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CURRENT THERAPEUTIC OPTIONS FOR MULTIPLE MYELOMA

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For the past 25 years intermittent melphalan/prednisone has been widely used in the treatment of multiple myeloma. Several drug combinations have improved the management of refractory disease. More recently, the myeloablative approach has shown promising results.[1-5] The availability of different chemotherapeutic options requires particular attention to treatment strategies applied to specific disease phases and patient conditions, as well as emphasis on clinical trials promising substantial future gain.

Standard primary chemotherapy

A meta-analysis was performed on 18 published trials that contained 3814 patients whose initial treatment was randomized for either melphalan/prednisone or various combination chemotherapeutic regimens.[6] This analysis showed that melphalan/prednisone was superior in patients with a good prognosis and inferior in those with a poor prognosis.[6] New therapeutic approaches should be primarily administered to patients with poor prognosis.

More recently, high-dose glucocorticoid-based regimens have been developed.[7,8] Dexamethasone alone was as effective as VAD, its response rate being only 15% lower than VAD.[8] For melphalan/prednisone, survival was positively correlated to the dose of corticosteroids but not to the dose of melphalan.[9] Increasing the dose intensity of corticosteroids is the main stream method of improving the effect of combination chemotherapy.

In some randomized studies, interferon maintenance therapy prolonged remission duration in responding patients,[10,11] but the most important results were obtained by the association of α-interferon with glucocorticoids. This intensified maintenance therapy induced a further M-component reduction (>50%) in responding patients after conventional chemotherapy.[12] Induction failures received interferon and glucocorticoids after conventional chemotherapy; a median survival of 48 months was observed in the interferon/dexamethasone group as compared with 34 months for responding patients receiving interferon only.[13] The association interferon plus glucocorticoids prolonged progression-free survival.

Salvage regimen

Myeloma may be resistant to treatment or relapse while in remission, and the two conditions require different specific treatments. For relapse, the outcome is poor with a median survival of 12 months.[14] For patients relapsing 12 months after induction chemotherapy, repetition of the initial treatment is suggested.[15] For patients relapsing before 12 months, VAD therapy is the treatment of choice.[16] For primary resistant disease, VAD or high-dose dexamethasone have been used,[17] but the myeloablative approach induced response in 70% of patients and significantly prolonged survival.[18]

When myeloma becomes refractory to both melphalan and doxorubicin-containing regimens, median survival is usually 6 months. In these patients, cyclophosphamide (3.6 g/m^2) induced 50% response and prolonged survival to 12 months.[19] The combination of cyclophosphamide (3 g/m^2) and etoposide (900 mg/m^2) showed similar results.[20] Adequate doses of cyclophosphamide seem to be the third-line treatment of choice. Low doses of intravenous

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melphalan (20-40 mg/m^2) seem more feasible as a fourth line of treatment for heavily pretreated patients; this induces less hematological toxicity and allows repetition of chemotherapy. The goal of this approach is to maintain the tumor under control and prolong survival, rather than induce a high response rate.[21] Intensified maintenance therapy with interferon plus glucocorticoids represents the management of choice for second and subsequent remissions, as previously described.

Myeloablative approach

In recent years, many patients have been treated with high-dose chemotherapy and peripheral blood progenitor cell support, as lucidly reviewed in this issue by Caligaris Cappio *et al.*[22] Most experts agree that autologous transplant is not suitable for patients older than 65 or with major medical problems. In a large transplant trial, intention to treat for patients under 60 was 82%, but dropped to 56% for those over 60.[23] The median age at diagnosis for multiple myeloma is 69 for men and 71 for women.[24]

Worldwide experience on 571 patients treated within 12 months of diagnosis has been summarized:[25] median age was 50 years old, complete remission rate was 42%, event-free survival 30 months, and overall survival 4 to 5 years. Preliminary data from a randomized trial comparing autotransplant (melphalan 140 mg/m^2 plus TBI) versus conventional chemotherapy (VMCP-VBAP) suggested that autotransplant may improve event-free survival (28% *versus* 10% at 5 years) and overall survival (52% *versus* 12% at 5 years).[26] High-risk patients (high-labelling index) were transplanted and their outcome compared with controls treated with conventional chemotherapy. The duration of both freedom from progression (38 months) and overall survival (41 months) were significantly superior in the transplant group as compared to the historical controls (overall survival, 14 months).[27]

In several series, myeloablative regimens showed encouraging results for patients treated during the early phases of disease,[18,28] but little value has been observed during later stages.[17] The value of early myeloablative therapy was assessed in patients treated within 1 year of initial therapy. Patients were consolidated during remission or treated for primary refractory disease. Outcomes were compared with those treated with conventional chemotherapy. Among patients who responded to standard induction treatment, myeloablative therapy did not prolong survival. Among patients with primary resistant disease, myeloablative therapy prolonged survival.[18] After primary resistance for more than 1 year, survival was similar to that of patients treated with conventional chemotherapy.[29] Thus, myeloablative therapies seem to offer a survival advantage over conventional chemotherapy, especially for primary resistant and high-risk patients.

Allogeneic marrow transplantation is currently limited to 5% of patients under 50 years of age and have an HLA-compatible sibling. Results of major allotransplant trials on 268 patients have been summarized.[25] Approximately 50% of patients died within a year, 40% achieved a complete remission, and 4-year projections of event-free survival and overall survival were approximately 35%. A few patients have been in remission for 7 or more years, suggesting the possibility of a cure, perhaps as a result of *graft versus myeloma* effects. Some investigators identified early transplantation and lower tumor mass as favorable variables; at 3 years, event-free survival and overall survival were 48% and 68%, respectively.

Treatment strategies and future directions

Development of optimal treatment strategies (Figure 1) is absolutely vital to obtaining the best survival advantage for the single patient. At diagnosis, patients must be stratified by age; younger patients (<55-60 years) may benefit from the myeloablative approach, while melphalan/prednisone remains the standard treatment for the others. Adequate dose reduction is a requisite in the elderly. The melphalan/prednisone regimen is not recommended for high-risk patients. The sequence melphalan per os for induction, doxorubicin-containing regimen for first relapse, cyclophosphamide for second

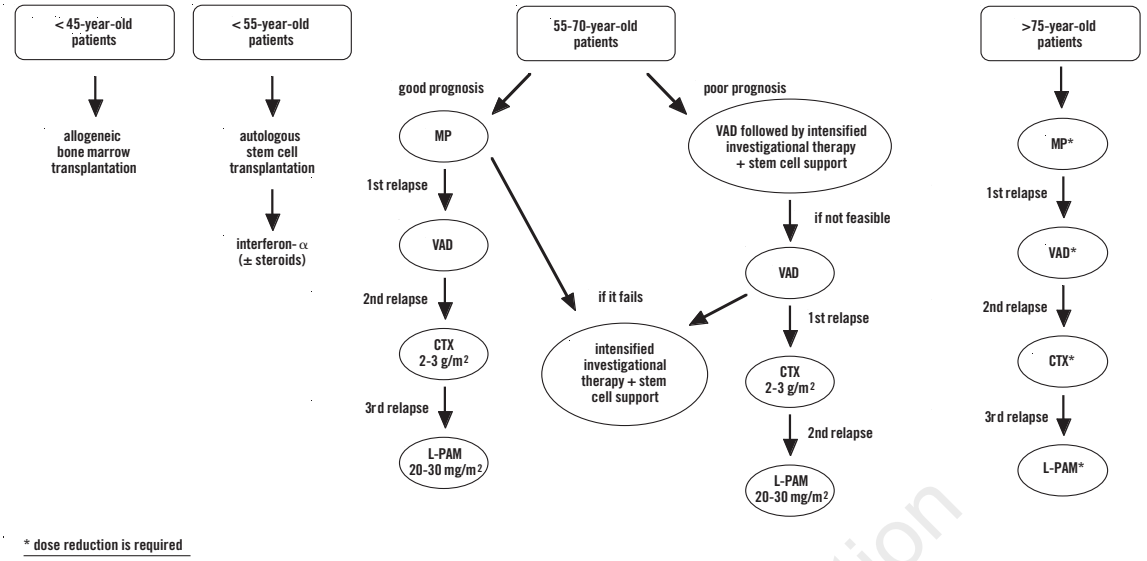

Figure 1. Schematic treatment approach to myeloma patients.

relapse, i.v. low-dose melphalan for third relapse achieved the best results. Maintenance treatment with interferon plus glucocorticoids has been used for second and subsequent remissions with significant benefits.[30] Myeloablative approaches must be considered for younger patients at diagnosis or in the early phases of disease. The major advantage is for primary resistant and high-risk patients.

Clinical research must pursue novel therapeutic avenues and new agent evaluation has to continue, especially for entirely new classes of drugs. Among the old classes, dose intensity must be analyzed, since different doses might induce significantly different responses. Tailored therapy should be instituted for selected patients. Induction must be followed by a coordinated sequence of salvage regimens for effective control of the tumor. Salvage therapy should be aggressive enough to control the disease, but gentle enough to avoid severe hematological toxicity so as to allow delivery of subsequent effective treatment.

The coming years will clarify to what extent high-dose chemotherapy (melphalan 140-200 mg/m^2) is superior to conventional chemotherapy. The optimal dose, sequence and timing must be still determined. In the autotransplant area, tumor cell removal from autografts can be accomplished by both positive and negative selection.[31] Whether or not these purification procedures have an impact on prognosis is under evaluation.

Post-transplant maintenance strategies involve predominantly interferon therapy. Alternative approaches include a tumor-specific anti-idiotype vaccination, already piloted in myeloma.[32] Allogeneic G-CSF-mobilized circulating progenitor cells are under consideration for allogeneic transplant in an attempt to reduce toxicity, improve engraftment, and increase graft versus myeloma.

Intensified regimens (melphalan 60-100 mg/m^2) with circulating progenitor cell support delivered to elderly patients with health care usually given for conventional chemotherapy will have a growing impact on myeloma therapy. This approach allows a drastic dose-intensification and increases the response rate, while toxicity rremains similar to standard regimens. For this new class of regimens, dose-finding, best timing of administration and effects on outcome are the future challenge.[33]

References

1. Alexanian R, Dimopolous M. The treatment of multiple

myeloma. N Engl J Med 1994; 330:484-6.
2. Boccadoro M, Pileri A. Standard chemotherapy for myelomatosis: an area of great controversy. Hematol Oncol Clin N Am 1992; 6:371-82.
3. Mac Lennan ICM, Drayson M, Dunn J. Multiple myeloma. Br Med J 1994; 308:1033-6.
4. Oken MM. Standard treatment of multiple myeloma. Robert Kyle Symposium on Monoclonal Gammopathies-Part II. Mayo Clin Proc 1994; 69:781-6.
5. Barlogie B, Vesole D, Jagannath S. Salvage therapy for multiple myeloma: the University of Arkansas Experience. Mayo Clin Proc 1994; 69:787-95.
6. 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; 10:334-42.
7. Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 1990; 33:86-9.
8. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment in multiple myeloma. Blood 1992; 80:887-90.
9. Palmer M, Belch A, Hanson J, et al. Dose intensity analysis of melphalan and prednisone in multiple myeloma. J Natl Cancer Inst 1989; 80:414-8.
10. Avvisati G, Mandelli F. The role of interferon-α in the management of myelomatosis. Hematol Oncol Clin N Am 1992; 6:395-405.
11. Mandelli F, Avvisati G, Amadori S, et al. Maintenance treatment with recombinant interferon α-2b in patients with multiple myeloma responding to conventional induction chemotherapy. N Engl J Med 1990; 322:1430-4.
12. Palumbo A, Boccadoro M, Garino LA, Gallone G, Frieri R, Pileri A. Multiple myeloma: intensified maintenance therapy with recombinant interferon α-2b plus glucocorticoids. Eur J Haematol 1992; 49:93-7.
13. Salmon SE, Crowley JJ, Grogan TM, Finley P, Pugh RP, Barlogie B. Combination chemotherapy, glucorticoids and interferon alpha in the treatment of multiple myeloma: a Southwest Oncology Group study. J Clin Oncol 1994; 12:2405-14.
14. Boccadoro M, Marmont F, Tribalto M, et al. Multiple myeloma: VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisone even in high-risk patients. J Clin Oncol 1991; 9:444-8.
15. Buzaid AC, Durie BGM. Management of refractory myeloma: a review. J Clin Oncol 1988; 6:889-905.
16. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 1984; 310:1353-6.
17. Alexanian R, Barlogie B, Dixon DO. High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med 1986; 105:8-11.
18. Alexanian R, Dimopoulous MA, Hester J, Delasalle KB, Champlin R. Early myeloablative therapy for multiple myeloma. Blood 1994; 12:4278-82.
19. Palumbo A, Boccadoro M, Bruno B, Triolo S, Pileri A. Cyclophosphamide (3.6 g/m^2) therapy with G-CSF support for resistant myeloma. Haematologica 1994; 79:513-8.
20. Dimopoulos MA, Delasalle KB, Champlin R, Alexanian R. Cyclophosphamide and etoposide therapy with GM-CSF for VAD-resistant multiple myeloma. Br J Haematol 1993; 83:240-4.
21. Petrucci MT, Avvisati G, Tribalto M, Cantonetti M, Giovangrossi P, Mandelli F. Intermediate-dose (25 mg/m^2) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment. Eur J Haematol 1989; 42:233-7.
22. Caligaris Cappio F, Cavo M, De Vincentiis A, et al. Peripheral blood stem cell transplantation for the treatment of multiple myeloma: biological and clinical implications. Haematologica 1996; 81:357-76.
23. Attal M, Harousseau IL, Stoppa AM, et al. High dose therapy in multiple myeloma: a prospective randomized study of the *Intergroupe Français du Myelome* (IFM). Multiple myeloma from biology to therapy: current concepts. Mulhouse 1994; (abs), p. 84.
24. Ries LAG, Hankey BF, Miller BA, et al. Cancer statistic review, 1973-1988 (DHHS publ - NIH - n. 91-2789). Washington, DC, US Govt Printing Office, 1991.
25. Barlogie B, Jagannath S, Vesole D, Tricot G. Autologous and allogenic transplants for multiple myeloma. Semin Hematol 1995; 32:31-44.
26. Attal M, Harousseau JL, Stoppa AM, et al. High dose therapy in multiple myeloma: final analysis of a prospective randomized study of the *Intergroup Français du Myelome*. Blood 1995; 86:10(suppl 1)485a (Abs).
27. Gianni M, Tarella C, Bregni M, et al. High-dose sequential chemoradiotherapy, a widely applicable regimen, confers survival benefit to patients with high-risk multiple myeloma. J Clin Oncol 1994; 12:503-7.
28. Jagannath S, Barlogie B, Dicke K, et al. Autologous bone marrow transplantation in multiple myeloma: identification of prognostic factors. Blood 1990; 76:1860-5.
29. Alexanian R, Dimopoulos M, Smith T, Delasalle K, Barlogie B, Champlin R. Limited value of myeloablative therapy for late multiple myeloma. Blood 1994; 83:512-6.
30. Palumbo A, Boccadoro M, Garino LA, Gallone G, Frieri R, Pileri A. Interferon plus glucorticoids as intensified maintenance therapy prolongs tumor control in relapsed myeloma. Acta Haematol 1993; 90:71-6.
31. Lemoli RM, Fortuna A, Motta MR, et al. Concomitant mobilization of plasma cells and hematopoietic progenitors into pheripheral blood of multiple myeloma patients: positive selection and transplantation of enriched CD34$^+$ cells to remove circulating tumor cells. Blood 1996; 87:1625-34.
32. Kwak LW, Campbell MJ, Zelenetz AD, et al. Transfer of specific immunity to B cell lymphoma with syngeneic bone marrow in mice: a strategy for using autologous marrow as an anti-tumor therapy. Blood 1991; 78:2768-71.
33. Palumbo A, Boccadoro M, Omedè P, et al. Schema sequenziale ciclofosfamide-melphalan (CM) con supporto di cellule progenitrici circolanti non criopreservate nel mieloma refrattario. 35° Congresso Nazionale Società Italiana di Ematologia, Pavia-Cernobbio 1995, C071.