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Autologous peripheral blood stem cell transplantation in patients with multiple myeloma — one single-centre experience

Autologiczne przeszczepianie obwodowych komórek macierzystych szpiku u chorych na szpiczaka plazmocytowego

INTRODUCTION

Multiple myeloma (MM) is a neoplasm characterised by the proliferation of malignant plasma cells in the bone marrow, producing a monoclonal immunoglobulin. This disease is associated with osteolytic lesions, hypercalcemia, anemia and renal failure. The standard treatment is the combination of melphalan and prednison (MP), which induces an objective response in 60% of patients, usually lasted 2 years and followed by a relaps [1]. Combination chemotherapy (e.g. VCMBP: vincristine, cyclophosphamide, melphalan, BCNU, prednisone) produces the response rates significantly higher than MP regimen, however there is no significant difference in overall survival [5]. In patients with refractory disease the highest response has been reported with VAD (vincristine, doxorubicin, dexamethasone) and medium-dose of melphalan (50 mg/m^2) [4]. Recently, high-dose chemotherapy with autologous or allogeneic hematopoietic stem cell support has been introduced. Autologous peripheral blood stem cell transplantation (APBSCT) is applicable to more patients because the age limit is higher (65 years and even more) and a matched donor is unnecessary [16]. Despite of this allogeneic transplantation is associated with high transplant-related mortality (20–40%) [6].

PATIENTS AND METHODS

Patients selection

Between November 1997 and September 2000, 22 patients received APBSCT at The Haematology Department, University Medical School in Lublin. Thirteen patients were males and nine females; median age at transplantation was 47.6 (range, 39–65). At diagnosis, 9 patients were in stage II and 13 in stage III, according Durie-Salmon Staging System. The monoclonal component was IgG in 19 patients, IgA in 2 patients and both IgG and IgA in 1 patient.

Induction therapy

The therapy plan is presented in Figure 1. Fifteen patients were after one line chemotherapy (2–6 courses of VAD regimen), seven after two or more lines (MP, VMBCP, VAD, thalidomide). Before mobilisation procedure 14 patients were in complete remission (CR: 1) 5% or fewer plasma cells of normal morphology on bone marrow aspiration, 2) no measurable paraprotein in serum), 8 patients in partial remission remission (PR: 50% decrease in measurable paraprotein or bone marrow infiltrafion).

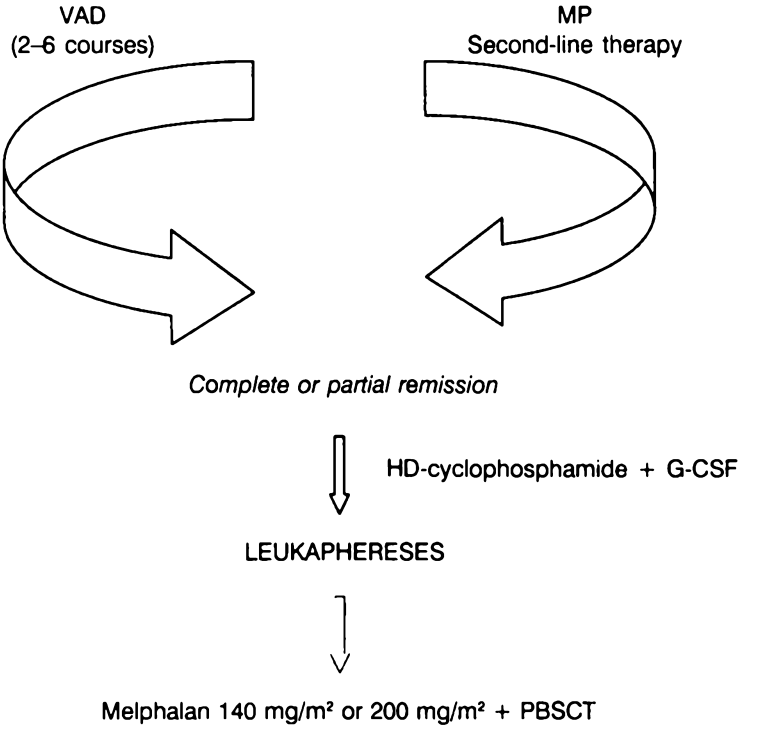

Figure 1. The plan of autologous peripheral blood stem cell transplantation management of patients with multiple myeloma

Mobilisation procedure

All patients were treated with cyclophosphamide at 4 g/m^2 followed by recombinant human G-CSF (Neupogen, Roche) given at a dose 10 μg/kg as a single or twice daily subcutaneous or intravenous injection, from day 6 of start of chemotherapy until the end of leukaphereses. Peripheral stem cells were collected with Haemonetic MCS3p (Haemonetics) continuous flow cell separator when minimal count of CD34 positive cells were above 20 x 10^9 /l. Stem cells were stored with dimethylsulphoxide (DMSO) at –180°C in the vapour phase of liquid nitrogen without rate controlled freezing.

Treatment regimen

The conditioning regimen was melphalan 200 mg/m^2 (12 patients) or 140 mg/m^2 (10 patients) given 48 h prior to cell infusion. The mean number of CD34 positive cells reinfused was: 3.46 x 10^6/kg (range, 1.15–6.15). G-CSF at a dose 5–10 μg/kg daily was administered following transplantation until neutrophil count reached 0.5 x 10^9 /l. After stable engraftment patients were receiving maintenance therapy with interferon alpha or thalidomide.

RESULTS

Toxicity during autograft

All patients had neutropenia in grade IV according to WHO grading. Median number of days for neutrophil recovery to more than 0.5 x 10^9 /l was 13 (range, 10–17). The median number of days to recovery of platelets to more than 50.0 x 10^9 /l was 21 (range, 12–35). None of the patients developed serious sepsis. Eight of the patients had grade II and two grade III–IV mucositis.

Supportive treatment

G-CSF (5–10 μg/kg daily) was administered for 13.6 days (range, 8–20). Red cells and platelet cells were transfused 2.4 units and 14.2 units per one patient, respectively.

Response

Until now 21 patients are alive (95.4%); 15 patients remain in CR (68.2%), 5 patients in PR (22.7%). Two patients (9%) relapsed 6 and 16 months after APBSCT. The first of them died 9 months after transplantation.

DISCUSSION

APBSCT has currently become the most common therapy for younger patients with multiple myeloma. Many randomised trials have shown a superiority of this method comparing to conventional chemotherapy. In French Myeloma Study Group experience the rate of response (81% vs. 57%) and complete remission (22% vs. 5%) was superior in the transplant group. A higher rate of five-year event-free survival (EFS: 28% vs. 10%) and overall survival (OS: 52% vs. 12%) occurred also in the trans-

plant group [11]. The Nordic Myeloma Study Group results were as follows: with a median follow-up of 32 months, the intensive therapy group was superior to the conventional therapy group regarding response rate (77% vs. 55%), EFS (3-year probability 40% vs. 16%) and OS (3-year probability 71% vs. 55%) [12]. APBSCT is applicable for more patients than autologous bone marrow transplantation because engraftment is more rapid and there is a less contamination of myeloma cells in the graft. Next advantage of APBSCT is relatively high safety. Mortality is only 1% if patients are appropriately selected [11]. In our group there is no any mortal case. In the IFM 90 trial, the 6-year EFS is only 25% in the autologous transplantation arm and there is no plateau of survival curves [8]. Similar results (EFS at 8 years after transplantation 20%) was published by EBMT registry [3]. Our observations are too short to draw conclusions concerning EFS, but basing on the above cited data there is no doubt that APBSCT prolongs significantly OS in these patients. Strategies to improve the results of APBSCT are different. Selection of CD34-positive cells, similarly like tandem transplantation and total body irradiation in the preparative regimen did not improve event-free and overall survival [7]. It has been suggested that better results could be obtained with the consolidation intensive chemotherapy (2–3 courses) given after the autologous transplantation [14]. Minimal residual disease may be eliminated also by biological methods: monoclonal antibody (Rituxan) [13, interferon alpha, gamma [2], idiotypic and DNA vaccines [10, 17], dendritic cells [15], and thalidomide [9]. The studies with this last drug are currently going on in our Depatment. The pilot results are very promising.

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STRESZCZENIE

Przeszczepianie obwodowych komórek macierzystych szpiku (APBSCT) jest obecnie najbardziej powszechnym sposobem leczenia młodych chorych na szpiczaka plazmocytowego (sz.p.). W Klinice Hematologii Akademii Medycznej w Lublinie w okresie od listopada 1997 r. do września 2000 r. metodą tą leczonych było 22 chorych na sz.p. (9 kobiet i 13 mężczyzn; średnia wieku 47,6 lat). Piętnastu chorych otrzymało uprzednio jedną linię chemioterapii (2–6 VAD), siedmiu było po 2 lub więcej liniach. Przed rozpoczęciem mobilizacji 16 chorych miało całkowitą remisję (CR), a 8 częściową (PR). Komórki macierzyste były zbierane po zastosowaniu cyklofosfamidu w dawce 4 g/m^2 i G-CSF, podawanego w dawce 10 ug/kg/dobę. Schemat kondycjonujący polegał na zastosowaniu melfalanu w dawce 200 mg/m^2 (12 chorych) lub 140 mg/m^2 (10 chorych). Liczba przeszczepianych komórek CD34-dodatnich wyniosła średnio 3,46 x 10^6/kg. Średni czas trwania neutropenii (< 0,5 x 10^9/l) i trombocytopenii (< 50,0 x 10^9/kg) wyniósł odpowiednio 13 i 21 dni. Do chwili obecnej 21 chorych żyje (95,4%); 15 pozostaje w CR (68,2%), 5 w PR (22,7%). U dwóch chorych (9%) wystąpił nawrót w czasie 6 i 16 miesięcy po APBSCT. Pierwszy z nich zmarł w czasie 9 miesięcy po transplantacji. Obecnie prowadzone są badania nad leczeniem podtrzymującym (interferon alfa, talidomid).