NOWOTWORY 2000 / volume 50
Number 6 / 581–586

Orginal contributions

High dose chemotherapy combined with transplantation of haematopoietic progenitor cells in the treatment of resistant and recurrent Hodgkin's disease

Jarosław Czyż, Wanda Knopińska-Posłuszny, Andrzej Mital,
Krzysztof Lewandowski, Andrzej Hellmann

Introduction. Hodgkin's disease is usually characterised by favourable prognosis, even in its advanced form. Primary resistance and relapse, in particular in the period prior to a year from achieving remission, is most negatively affected prognostically. Standard treatment leads to secondary remission only in 29% of patients undergoing treatment. Recently, the treatment of resistant and recurrent Hodgkin's disease employs high dose chemotherapy combined with autologous haematopoietic cell transplantation

Material and methods. The effect of such treatment in 40 patients is presented. The therapeutic indications for transplantation were: primary resistance in 15 cases; partial remission in two; early relapse in five; late relapse in two; second and further relapses in the remaining 16 cases. The haematopoietic cells originated exclusively from peripheral blood. The transplantation was preceded by cytoreductive chemotherapy according to the DexaBEAM scheme, in standard doses. At the time of transplantation complete remission was observed in 15 patients, partial remission in 17, and in eight cases the disease progressed. CBV was utilised for conditioning, and replaced later by BEAM.

Results. Remission was achieved in 32 out of 40 cases, partial remission was noted in five cases and progression of the disease in on. Haematological recovery was reasonably quick in a majority of patients, and no cases of lack of or incomplete engraftment of bone marrow were observed. After 100 days after transplantation, the progression of the disease was the major death cause. Only one patient died due to haematological complications not associated with Hodgkin's disease, i.e. acute myeloblastic leukaemia. Three year overall survival was assessed at 56%, and disease free survival – at 42%. The factors negatively affecting prognosis were: primary and secondary resistance to chemotherapy, and LD histopathological type. Relapse of Hodgkin's disease was the most common reason for ineffective treatment.

Conclusions. High dose chemotherapy proved to be a very effective method in the treatment of Hodgkin's disease, considering the fact that it was impossible to achieve remission only in six cases. The high percentage of relapses observed, however, remains a challenge. Relapses of Hodgkin's disease occurred, in particular, in patients who were resistant to previous chemotherapy and in those resistant to intensified treatment preceding transplantation. The results in the first group were unfavourable to the extent that therapeutic indications for high dose chemotherapy were considered questionable.

Wysoko dawkowana chemioterapia w połączeniu z przeszczepianiem autologicznych komórek krwiotwórczych w leczeniu opornych i nawrotowych postaci ziarnicy złośliwej

Wstęp. Ziarnica złośliwa jest zazwyczaj chorobą o dobrym rokowaniu, nawet przy rozpoznaniu w okresie znacznego jej zaawansowania. Pierwotna oporność na chemioterapię oraz nawrót, szczególnie przed upływem roku od zakończenia leczenia, bardzo niekorzystnie wpływają na prognozowanie. Klasyczne leczenie jest w stanie doprowadzić do kolejnej remisji zaledwie około 29% pacjentów. W leczeniu pierwotnie opornej oraz nawrotowej ziarnicy złośliwej stosuje się w ostatnich latach wysoko dawkowaną chemioterapię, połączoną z przeszczepianiem autologicznych komórek krwiotwórczych.

Materiały i metody. Zaprezentowano efekty powyższego leczenia, przeprowadzonego u 40 chorych. Wskazaniami były: pierwotna oporność u 15, częściowa remisja u 2, wczesny, pierwszy nawrót u 5, późny nawrót u 2, drugi i następne nawroty

Department of Haematology, Institute of Medicine, Medical University of Gdańsk, Poland

u pozostałych 16 chorych. Komórki krwiotwórcze wykorzystywane do przeszczepu pochodziły wyłącznie z krwi obwodowej. Przeszczep poprzedzało zazwyczaj leczenie cytoredukcyjne, według schematu DexaBEAM. W chwili przeszczepu 15 chorych było w całkowitej remisji, 17 w częściowej, a u 8 miała miejsce progresja choroby. W kondycjonowaniu stosowano początkowo CBV, potem BEAM.

Wyniki. Spośród 40 chorych poddanych powyższemu leczeniu, u 32 doszło do remisji, 5 znalazło się w częściowej remisji, a w jednym przypadku doszło do progresji choroby. W większości wypadków regeneracja hematologiczna była stosunkowo szybka, nie obserwowano przypadków braku lub niepełnego wszczepienia się szpiku. Śmiertelność okołoprzeszczepowa wyniosła 5%. W okresie późniejszym niż w 100 dniu po przeszczepie w zdecydowanej większości przypadków przyczyną zgonu była progresja choroby. Z powodu powikłań hematologicznych, niezależnych od ziarnicy, zmarła tylko jedna osoba; doszło u niej do rozwinięcia się objawów ostrej białaczki szpikowej. Szacowane 3-letnie całkowite przeżycie wynosi 56%, bez objawów progresji choroby 42%. Czynnikami obciążającymi rokowanie okazały się: pierwotna oraz wtórna oporność na chemioterapię oraz typ histopatologiczny LD. Przyczyną niepowodzenia leczenia był zazwyczaj nawrót ziarnicy.

Wnioski. Wysoko dawkowana chemioterapia okazała się bardzo skuteczną metodą eliminacji nowotworu, tylko u 6 chorych nie uzyskano całkowitej remisji. Istotnym problemem pozostaje wysoki odsetek obserwowanych nawrotów. Miały one miejsce zazwyczaj u chorych, od samego początku wykazujących oporność, a także u niewrażliwych na intensyfikowaną chemioterapię, poprzedzającą przeszczep. Złe rezultaty uzyskane w pierwszej z wymienionych grup każą zastanowić się nad zasadnością stosowania tej metody leczenia.

Key words: resistant and recurrent Hodgkin's disease, high dose chemotherapy, autologous haematopoietic cell transplantation, CBV, BEAM

Słowa kluczowe: Pierwotnie oporna oraz nawrotowa ziarnica złośliwa, wysoko dawkowana chemioterapia, przeszczepianie autologicznych komórek krwiotwórczych, CBV, BEAM

Introduction

Hodgkin's disease is usually often characterised by favourable prognosis, and even in its advanced form, complete remission after chemotherapy was observed in 64--84% of the cases [1]. In a majority of cases remission leads to recovery. Relapse, in particular in the period prior to a year from achieving remission is, in turn, most negatively affected prognostically. Standard treatment led to secondary remission merely in 29% of the patients undergoing treatment [2]. The prognosis is yet more unfavourable in patients, who did not respond to chemotherapy. Long-term remission was observed in only 0-20% of the patients [3].

In the last decade, high dose chemotherapy combined with transplantation of haematopoietic cells has been employed in patients with unfavourable prognoses [4, 5]. Regardless of the high number of reports concerning the effectiveness of the procedures mentioned above, randomised studies, that would explicitly confirm their advantage over classical chemotherapy, were not conducted. Besides, it was not established which patients may take the most advantage of high dose chemotherapy. Hence the importance of retrospective analysis. In our work we have decided to present our own experience in the employment of high dose chemotherapy combined with transplantation of haematopoietic progenitor cells in patients suffering from resistant and recurrent Hodgkin's disease.

Materials and methods

40 patients with Hodgkin's disease underwent treatment employing autologous transplantation of progenitor cells between 1995-1999. The group consisted of 19 women and 21 men aged between 17 and 50 years (median 29). Among those qualified for treatment were 25 patients with a histopathologically diagnosed NS type, 11 with an MC type and four with an LD type. The therapeutic indications for transplantation were as follows: primary resistance in 15 patients; partial remission in two; early, primary relapse in five; late relapse in two; second and further relapses in the remaining 16 patients. Primary resistance was recognised as lack of complete remission after a minimum of two cycles of standard treatment. Early relapse was defined as such that occurred prior to one year from achieving remission. The first transplanted patient underwent conditioning immediately after completing second line treatment, the symptoms of active disease being evident. In the remaining patients, the autologous transplantation was preceded by cytoreductive chemotherapy according to the Dexa BEAM scheme in standard doses [6]. Generally two cycles of treatment were employed. If earlier remission was observed only one cycle was administered. In one case, due to the progression of the disease after Dexa BEAM treatment, DHAP was administered, but to no avail. At the time of transplantation complete remission was observed in 15 patients, partial remission in 17, and in eight cases the disease progressed. To verify remission computer tomography and other image examinations were used. In cases of controversial lesions in the mediastinum diagnosis included gallium scan.

Progenitor cells utilised in transplantation originated exclusively from peripheral blood. The mobilisation consisted of Dexa BEAM chemotherapy, followed by daily subcutaneous administration of rhG-CSF (Neupogen, Roche). G-CSF was administered in doses of 300 μg in patients, weighing under 60 kg and 480 μg in the remaining patients. Cells were collected after nadir on growth of leucocytosis to a level of above 6.0 G/l (from November 1998 – 10.0 G/l). Cytapheresis was conducted by the cell separator Fenwall CS3000 Plus. The products of cytapheresis were assessed basing on the number of mononuclear cells, CD34 positive cells and CFU-GM (granulocyte-monocyte colony forming units) cells in relation to patients weight. Cell collections were terminated on receipt of a number of CD34+ cells above 2.0×10^6/kg of the patients' b. w. In the conditioning regimen CBV was initially utilised (Cyclophosphamide 7200 mg/m^2, BCNU 450 mg/m^2, Etoposide 1600 mg/m^2). In patients, who

Tab. 1. Patients characteristics

Total number of patients	40
Age, years	29
Range	17- 50
Sex	
Female	19
Male	21
Histopatology	
NS	25
MC	11
LD	4
Indications for the transplant	
Primary resistance	15
Partial remission	2
Early relapse	5
Late relapse	2
Secon and further	16
Status at transplant	
Complete remission	15
Partial remission	17
Progressive disease	8

did not achieve remission during previous treatment Cisplatin (150 mg/m^2) was additionally introduced. From May 1997 the standard procedure for all patients was conditioning regimen according to the BEAM scheme (BCNU 300 mg/m^2, Etoposide 1200 mg/m^2, ARA-C 1600 mg/m^2, Melphalan 140 mg/m^2).

In the period following transplantation antibacterial (quinolone group), anti fungal (Fluconazole) and antiviral (Aciclovir up to day +30) prophylaxis was introduced. At a later time antibacterial prophylaxis was discontinued and Acyclovir administration was extended to day +100. Confronted with a high risk of hepatitis B infection, in spite of preventive vaccinations (60% transplanted patients were infected between 1995-1996), commencing from 1997 routine administration of anti-HBs serum (Hepatect) was introduced. Since then no new infection was noted. Haematopoietic growth factors were not routinely used. Seven patients who were in complete remission at the time of transplantation had Proleukin and Roferon administered immediately after achieving haematological recovery, in order to decrease the risk of relapse [7]. Due to the small size of this group and short observation time independent analysis of the group is not possible.

Statistical analysis concerned the following parameters: histopathological type, sex, presence of clinical symptoms, clinical progression of the disease at the time of transplantation, response to prior treatment, therapeutic indications to transplantation (resistance, early or late relapse) and the type of conditioning regimen (BEAM, CBV). Statistical analysis was conducted based on the Kaplan-Meier method, utilising the log-rank test. The STATISTICA 5.0 (StatSoft Inc.) programme was used.

Results

From among 40 patients who underwent autologous progenitor cell transplantation in 38 cases complete haematological recovery was achieved. Two patients died due to the toxicity of the procedure employed, namely, due to pneumonia and septic shock at the time of bone marrow aplasia. In the early post transplant period another death occurred due to rapid progression of the disease accompanied by prompt haematological recovery. In a great majority of patients reconstitution of haematopoiesis was quick and complete: leucocytosis of above 1.0 G/l was achieved on day +13 (range 7-26), neutrophils achieved a number of 0.5 G/l on day +14 (range 10-24), platelets reached a number of 50 G/l on day 16 (range 10-90) after progenitor cell infusion.

After transplantation no symptoms of active disease were observed in 32 patients, partial remission was noted in five cases and in one case progression of the disease was noticed. Regression of symptoms of the disease was achieved in 18 cases, the remaining 14 patients being in remission at the time of initiating preparative chemotherapy, the conducted transplantation constituting consolidation therapy. At a period later than 100 days after transplantation the progression of the disease was the cause of death in a majority of cases. Only one patient died due to haematological complications independent of Hodgkin's disease. This patient developed acute myelogenous leukaemia. Cytogenetic examination (7q-) showed that leukaemia could have been induced by earlier chemo- or radiotherapy. At the time of death the patient was in complete remission of Hodgkin's disease.

At present 28 of the 40 patients who underwent autologous progenitor cell transplantation are alive. At an average time of observation of 507+ days (range 14-1520) assessed three year survival in the examined group is 56% and three year disease free survival is 42%. The average time of relapse was 527 days, the latest one observed being on day 1097. In two patients relapse occurred later than two years after transplantation.

The most important factor for successful treatment was sensitivity to chemotherapy preceding transplantation. Patients in complete remission at the time of transplantation showed statistically significant favourable prognosis concerning overall survival (p=0.006) in comparison to those in whom progression of the disease was observed following preceding therapy. Similarly, favourable prognosis concerning disease free survival, was evident in patients with partial remission (p=0.020). No statistically significant prognostic factors were revealed between

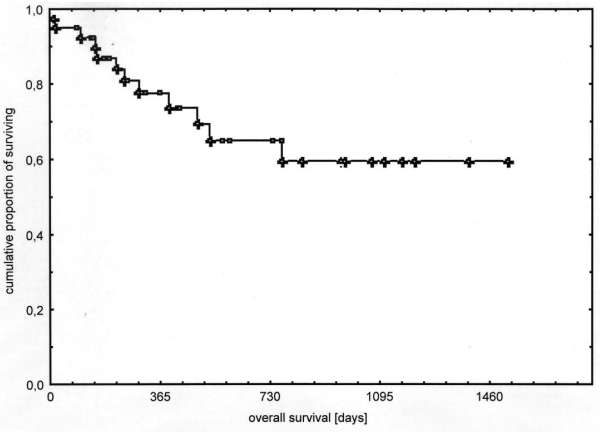

Fig. 1. Actuarial overall survival in 40 patients transplanted for Hodgkin's disease

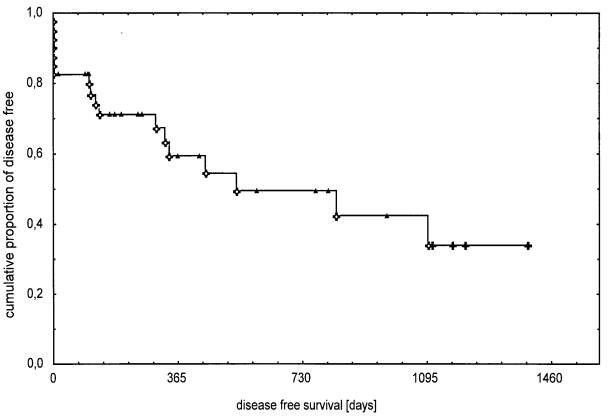

Fig. 2. Disease free survival of 40 transplanted patients (median 528 days)

patients in complete or partial remission at the time of transplantation.

As was already mentioned the therapeutic indications for high dose chemotherapy and progenitor cell transplantation were as follows: primary resistance to standard doses of chemotherapy, early relapse after standard therapy and further relapses of the disease. The group with the least favourable prognosis consisted of patients with primary resistance to chemotherapy. The risk of disease progression was significantly higher in that group than for those who underwent transplantation due to relapse (p=0.016). Assessed three – year survival was 39% and the longest survival with no progression of the disease was 536 days. The results of the therapy in patients treated for relapse were entirely different: three year overall survival was assessed at 71%, disease free survival being 64%. As indicated above histopathological diagnosis was also prognostically significant. Although only four patients with LD type were transplanted, their prognosis concerning survival was significantly worse than in the case of NS type (p=0.041). It was not confirmed that the employed conditioning regimen had any influence on the achieved results for the reason that late effects of the utilisation of the CBV scheme with or without Cisplatin did not differ significantly from those achieved by means of the BEAM scheme. No advantages resulting from increasing the dose of Etoposide were observed. From among five patients treated in this manner two died in the early post-transplant period and two others suffered from early relapse. The small size of the group does not however allow us to reach univocal conclusions.

Discussion

Chemotherapy combined with autologous progenitor cell transplantation has become a standard procedure in the treatment of resistant and recurrent Hodgkin's disease. In 1998 the European Group for Blood and Marrow Transplantation registered 1087 such procedures [8]. Transplantations from peripheral blood are preferred for the reason that a shorter time of haematological recovery is involved, entailing lower costs [9]. Moreover the risks associated with employing this procedure are lower than in the case of utilising progenitor cells from bone marrow [10]. Those are the reasons for introducing peripheral progenitor cell transplantations in our department. Only two treatment-related deaths have been registered, from among 40 patients who underwent transplantation. This result does not differ from those reported by other authors [11, 12]. In the majority of patients haematological recovery was reasonably quick and no cases of either lack of nor incomplete engraftment of bone marrow were observed.

High dose chemotherapy has proved to be a very effective method of eliminating tumours. Only one patient was completely and five partially resistant to this treatment. Unfortunately, the high percentage of relapses observed remains a major problem. The type of conditioning regimen is not a decisive risk factor for relapses. Attempts to increase the dose of Etoposide from 1200 to 1600 mg/kg of b.w. caused merely a noticeable increase of the toxicity of treatment. Relapses of Hodgkin's disease occurred particularly in patients who were resistant to chemotherapy and in those resistant to intensified treatment preceding transplantation. The results in the first of the mentioned groups were unfavourable to the extent that therapeutic indications for high dose chemotherapy were considered questionable. Reports from other works suggest that bone marrow transplantation should be utilised even though its advantage over standard chemotherapy is not great. The results of retrospective studies comparing survival of patients, registered in the data base of the French Society of Bone Marrow Transplantation (Society Franchise de Gruff de Moelle), who did not achieve remission, and treated by means of intensified or standard chemotherapy, revealed a tendency for increased survival among patients who underwent transplantation (the difference in six year survival at a level of significance α=0.58) [13]. Earlier, similar reports originating from Stanford indicated advantages only in relation to disease free survival [14]. The procedure presently adopted in order to improve the prognosis of this group of patients is to administer a maximally large dose of standard chemotherapy at the initial stage of treatment, to prevent the development of resistance. The presented results show the advantage of this procedure over standard chemotherapy [15].

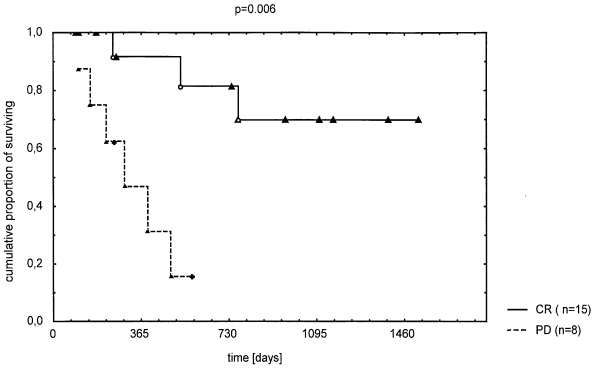

Fig. 3. Comparison of overall survival according to status at transplantation (complete remission versus progressive disease)

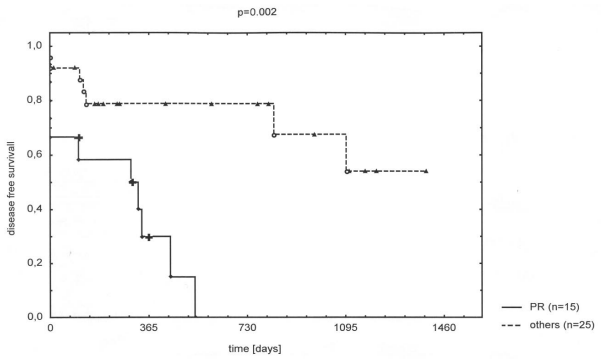

Fig. 4. Disease free survival after transplantation according to response to previous therapy (PR – primary resistant)

Sensitivity to chemotherapy remains an important prognostic factor also in the case of recurrent disease [16]. Unfavourable prognosis is associated with relapse occurring earlier than one year after terminating standard treatment and also in the case of successive relapses [17]. Those are simultaneously the basic therapeutic indications for autologous progenitor cell transplantation. The results of treatment of late relapse (over 12 months after achieving remission) are favourable. Utilising high dose chemotherapy in such instances is questionable [18].

On deciding to utilise high dose chemotherapy one must remember about potential complications related to the transplantation. According to the French Society of Bone Marrow Transplantation, quoted above, the risk of death in the case of toxicity of the transplantation is 8%, and the possibility of the occurrence of secondary neoplasia in the period of five years after transplantation is 8.9%. Compared to a group of patients treated by means of standard chemotherapy and selected according to risk factors, increased vulnerability to complications was not associated with the progression of the disease ($p=0.024$), including secondary solid tumours, with a similar risk of acute leukaemia or myelodysplastic syndrome, was demonstrated [19]. A characteristic karyotype suggests that the acute leukaemia one of our patients suffered from was associated with the therapy which the patient had undergone. According to one of the reports all the patients who developed acute leukaemia or myelodysplastic syndrome revealed the presence of cytogenetic anomalies already at the time of transplantation. Routine cytogenetic analysis and disqualification of patients showing cytogenetic aberrations from transplantation will prevent the occurrence of similar complications in the future [20].

The influence of histopathological type of Hodgkin's disease on the effects of transplantation is the observation that evoked most doubts. Similar observations have not been reported by other authors. Particular care should be taken considering the fact, that we are dealing with LD type, whose recognition requires increased insight of the pathomorphologist and the utilisation of monoclonal antibodies [21]. Most of our patients were diagnosed in regional clinics and were not supported by the analysis of immunophenotypes. For this reason we are unable to reach final conclusions concerning the influence of the histological type of Hodgkin's disease on successful transplantation.

Jarosław Czyż M.D. Ph.D.
Department of Haematology, Institute of Medicine,
Medical University of Gdańsk
Dębinki 7
80-211 Gdańsk, Poland

References

1. De Vita VT, Huber SM. Hodgkin's disease. *New Engl J Med* 1993; 328: 560-565.
2. Fisher RI, De Vita VT, Hubbard SM, et al. Prolonged disease free survival in Hodgkin's disease with MOPP reinduction after first relapse. *Ann Intern Med* 1979; 90: 761-63.
3. Horning SJ. Primary refractory Hodgkin's disease. *Ann Oncol* 1998; 9 Suppl 5: 97-101.
4. Kessinger A, Biermann PJ, Vose J, et al. High dose cyclophosphamide, carmustine and etoposide followed by autologous peripheral stem cell transplantation for patients with relapsed Hodgkin's disease. *Blood* 1991; 77: 2322-25.
5. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of BNLI randomised trial. *Lancet* 1993; 341: 1051--1054.
6. Pfreundschuh MG, Rueffer U, Lathan B, et al. Dexa-BEAM in patients with Hodgkin's disease refractory to multidrug chemotherapy regimens: a trial of German Hodgkin's Disease Study Group. *J Clin Oncol* 1994; 12: 580-586.
7. Nagler A, Ackerstain A, Or R, et al. Immunotherapy with recombinant human interleukin-2 and recombinant interferon α, in lymphoma patients post autologous marrow or stem cell transplantation. *Blood* 1997; 89: 3951-3959.
8. Gratwohl A, Bakdomero H. HSC Transplantation: 1998 activity report. *EBMT News* 1999; 9: 2-3.
9. Smith TJ, Hilln BE, Schmitz N, et al. Economic analysis of a randomised clinical trial to compare filigrastim mobilised peripheral blood progenitor cell transplantation and autologous bone marrow transplantation in patients with Hodgkin's and non Hodgkin's lymphoma. *J Clin Oncol* 1997; 15: 5-10.
10. Schmitz N, Linch DC, Dreger P, et al. Randomised trial of filigrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone marrow transplantation in lymphoma patients. *Lancet* 1996; 347: 353-359.
11. Horning S, Chao JN, Negrin RS, et al. High-dose therapy and autologous hematopoietic progenitor cell transplantation for recurrent or refractory Hodgkin's disease: analysis of the Stanford University results and prognostic indices. *Blood* 1997; 89: 801-813.
12. Nademanee A, O'Donnell MR, Snyder DS, et al. High-dose chemotherapy with or without total body irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed or refractory Hodgkin's disease: results in 85 patients with analysis of prognostic factors. *Blood* 1995; 85: 1381-1390.
13. Andre M, Henry-Amar H, Pico JL, et al. Comparison of high-dose therapy and autologous stem-cell transplantation with conventional therapy for Hodgkin's disease induction failure: a case control study. *J Clin Oncol* 1999; 17: 222-229.
14. Yuen AR, Rosenberg SA, Hoppe RT, et al. Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent and refractory Hodgkin's disease *Blood* 1997; 89: 814-822.
15. Sieber M, Ruffer U, Jostin A, Diehl V. Treatment oh Hodgkin's disease: current strategies of the German Hodgkin's Lymphoma Study Group. *Annals Oncol* 1999; 10: 12.
16. Jonest RJ, Piantadosi S, Mann RB, et al. High-dose cytotoxic therapy and bone marrow transplantation for relapsed Hodgkin's disease. *J Clin Oncol* 1990; 8: 527-537.
17. Lohri A, Barnett M, Fairey RN, et al. Outcome of treatment of first relapse of Hodgkin's disease after primary chemotherapy: identification of

risk factors from British Columbia experience 1970-1988. *Blood* 1991; 77: 2292-2298.
18. Czyż J. Próba ustalenia wskazań do leczenia ziarnicy złośliwej przy pomocy chemioterapii w wysokich dawkach połączonej z przeszczepieniem szpiku. *Nowotwory* 1997; 47: 797-802.
19. Andre M, Henry-Amar M, Blaise D, et al. Treatment-related deaths and second cancer risk after autologous transplantation for Hodgkin's disease. *Blood* 1998; 92: 1933-1940.
20. Chao NJ, Nademanee AP, Long GD et al. Importance of bone marrow cytogenetic evaluation before autologous bone marrow transplantation for Hodgkin's disease. *J Clin Oncol* 1991; 9: 1575-1579.
21. Stein H, Mason D, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood* 1985; 66: 848-858.

Paper received: 6 April 2000
Accepted: 6 November 2000