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The Value of Ifosfamide in the Treatment of Multiple Myeloma

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Key Words
Multiple myeloma · Alkylators · Ifosfamid · Peripheral blood progenitor cells · Mobilisation

Summary
Primary high-dose therapy with autologous peripheral blood progenitor cell (PBPC) reinfusion for advanced multiple myeloma (MM) appears superior to classic conventional chemotherapy with alkylators and corticosteroids. Long-term conventional therapy with the standard alkylating agent melphalan critically reduces the PBPC pool. Moreover, cases of highly proliferative MM respond less readily to melphalan than to a combination of other alkylating agents. Oxazaphosphorines like ifosfamide (IFO), either as single agent or in combination with other drugs show satisfactory response rates without jeopardising the PBPC reserve. IFO-containing combinations as primary induction treatment show reliable PBPC mobilising potency (median 6.1×10^6 CD34 positive PBPC in a median of 2.5 leucapheresis). leucocytes Combination with epirubicin and dexamethasone leads to response rates equivalent to infusional protocols (67.2% CR and PR according to MRC criteria; median paraprotein reduction to 27% of the initial value) even in melphalan-pretreated patients. The tubulotoxic effect of IFO in patients with compromised renal function is rare and reversible, allowing the use of this agent in 66 out of 69 patients eligible for autologous transplant in our series. Apart from this, IFO at doses up to and beyond 6 g/m^2 appears to be an effective and nontoxic component of induction PBPC mobilising treatment in MM.

Schlüsselwörter
Multiples Myelom · Alkylantien · Ifosfamide · Periphere Blut-Progenitor-Zellen · Mobilisation

Zusammenfassung
Bei der Primärtherapie des fortgeschrittenen multiplen Myeloms (MM) zeigen z. T. randomisierte Studien die Überlegenheit der Hochdosistherapie mit autologer Blutprogenitorzell (PBPC)-Reinfusion gegenüber der klassischen konventionellen Chemotherapie mit Alkylantien und Corticosteroiden. Eine langfristige konventionelle Chemotherapie mit dem standardmäßig eingesetzten Alkylans Melphalan schränkt die Reserve an mobilisierbaren PBPC ein. Außerdem ist die Wirksamkeit von Melphalan bei Myelomen mit hoher Proliferationsrate eingeschränkt. Hier zeigen höher dosierte Oxazaphosphorinderivate wie Ifosfamid (IFO) als Monotherapie oder in der Kombination mit anderen Substanzen befriedigende Ansprechraten ohne Beeinträchtigung der PBPC-Reserve. IFO-haltige Kombinationen als Induktionsprotokoll zeigen eine zuverlässige PBPC-mobilisierende Potenz (Median $6{,}1\times10^6$ CD34-positive Progenitoren in median 2,5 Leukapheresen); bei Kombination mit Epirubicin und Dexamethason läßt sich eine Ansprechrate (67,2% CR und PR nach MRC-Kriterien; mediane Paraproteinreduktion auf 27% des Ausgangswertes) erreichen, die mit jener von Dauerinfusionsprotokollen vergleichbar ist, selbst bei Melphalan-vorbehandelten Patienten. Die tubulotoxische Wirkung von IFO bei Patienten mit eingeschränkter Nierenfunktion ist selten und reversibel, so daß in unserer Serie IFO bei 66 von 69 für eine Tandem-Hochdosistherapie qualifizierenden Patienten eingesetzt werden konnte. Abgesehen hiervon erwies sich der Einsatz von IFO bei Dosen um 6 g/m^2 und darüber als wirksame und wenig toxische Komponente der Induktions- und Mobilisationstherapie beim MM.

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Introduction

Alkylating agents at low to moderate doses are the cornerstone of conventional cytotoxic treatment for multiple myeloma (MM). Melphalan combined with corticosteroids shows an objective response rate of 50–60% and clinical benefit (pain relief and stabilisation of paraprotein levels) in a further 15–20% [1]. Retreatment upon progression is often successful. This simple strategy forms the standard initial care for patients with an indolent evolution or beyond 65 years of age, as survival with melphalan is equivalent to more intensive combination or infusional treatment schedules except in younger patients with a more aggressive course of the disease [2]. Nevertheless, treatment outcome is unsatisfactory, with resistance to melphalan evolving between two and three years after the start of systemic treatment, and a 5-year survival rate around 20% [3]. Complications associated with progressive myeloma are the primary cause of death [4]. High-dose melphalan and later myeloablative approaches with autologous haematopoietic support have long been introduced into the treatment of MM. A significant survival benefit for patients undergoing high-dose therapy has now been defined through randomised and case-control studies [5, 6], although this effect has been attributed exclusively to patient selection by other authors [2]. Therefore, single or tandem autologous transplant supported by peripheral-blood progenitor cells (PBPC) has become the treatment of choice for patients younger than 65 years at many haematologic institutions. PBPC procurement is critical especially in patients scheduled for tandem procedures or ex vivo processing. In an ongoing study evaluating the role of selection of CD34-positive PBPC, we have investigated the response rate, mobilising efficiency and toxicity of a regimen combining a moderate dose of IFO with dexamethasone and epirubicin as induction and PBPC mobilising treatment for patients with no or little pretreatment with standard chemotherapy.

Materials and Methods

13 academic haematology/oncology departments in Germany and Austria recruited 69 patients after informed consent up to Sep. 15, 1997 in an ongoing prospective randomised study evaluating the role of CD34-positive cell selection for autologous support of tandem high-dose therapy for MM. Participation in the study required prior approval by the institution's ethical committee. Induction treatment (DIME) consisted of epirubicin 80 mg/m^2 day 1 i.v., IFO 3,000 mg/m^2 days 1+2 c.i.v., dexamethasone 24 mg p.o. days 1–4 and days 10–13. Cycles were repeated at 3 week intervals. Uroprotection with mesna was administered previous to, during and 8 hours after the IFO infusion, with 20 , 60 and 20% of the daily IFO dose, respectively. In case of nephrotoxicity, ifosfamide was scheduled to be changed to cyclophosphamide 1,200 mg/m^2 days 1+2, but patients were no longer evaluable for response to DIME. All drugs were administered via peripheral venous access. Patients were discharged after the end of infusion, unless indicated otherwise due to concomitant medical problems. No haematopoietic growth factors for abbreviation of leucocyte nadirs nor prophylactic antibiotics were prescribed. Complete blood counts were evaluated after 7, 10 and 15 days to monitor haematopoietic regeneration. In patients with an objective response or stable disease after two cycles as shown by evaluation of clinically relevant lesions and serum/urinary paraprotein levels, PBPC mobilisation was initiated after the third cycle of DIME with filgrastim 5 mg/kg b.w. once daily s.c. starting 24 h after the end of IFO infusion until completion of leucaphereses. PBPC harvesting was carried out in the phase of leucocyte recovery (WBC > 1 G/l and CD34-positive cell counts > 10/ml). Apheresis was stopped after collecting > 8×10^6 CD34-positive cells or if, after 3 leucaphereses, the CD34-positive cell counts had declined to levels < 10/ml. In case of unsatisfactory harvesting, a 4th course was scheduled supported by filgrastim at 10 mg/kg b.w. once daily s.c. In case of progression, mobilising treatment was changed to cyclophosphamide 6 g/m^2 given i.v. over two days, complemented by filgrastim at 5 mg/kg b.w. once daily subkutameously. In patients randomised to immunoselection of CD34-positive cells, this was performed with the Ceprate® SC immunoadsorption device (CellPro, Brussels, Belgium). Myeloablative conditioning followed the original Little Rock tandem high-dose protocol [8]. A minimum of 2×10^6 CD34-positive cells was reinfused at least 24 h after the end of melphalan infusion.

Results

Patients' demographic status, paraprotein subtype, disease stage and pretreatment were as shown in table 1.

Toxic effects: There were no acute complications during treatment administration. 3 patients experienced a transitory rise in serum creatinine up to 2.34.0 mg/dl 3 to 7 days after the 1st course, obviating further treatment with this regimen, as reexposure to an experimental treatment was judged inappropriate by the investigators. All but one patient normalised their serum creatinine within 8 weeks. There were five cases of febrile neutropenia, three after the 1st course and two after the second. All resolved promptly with admission to hospital and administration of i.v. antibiotics. One patient developed pneumonia while in prolonged leucopenia after the first course; she had her 2nd cycle postponed for 10 days and recovered uneventfully, but progressed before the third course. Other toxicities were not seen.

Response (table 2): Among 64 patients who received > 1 cycle of DIME and were evaluable for paraprotein reduction,

Table 1. Patient characteristics

Male/female	38/31
Age (years; median / range)	54.5/28–62
Paraprotein subtypes (n)	
IgG	36
IgA	17
IgD	2
IgM	1
Light chain (LC)	11
Non-secretory	2
Stage I	2
Stage II	17
Stage III	50
A (no impairment of renal function)	51
B (serum creatinine > 2 mg/dl)	18
Labeling index (%; median/range)	2.6/1.2–7.9
Time from diagnosis to treatment (months; median/range)	3.5/2–17
Pretreatment	
Melphalan < 5 cycles	8
Other alkylators	2
VAD or related infusional protocols	5
Major radiation (>66% of thoracic / lumbar spine and pelvis)	9

Table 2. Response according to paraprotein subtype

Ig subtype	IgG	IgA	IgM	IgD	light chain
CR	1	–	–	–	–
VGPR	1	–	1	–	1
PR	21	8	–	2	6
MR	5	5	–	–	3
NC	3	1	–	–	2
PD	2	1	–	–	–

Abbreviations: see text; MR: minor response (>25% <50% reduction);
NC: no change (<25% decrease or increase in paraprotein);
PD: progressive disease.

there were 43 objective responses, including 4 patients with complete (CR = paraprotein on normal cellulose acetate electrophoresis no longer recognisable and no Bence-Jones proteinuria) or very good partial remission (VGPR; >90% paraprotein reduction) and 39 partial remissions (PR; >50% reduction). Median serum paraprotein (IgG: 63.7 g/l; IgA: 46.2 g/l; LC: 4.8 g/24 h) declined to 27% of the original level (IgG: 12.8 g/l; IgA: 14.0 g/l; LC: 0.9 g/24 h).

There was no evident difference in rates of objective remission between chemotherapy-pretreated and non-pretreated patients (overall response rate in 19 pretreated patients: 63.2%; chemonaive, 45 patients: 68.9%).

Mobilising efficiency: PBPC mobilisation after a single cycle of DIME followed by standard dose of filgrastim led to collection of a median of 6.1×10^6 CD34-positive cells (range, 1.6 to 86.4) / kg b.w. in a median of 2.5 aphereses. Peak mobilisation occurred at day 12 post start of chemotherapy. 2 patients required one further cycle to complete PBPC collection for tandem high-dose therapy. In 3, scheduled immunoselection of CD34-positive cells could not be performed for fear of excessive cell loss.

Discussion

High response rate, preservation of the haematopoietic reserve and efficient mobilisation of PBPC are the primary goals of induction treatment schedules preparing for myeloablative strategies. Cyclophosphamide, IFO, etoposide and cytarabine have traditionally been incorporated into mobilising treatment protocols to meet this purpose. These substances can be escalated to doses mobilising high numbers of PBPC without resulting in prohibitive non-haematopoietic toxicity. Due to extent of pretreatment, bone marrow infiltration and other mechanisms awaiting elucidation, PBPC yield is less efficient in MM than in diseases such as breast cancer or non-Hodgkin's lymphoma [7]. Escalation of mobilising cytotoxic drugs therefore appears especially relevant in this disease. Both the oxazaphosphorines and etoposide have been successsfully employed within combination treatment for younger patients with aggressive or relapsing disease [8–9]. High-dose IFO combined with etoposide and/or anthracyclines followed by G-CSF shows a shorter time to granulocyte recovery and comparable mobilising efficiency than reported for high-dose cyclophosphamide in patients with non-Hodgkin's lymphoma. It appeared logical to adapt these schedules to the induction treatment of patients with MM.

We have seen satisfactory responses and PBPC mobilising effects at no expense regarding toxicity in recently diagnosed patients with multiple myeloma even in a multicentric setting. A central venous line was not necessary for treatment administration, and response rates remained comparable to VAD. Mobilising efficiency was not significantly inferior to that reported with high-dose cyclophosphamide [10]. Further escalation of ifosfamide and/or epirubicin could lead to more efficient translocation of haematopietic progenitors into peripheral blood. A minority of patients experienced some degree of transitory elevation of serum creatinine levels. Change of ifosfamide to cyclophosphamide proved to be a viable alternative. The use of this regimen can therefore be regarded as a safe and effective induction treatment in patients with multiple myeloma heading for autologous transplantation.

References

1 Alexanian R, Dimopoulos M: The treatment of multiple myeloma. N Engl J Med 1994;330:484–489.

2 Bladé J, Kyle RA, Greipp PR: Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. Br J Haematol 1996; 93:345–351.

3 Gregory WM, Richards MA, Malpas JS: Combination chemotherapy versus melphalan and prednisone in the treatment of multiple myeloma: An overview of published trials. J Clin Oncol 1992;10:334–343.

4 Kyle RA: Multiple myeloma: review of 869 cases. Mayo Clin Proc 1975;50:29–40

5 Barlogie B, Jagannath S, Vesole DH, Tricot G: Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood 1997;789–793.

6 Attal M, Harousseau JL, Stoppa AM (IFM): Autologous bone marrow transplantation versus conventional chemotherapy in multiple myeloma: A prospective, randomized trial. N Engl J Med 1996;335: 91–97.

7 Engelhardt M, Winkler J, Waller C, Lange W, Mertelsmann R, Henschler R: Blood progenitor cell (BPC) mobilization studied in multiple myeloma, solid tumor and non-Hodgkin's lymphoma patients after combination chemotherapy and G-CSF. Bone Marrow Transplant 1997;19:529–537.

8 Malhotra H, Dhabhar BN, Saikia TK, Gopal R, Nadkarni KS, Nair CN, Advani SH: Ifosfamide in plasma cell leukemia: A report of two cases and review of the literature. Am J Hematol 1992;40: 226–228.

9 Ikeda K, Abe N, Morioka A, Inoo M, Nagai M, Kubota Y, Irino S: Etoposide and ifosfamide for MP (melphalan and prednisolone)- and VAD (vincristine, adriamycin and dexamethasone)-resistant plasma cell myeloma: A case report. Jpn J Med 1990;29:516–518.

10 Golschmidt H, Hegenbart U, Moos M, Eugenhart R, Wannenmacher M, Haas R, Hunstein W: Sequential high-dose treatment with peripheral blood progenitor transplantation in patients with multiple myeloma. Stem Cells 1995;13(suppl 3):36–41.