,4] We report the results obtained in 28 patients with Hodgkin's disease who failed conventional therapy or were in first relapse of the disease, and were treated with salvage chemotherapy followed by a peripheral blood stem cell transplant (PBSCT) or autologous bone marrow transplant (ABMT). All the 28 patients received 3 cycles of IEV regimen followed by autotransplant.

## Design and Methods

We retrospectively reviewed the clinical data of 28 patients observed at our Institute between February 1995 and January 2000, who were affected by HD refractory to first-line therapy or who had relapsed within 24 months off therapy. The patients' characteristics are presented in Tables 1 and 2. Patients were treated with salvage chemotherapy consisting of 3 cycles of IEV regimen (cyclophosphamide 2,500 mg/m$^2$ days 1-3, etoposide 150 mg/m$^2$ days 1-3, epirubicin 100 mg/m$^2$ day 1).[5] On the fifth day after the start of the second cycle, they were stimulated with granulocyte colony-stimulating factor (G-CSF) to collect peripheral blood progenitor cells by apheresis. The minimum target for stem cell collection was $2\times10^8$ cells/kg. Thereafter, patients received BEAM conditioning regimen[6] followed by PBSCT or ABMT (when the procedure had been performed before 1996).

### *Response criteria and statistical analysis*

Complete remission (CR) was defined as complete resolution of all signs and symptoms of disease and

**Table 1. Patients resistant to first-line therapy and those relapsing early: characteristics at diagnosis.**

| | *N° (%)* |
|---|---|
| Total patients | 14 |
| Sex | |
| Males/females | 4 (29)/10 (71) |
| Age (Median/Range) | 31 (19-49) |
| Histology | |
| Nodular sclerosis | 8 (57) |
| Mixed cellularity | 5 (36) |
| Not otherwise specified | 1 (7) |
| Ann Arbor stage | |
| II/III-IV | 4 (29)/10 (71) |
| B-symptoms | 10 |
| Bulky disease | 8 (57) |
| IPI* ≥ 3 | 5 (36) |
| ESR ≥ 40 | 9 (64) |
| First-line therapy | |
| ABVD | 9 (64) |
| ABVD/MOPP | 3 (22) |
| ABVD/OPP | 1 (7) |
| VEBEP | 1 (7) |

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**Table 2. Patients who relapsed > 6 months off therapy: characteristics at diagnosis.**

| | *N° (%)* |
|---|---|
| Total patients | 14 |
| Sex | |
| Males/females | 6 (43)/8 (57) |
| Age (Median/Range) | 28 (21-40) |
| Histology | |
| Nodular sclerosis | 10 (71) |
| Mixed cellularity | 3 (22) |
| Lymphocyte prevalence | 1 (7) |
| Ann Arbor stage | |
| II/III-IV | 4 (29)/10 (71) |
| B-symptoms | 12 (86) |
| Bulky disease | 5 (36) |
| IPI* ≥ 3 | 2 (14) |
| ESR ≥ 40 | 9 (64) |
| First-line therapy | |
| ABVD | 9 (65) |
| ABVD/OPP | 3 (21) |
| ABVD/MOPP | 2 (14)) |

**Hasenclever et al.[17]*

disappearance of measurable masses by radiological investigations. Partial remission (PR) was defined as a reduction ≥ 50% and < 80% of measurable disease. All the responses < 50% were considered resistance. Overall survival (OS) was calculated from the beginning of salvage therapy to death or the last follow-up. Event-free survival (EFS) was calculated from the autograft to the first event (resistance to treatment, relapse, second neoplasia, death, last follow-up). Survival analysis was performed with the Kaplan and Meier method. Pearson $\chi^2$ test was used for the univariate analysis of qualitative data, and Whitney's test was used for univariate analysis of quantitative data.

## Results

The mean number of apheretic procedures was two (range 1-3); the mean number of collected stem cells was $2.49\times10^8$/kg. A sufficient number of stem cells was collected for all patients.

### *Patients responding to first-line therapy who relapsed > 6 months off therapy*

Fourteen patients had relapsed at a median time of 18 months off-therapy (range 8-24). All were treated with 3 cycles of IEV regimen and PBSCT (11 patients) or ABMT (3 patients). After the 3 IEV courses, 12 patients achieved CR and 2 patients PR. Of the 12 patients who underwent autotransplant in CR, 9 are presently in CR 16 to 119 months from transplant (median 29 months), one patient, while in CR at 24 months off therapy, developed an acute myeloid leukemia and died soon after of related complications, 2 patients relapsed 4 and 36 months off-therapy; of these, one is alive with disease at 39 months whereas the other died of disease 63 months later. Of the 2 patients who underwent autotransplant in PR, both achieved CR; one relapsed 42 months later and is alive with disease 83 months after transplantation, the other one is alive in CR 80 months off-therapy.

After a median follow-up of 35.5 months (range 14-119), 10 patients (72%) are alive, well, and in CR; 2 patients (14%) are alive with disease at 39 and 83 months from transplant, 2 patients (14%) died 26 and 63 months after their transplant from acute myeloid leukemia and HD, respectively. At a median follow-up of 39 months, the OS is 68% and the EFS is 56% (Figures 1, 2).

### *Patients refractory to first-line therapy or who relapsed very early*

All the 14 patients refractory to first-line therapy or who relapsed ≤ six months off-therapy were treated with 3 cycles of IEV regimen and autotransplantation (13 with peripheral blood and one with bone marrow stem cells).

After the 3 IEV courses, 9 patients achieved CR, 3 patients achieved PR and 2 patients were resistant to this chemotherapy. Of the 9 patients who underwent autotransplantation in CR, 7 are presently in

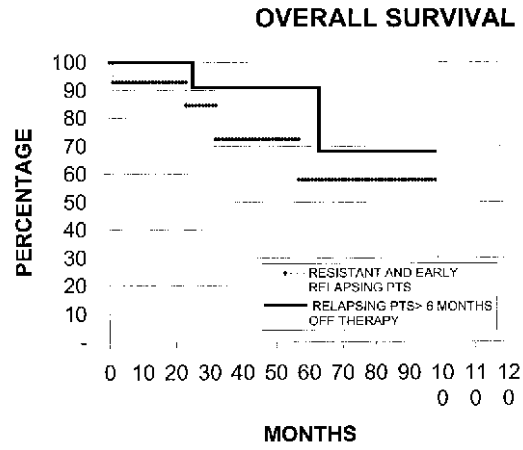


**Figure 1. Overall survival.**

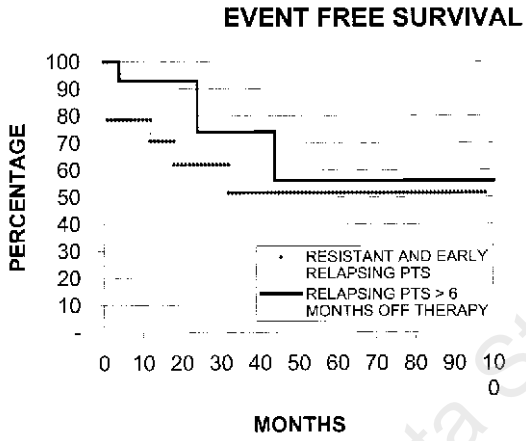


**Figure 2. Event-free survival.**

CR 11 to 73 months from transplant (median 45 months), one patient died 32 months later of myelodysplasia, and one patient relapsed one year later and died of disease progression. Of the 3 patients who underwent transplant in PR, 2 achieved CR and, to date, are alive in CR at 51 and 98 months; one patient remained in PR and died 57 months later of disease progression. Of the 2 patients who did not respond to the IEV regimen, neither benefited from transplantation; one is alive with disease 28 months from the transplant, the other died soon after with disease, because of an infectious complication. In summary, at a median follow-up of 30 months (range 1-98), 9 patients (64%) are alive in CR, 1 patient (7%) is alive with disease and 4 patients (29%) have died of disease (3 patients) or myelodysplasia (1 patient). The OS is 58% and the EFS is 52% (Figures 1 and 2).

### *Toxicity*

The median time to recovery of neutrophils and platelets was 12 days (range 10-32) and 20 days (range 10-50), respectively. Twelve patients (43%) required blood transfusions (1-5 units) and 13 patients (46%) needed platelet transfusions (range 4-41 units). Twelve patients (43%) had bacterial infections. Hematologic and non-hematologic toxicities were acceptable. No death resulted from toxicity due to the conditioning regimen.

### *Statistical analysis*

To evaluate the presence of prognostic factors at the moment of diagnosis that might have indicated a negative evolution of the disease in the present series of patients, univariate analyses of qualitative data (Pearson's $\chi^2$ test) and of quantitative data (Mann-Whitney's test) were performed. First of all, we distinguished patients responding to the first-line therapy and relapsing > 6 months off-therapy from patients relapsing ≤ 6 months or patients who were refractory to first-line therapy, and we considered histology, stage, symptoms, International Prognostic Index (IPI), median age, and erythrocyte sedimentation rate (ESR). Using Pearson's $\chi^2$ test, the presence of symptoms ($p$= 0.0028), an IPI ≥ 3 ($p$= 0.021), and an ESR ≥ 40 ($p$= 0.0075) resulted to be negative prognostic factors for response to treatment. However, they did not significantly influence survival. Then, we considered the final state of the patients (alive in CR versus alive with disease or dead) and we analyzed the different variables (sex, histology, stage, symptoms, bulky disease, IPI, age, ESR, response to first line therapy, response to IEV, and response to autotransplant). We found that the only significantly negative prognostic factors were the response to the first-line treatment ($p$= 0.026), to IEV ($p$= 0.056) and to autotransplant ($p$= 0.06).

## Discussion

Patients with refractory HD or with early relapse after first-line therapy, still represent an unsolved problem because of their poor outcome.[7,8] There is now a broad agreement on the indications for ABMT for patients failing to achieve CR with first-line treatment, patients relapsing within six months after CR obtained with conventional first line therapy and patients who initially fail to benefit from radiotherapy and subsequent chemotherapy.[9] However, few randomized studies have compared the transplant approach with conventional salvage strategies.

In the Sloan-Kettering Cancer Centre (MSKCC) experience,[10] 50 patients with advanced stage HD not responding to at least two alternating or sequential chemotherapy combinations were treated with

two different high-dose therapy regimens and ABMT. The authors concluded that the most important factor to remain disease-free was the achievement of response immediately prior to intensive therapy, irrespective of the conditioning regimen used. On the other hand, it was not advisable to offer the aggressive program of ABMT to patients who were completely refractory to multiple salvage efforts. Gianni *et al.*[11] explored the efficacy and tolerance of a high-dose regimen followed by PBSCT in 25 patients with persistent HD or who had relapsed early after treatment. At a median follow-up of 43 months, they observed an OS of 54% and an EFS of 49%. The procedure was well tolerated because of the rapid hematologic recovery due to the use of peripheral blood progenitors. In 1993 Linch *et al.*[5] undertook a randomized trial comparing high-dose chemotherapy (BEAM) followed by ABMT in 20 patients, with the same drugs at lower doses in those not requiring bone marrow rescue (mini-BEAM) in another 20 patients. After a median follow-up of 34 months, EFS and progression free survival (PFS) were statistically significantly different in favor of BEAM plus ABMT. OS was also higher in the group of patients treated with this regimen, but the difference had not reached statistical significance.

Burns *et al.*[12] analyzed clinical data from 62 patients with refractory or recurrent HD treated with CBV (cyclophosphamide, carmustine, etoposide) followed by ASCT. Seventy-six percent of patients achieved CR after CBV and transplant. Disease-free survival (DFS) at three years was 100% for patients who received salvage chemotherapy and were transplanted in CR, versus 39% for patients transplanted in PR and only 11% for patients with no response to salvage chemotherapy ($p = 0.0001$). The authors concluded that CBV and ASCT could produce durable remission, with acceptable toxicity, in a substantial proportion of patients who were in CR at the time of transplantation.

Another retrospective study by Yuen *et al.*[4] compared conventional salvage therapy from high-dose therapy plus autografting in patients with refractory or recurrent HD. The response to cytoreductive or salvage therapy was the most important predictor for OS and EFS. The Kaplan-Meier curves comparing the two groups of patients showed an advantage with high-dose therapy in EFS and failure from progression (FFP). OS was also improved, but the difference did not reach statistical significance.

Bierman *et al.*[13] evaluated the results of chemotherapy and autologous hematopoietic rescue in 85 HD patients who had relapsed after a CR achieved with initial chemotherapy; they concluded that this approach should be considered for any patient with relapsed HD, regardless of the duration of the first remission or the type of initial chemotherapy.

Lazarus *et al.*[14] and Sweetenham *et al.*[15] reviewed the data from the *Autologous Blood and Marrow Transplant Registry* and the *European Group for Blood and Marrow Transplantation*, respectively. Both authors concluded that autotransplant should be considered in patients affected by HD resistant to first-line therapy. In a recent retrospective study,[16] a database on 494 Spanish patients with HD who received ASCT were reviewed and the disease status before ASCT resulted to be the most important prognostic factor for the final outcome. Our study shows that salvage chemotherapy, such as the IEV regimen, followed by a conditioning regimen (BEAM) and autotransplantation was an effective, feasible and well-tolerated scheme of therapy not only for patients who relapsed > 6 months after their initial response but also for those who relapsed < 6 months or who were resistant to first-line therapy. In fact, although a lower OS was observed in resistant patients or those who relapsed ≤ 6 months off therapy as compared to in patients who relapsed after > 6 months (58 vs 68%), we did not find statistically significant differences in terms of OS and EFS between the two groups of patients. Moreover, statistical analysis confirms that the only really important prognostic factors for survival are the response to treatment and the disease status at the moment of transplant. The IEV scheme followed by the BEAM conditioning regimen and PBSCT seems to give better results than other similar approaches in this subset of patients. Our patients, relapsing after or resistant to first-line therapy, were soon submitted to salvage chemotherapy without being treated with second-line therapies; after 3 IEV courses, they were submitted to restaging and soon after, at a median time of 30-50 days, to autotransplantation. However, this is a retrospective study on a small number of patients, so it is not possible to draw definitive conclusions. A prospective, randomized study with other drug combinations and sequences should be considered in order to evaluate whether the IEV regimen followed by BEAM and PBSCT is the most advisable approach in these patients. At the same time, new approaches need to be explored to improve OS and EFS significantly in this subset of patients with an extremely negative prognosis.

*Contributions and Acknowledgments*

*APA and EC designed the study and wrote the paper. GM, GA, MC, VG contributed to the executio n of the study. RME and MFO performed the radio-*

*therapy treatment when needed. MET was responsible for statistical analysis. FM critically revised the paper and gave final approval for the submission. First and second author carried out the role of supervising the working group.*

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*Disclosures*

*Conflict of interest: none.*

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## Peer Review Outcomes

### *Manuscript processing*

This manuscript was peer-reviewed by two external referees and by Prof. Paolo G. Gobbi, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Prof. Gobbi and the Editors. Manuscript received November 28, 2001; accepted March 6, 2002.

### *What is already known on this topic*

Patients with refactory or early relapsing Hodgkin's disease usually show poor outcome both after conventional and high-dose therapies followed by ABMT.

### *What this study adds*

This study, using IEV megachemotherapy and ABMT rescue, demonstrates results only slightly poorer than, but substantially comparable with, those achievable in late relapsing patients.

### *Potential implications for clinical practice*

These results might stimulate new prospective clinical studies which involve this very unfavorable set of patients with a higher probability of success.

*Paolo G. Gobbi, Deputy Editor*