Monoclonal Gammopathies

The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy

We performed a dose-escalation study of bendamustine in 31 patients with multiple myeloma that had progressed after high-dose chemotherapy. Bendamustine 100 mg/m² on days 1 and 2 per cycle was found to be the maximal tolerated dose. The overall response rate was 55% with a median progression-free survival of 26 (0 – 61) weeks. Toxicity was mild and mainly hematologic.

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Autologous stem cell transplantation (ASCT) following high-dose melphalan has proven superior to standard treatment in patients with multiple myeloma up to the age of 70.[1,2] Since most patients relapse within only a few years from transplantation, the need for salvage therapies increases steadily.

We conducted a dose-escalation trial on bendamustine, a bifunctional alkylating agent, in patients up to 70 years old with progressive disease after ASCT. The objectives were to determine the maximal tolerated dose of bendamustine after high-dose chemotherapy and to assess response rates and duration. The initial dose of bendamustine was 60 mg/m², being half the approved dose, and was escalated in 10 mg/m² steps up to 100 mg/m². Bendamustine was given on days 1 and 2 of each 28-day cycle. After treatment of 4 to 6 patients with at least two cycles each, the dose was increased unless dose-limiting toxicity (DLT) occurred: absolute neutrophil count (ANC) $<0.5\times10^9$/L for 7 days; ANC $<0.1\times10^9$/L for 3 days; febrile neutropenia; platelet count $<25\times10^9$/L; non-hematologic toxicity ≥ grade 3 according to NCI-CTC. Less than two of six patients had to experience DLT for the maximum tolerated dose to have been reached. Response was assessed according to modified Blade criteria. Thirty-one patients (19 men, 12 women) with a median age of 58 (42–69) years were enrolled. Twelve subjects had received single, 13 tandem high-dose melphalan and an additional 6 patients total marrow irradiation, busulfan and cyclophosphamide.[3] The median event-free survival from ASCT to relapse was 42.5 (4–84) months. At relapse, 16 patients had elevated β2-microglobulin, 12 anemia, 6 elevated lactate dehydrogenase, and 4 elevated serum creatinine. Twenty-four patients presented with isolated increases of serum and/or urine monoclonal component (MC) while 16 subjects had increasing MC, bone marrow infiltration and – mostly bone-related – symptoms. Only one patient had isolated plasmacytoma (Table 1).

Five patients received bendamustine 60 mg/m², two of whom achieved partial remissions (PR) for 13 and 15 months and an additional two minor remissions (MR) for 5 and 11 months. Only four of eight patients in the 70 mg/m² group received at least two cycles of therapy, however without response. Three of the six patients in the 80 mg/m² group had MR for four (n=1) and eight months (n=2). Six patients received 90 mg/m², three of whom achieved PR for 7, 8 and 9 months each and one patient had a complete response (CR) for 6 months. Two

Table 1. Patients' characteristics.

Patients (n)	31
Median age (years)	58
Range	42–69
Male/female (n)	19/12
Diagnosis (n)	
IgG-/IgA-/IgD-myeloma	24
Bence Jones myeloma	6
Non-secretory myeloma	1
Previous treatment (n)	
Single autologous transplantation	
High-dose melphalan	12
Total marrow irradiation, busulfan, cyclophosphamide	6
Double autologous transplantation	
Tandem high-dose melphalan	13
α-interferon following ASCT (n)	
< 6 months	4
> 6 months	8
Median EFS after high-dose therapy (mo)	42.5
Range	4–84
Interval last transplant to salvage treatment	
< 1 year (n)	6
> 1 year (n)	25
Laboratory findings at relapse (n)	
β2-microglobulin > 2.5 mg/L	16
Hemoglobin < 10.0 g/dL	12
Lactate dehydrogenase > 230 U/L	6
Serum creatinine > ULN	4
Hypercalcemia	0
Relapse pattern (n)	
Increase of MC + BM-infiltration + other myeloma symptoms	16
Isolated increase of MC in serum + urine without symptoms	24
Isolated soft tissue plasmacytoma	1

ASCT: autologous stem cell transplantation; EFS: event-free survival; ULN: upper limit of normal; MC: monoclonal component; BM: bone marrow.

of the six subjects in the 100 mg/m² group achieved MR for 7 and 13+ months, two patients PR for 7+ and 10 months and one patient CR for 6 months. Seventeen patients responded for an overall response rate (ORR; MR, PR and CR) of 55%. The median progression-free survival for the whole study population was 26 (0–61) weeks and for the patients receiving 90 or 100 mg/m² it was 36 (0–56+) weeks. Grade 2 infection occurred in two patients. Dose-limiting toxicity, i.e. febrile neutropenia, developed in one patient after bendamustine 100 mg/m². Grade 2 nausea and emesis occurred in three while neurotoxicity did not occur in any patient.

Salvage therapy is becoming increasingly important in the treatment of multiple myeloma since relapse is common even with tandem autotransplantation.[4] In our dose-finding study on bendamustine, hematotoxicity was mild in all patients except one with a median ANC nadir of 3.8 (0.3-8.0)$\times10^9$/L and a median platelet nadir of 117 (78-351)$\times10^9$/L. Due to a DLT in the bendamustine 100 mg/m² cohort, this dose was found to be the maximum tolerated dose. An ORR of 55% was observed with a

median duration of response of 8 (4-15) months. Outcome was favorable in the cohorts receiving the two highest dose levels. At present, the significance of chromosomal aberrations (del 13) in bendamustine treatment is not clear due to the low number of assessable subjects. Of the several agents administered to heavily pretreated patients, thalidomide has been studied most extensively with documented response rates in patients after ASCT ranging from 43 to 78%.[5,6] However, thalidomide as well as bortezomib and arsenic trioxide have been associated with severe and sometimes disabling neurotoxicity and thalidomide also with thromboembolic complications.[7-9] We conclude that bendamustine 100 mg/m^2 is associated with considerable response rates and can be safely administered to patients with first or even subsequent relapse of multiple myeloma after high dose therapy. The drug has a unique mechanism of cytotoxicity by down-regulating PLK-1 (Polo-like kinase 1) and AurkA (Aurora A kinase) avoiding cross-resistance with other alkylating agents.[10] This may, at least in part, explain its activity in myeloma even after melphalan treatment has failed.

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References

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996; 335:91-7.
2. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348:1875-83.
3. Einsele H, Bamberg M, Budach W, Schmidberger H, Hess CF, Wormann B, et al. A new conditioning regimen involving total marrow irradiation, busulfan and cyclophosphamide followed by autologous PBSCT in patients with advanced multiple myeloma. Bone Marrow Transplant 2003;32:593-9.
4. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. InterGroupe Francophone du Myelome. N Engl J Med 2003;349:2495-502.
5. Fenk R, Hoyer B, Steidl U, Kondakci M, Graef T, Heuk R, et al. Single-agent thalidomide for treatment of first relapse following high-dose chemotherapy in patients with multiple myeloma. Leukemia 2005;19:156-9.
6. Richardson P, Schlossman R, Jagannath S, Alsina M, Desikan R, Blood E, et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. Mayo Clin Proc 2004;79:875-82.
7. Kropff MH, Lang N, Bisping G, Domine N, Innig G, Hentrich M, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. Br J Haematol 2003;122:607-16.
8. Rousselot P, Larghero J, Arnulf B, Poupon J, Royer B, Tibi A, et al. A clinical and pharmacological study of arsenic trioxide in advanced multiple myeloma patients. Leukemia 2004;18: 1518-21.
9. Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 2004; 127:165-72.
10. Leoni ML, Niemeyer C, Bendall LH, Reifert J, Bailey B. SDX-105 (Treanda™), Active in non-Hodgkin's lymphoma cells, induces the mitotic catastrophe death pathway. Blood 2004; 104;4593a[abstract].