Review Article

Multiple myeloma: current treatment

D. Samson

Department of Haematology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK

Introduction

Multiple myeloma remains a difficult disease to treat because of its marked resistance to chemotherapy. With conventional treatment not all patients respond, and even in responding patients complete remissions are rare and relapse inevitable. There are, however, a number of new approaches to treatment which have improved the outlook for myeloma patients.

The average survival is of the order of 2.5–3 years, but there is a wide variation in prognosis depending on factors such as haemoglobin level, serum albumin and renal function. The most important single prognostic factor is the level of serum beta-2 microglobulin,¹ which reflects both tumour mass and renal function. Younger patients and those with poor prognostic factors may be considered for more aggressive treatment approaches, whereas the elderly and younger patients with good prognostic factors may do as well, if not better, with simple treatment.

Patients with asymptomatic or equivocal myeloma, ie with normal haemoglobin, normal renal function and no bone lesions, and with only a modest increase in bone marrow plasma cells, should not be treated at this stage, since the disease may remain stable for a long time without problems developing. These patients however need careful follow-up, which should include periodic bone marrow examinations and skeletal X-rays as well as paraprotein measurements, since the first sign of progression is not infrequently the development of bone disease.

Conventional dose chemotherapy

Melphalan or cyclophosphamide with or without prednisolone

Before the introduction of melphalan and prednisolone (MP) by Alexanian *et al.*² the average

survival of myeloma patients was only 7 months. Intermittent oral MP has been shown in numerous studies to prolong survival to between 2 and 3 years, and this has remained the standard against which newer treatments must be judged. Oral or intravenous cyclophosphamide is equally effective.³ The inclusion of prednisolone in addition to melphalan has never been shown to improve long-term survival,³ but improves the speed of response and reduces myelotoxicity.

With this type of treatment 50–60% of patients will respond, usually over a period of 3–6 months, and will reach a stable plateau phase, during which the paraprotein level does not continue to fall but remains steady. In most studies, objective response is defined as a reduction in paraprotein of at least 50%, but patients who respond slowly and who do not reach this degree of tumour reduction may still have long survival. Complete remission, that is, disappearance of the paraprotein with a normal number of plasma cells in the bone marrow, is exceptional. Treatment is usually stopped when a stable plateau is reached, since giving further chemotherapy does not prolong the duration of the remission and may favour the development of drug resistance.⁴

Combination chemotherapy

Numerous studies have been carried out comparing combination chemotherapy (CCT) with simple melphalan and prednisolone (MP). The drugs used in combination regimens have usually included melphalan (M) and/or cyclophosphamide (C) with two or more of the following: adriamycin (A), vincristine (V), BCNU (carmustine) (B) and prednisolone (P). The most popular of these regimens have been VBMCP,⁵ VMCP/VBAP⁶ and ABCM.⁷ There is probably little difference in their effectiveness. They all induce objective response (that is, a given degree of tumour reduction, usually 50%) in significantly more patients than does MP, but a clear benefit in terms of survival has been difficult to establish. Only two studies have shown a statistically significant improvement in survival

Correspondence: D. Samson, F.R.C.P., F.R.C.Path.
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with CCT, an early study from the South West Oncology Group comparing VMCP/VBAP with MP,⁶ and the recently reported Myeloma V study from the Medical Research Council comparing ABCM with M alone.⁷ Many other studies have shown no difference or a difference in favour of MP. A recent meta-analysis of 18 published trials was carried out by Gregory *et al.*,⁸ who concluded that overall there was no difference in survival between combination therapy and MP. Further analysis, however, led them to suggest that in trials recruiting mainly good risk patients, MP proved superior, while in those recruiting mainly poor risk patients, CCT proved superior.

Even if one concludes that there may be a benefit of CCT particularly in poor risk patients, the magnitude of this benefit is relatively small. Thus in the MRC Myeloma V study, the difference in median survival between the two arms was only 10 months. This means that other approaches are needed to make a significant impact on survival, particularly in younger patients, while in older patients the use of CCT does not seem justified in view of the marginal benefit and more troublesome side effects, for example, nausea and alopecia. It is also reasonable to treat younger patients with good prognostic features with MP. In particular, the early use of anthracyclines may prejudice treatment at relapse by inducing drug resistance.

Infusional regimes

The first of these regimes to be introduced was the VAD regimen, used initially in relapsed patients.⁹ It is a combination of vincristine (V), Adriamycin* (A) and dexamethasone (D), but differs from conventional regimens in that the vincristine and Adriamycin are given not as bolus injections but by continuous infusion over 4 days. Modifications of the regimen include VAMP, where methyl prednisolone replaces dexamethasone, and MOD, where mitoxantrone is substituted for Adriamycin. The underlying rationale is that because myeloma cells are slowly dividing, usually with under 1% in S-phase at any time, drugs which act only against cycling cells were likely to kill more cells if given over a longer period. The VAD regimen was found to be very effective in relapsed patients⁹ and subsequently also in previously untreated patients.¹⁰ Over 80% of newly diagnosed patients will respond, with 10–20% achieving complete remission. Unfortunately these remissions are not durable, lasting on average only 18 months, even in patients who achieve complete remission. For most patients therefore, VAD is not superior to other chemotherapy combinations. Nevertheless, the regimen

has advantages in certain situations. Since none of the drugs are excreted renally, it can be given without dosage modification in patients in severe renal failure, including those on dialysis. It produces almost no myelosuppression and so is very useful in patients presenting with neutropenia or thrombocytopenia. The rate of response is dramatic, with most patients achieving 90% of their maximum response within 6 weeks, an advantage in patients who require rapid tumour reduction, for example, those with rapidly progressive bone disease. The main disadvantages are the necessity for a central venous line for administration and the high incidence of steroid-related side effects.

Steroids

Steroids are active against myeloma cells while sparing normal bone marrow, and hence form a useful part of the therapeutic repertoire. The addition of steroids to chemotherapy regimens can increase the speed of response and reduce myelosuppression, although it is not clear whether there is a long-term survival benefit.^{3,11} Dexamethasone has been shown to be an important part of the VAD regimen, in that response rate is lessened if the steroid dose is halved. Steroids alone can induce responses and control disease,¹² and can be a very useful treatment in relapsed elderly patients; for example, prednisolone 50 mg on alternate days continuously or dexamethasone 20 mg daily for 4 days every 2 weeks.

High-dose therapy

High-dose melphalan

With conventional dose chemotherapy, complete remissions are rare. By analogy with the treatment of leukaemia, it can be assumed that the first step to prolonging relapse-free survival (and ultimately to achieving cure in a proportion of patients) would be to achieve more frequent complete remissions. The first attempt to induce more complete remissions with high-dose therapy was with the use of high-dose melphalan, pioneered by McElwain and colleagues at the Royal Marsden Hospital. A single administration of melphalan at a dose of 140 mg/m² resulted in an encouraging 25% complete remission rate in previously untreated patients, in spite of a significant treatment-related mortality.¹³ However, with longer follow-up it became evident that these remissions were not durable, and the median duration of remission was only 18 months, even in patients who had achieved complete remission. (These results are very similar to those achieved with the VAD regimen, but at the expense of greater toxicity).

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Nevertheless this work provided an impetus for the subsequent development of even more intensive therapy combined with bone marrow or peripheral blood stem cell rescue. High-dose melphalan is still frequently used as part of transplantation schedules, either with total body irradiation, or as a single agent at very high dosage.

Allogeneic bone marrow transplantation

The question of whether it is possible to cure myeloma by myeloablative therapy is best addressed by considering the results of allogeneic bone marrow transplantation (BMT), where normal donor marrow is infused and where subsequent relapse must result from failure to eradicate myeloma in the patient, rather than from re-infused marrow, as may be the case with autologous BMT. The largest series of allogeneic transplants for myeloma is that collected by the European Group for Bone Marrow Transplantation (EBMT) who have reported the results of allogeneic BMT in 90 patients aged 25–55 years.¹⁴ Most of these patients were treated with a combination of high-dose cyclophosphamide and total body irradiation, a standard protocol for BMT in leukaemia. The results indicate that the procedure carries a high transplant-related mortality, of the order of 30–40%, albeit less in patients transplanted early in the course of their disease. The mortality is greater in patients with myeloma than in patients with leukaemia, partly because of their older age, but mainly because of increased susceptibility to infection. Nevertheless, there is a 5–6 year survival probability of 40%. Patients who are transplanted early in the course of the disease and who are still responsive to chemotherapy have a better chance of long-term survival. Similar data have been reported from the Seattle bone marrow transplant team.¹⁵ About half of the patients surviving at 5–6 years after allogeneic BMT are still in complete remission, and some of these patients have no detectable disease at the molecular level as indicated by inability to detect the tumour-specific immunoglobulin gene rearrangement in the bone marrow.¹⁶ It thus appears that allogeneic BMT can result in long survival and possible cure in some patients. Relapse, however, remains a significant problem, emphasizing the extreme resistance of myeloma to even the most intensive treatment. The possible role of interferon maintenance post-BMT in prolonging remission is under evaluation.

Autologous bone marrow or peripheral blood stem cell transplantation

Allogeneic BMT is only possible in patients under the age of 55 years with a suitably matched donor. Autologous transplant is a much safer procedure

and can be used in patients up to the age of 65 years. The problem with autologous transplantation is that, although the high-dose therapy can induce a significant proportion of complete remissions, the majority of patients relapse, with a median time to relapse of around 2 years and no plateau on the relapse-free survival curve.^{17–20}

There are at least three possible reasons for the increased rate of relapse after autologous as compared with allogeneic BMT. Firstly, the high-dose therapy regimens used have in general been less intensive than those used for allogeneic BMT. Secondly, there may be an immunological effect of donor marrow after allogeneic BMT, that is, a graft versus myeloma effect, which is absent after autologous transplant. The most important factor, however, seems likely to be the re-infusion of myeloma cells in the harvested marrow. Even when marrow is harvested in remission it usually contains residual myeloma cells. Purging of harvested marrow using monoclonal antibodies against B-lineage cells has been used in an attempt to remove residual myeloma cells, but the results are not encouraging.^{21,22} An alternative approach which is now being developed is the positive selection and re-infusion of normal stem cells from harvested marrow.

It has also been suggested that relapse risk might be reduced by the use of peripheral blood stem cells on the basis that these are less likely than marrow to be contaminated with myeloma cells, or at least to contain a smaller number of tumour cells. Since the advent of growth factors (GM-CSF and G-CSF) it has become relatively easy to harvest stem cells from the peripheral blood by leucapheresis, and the use of peripheral blood stem cells as an alternative to bone marrow is increasing, mainly because the time to engraftment is shorter. Whether there is an advantage in terms of relapse risk remains to be established, although it is clear that when sensitive molecular techniques are used, cells belonging to the malignant clone can be detected in the peripheral blood in the majority of patients.^{23,24} The currently available clinical data on peripheral blood stem cell transplantation in myeloma do not suggest that the relapse rate differs significantly from that seen after autologous marrow transplant.^{25,26}

Another approach to reducing relapse after autologous transplant is to administer maintenance treatment with alpha-interferon. The interim analysis of a randomized study from the Royal Marsden Hospital²⁷ suggests that interferon may significantly prolong remission duration after autologous BMT, from a median of 24 months to a median of 39 months, but it is too early to know if survival will be longer in the interferon-treated group.

In summary, there is no evidence at present to

indicate that autologous transplant can cure patients, but it may nevertheless prolong survival as compared with standard chemotherapy. This question can only be answered by randomized trials, a number of which are now in progress. Preliminary results from a French study comparing autologous BMT with combination chemotherapy suggest a survival benefit for the autologous BMT arm,²⁸ but the data are not yet mature and the number of patients is small, so further work is needed to answer this important question.

Interferon

Myeloma was one of the first malignancies in which an effect of interferon was demonstrated, though the exact mechanism of action is still unclear. Interferon- α (IFN) has been most widely studied clinically. When given as a single agent, IFN can produce responses in 10–20% of patients.

Interferon has chiefly been used as maintenance therapy in patients who have reached stable plateau phase after initial chemotherapy of different types. The first reported study indicated a very significant prolongation of remission duration as compared with patients receiving no further treatment, from 14 to 26 months.²⁹ The results of further such studies have proved conflicting, possibly because of differences in dosage and scheduling of IFN. Remission duration was prolonged by IFN in two of these studies^{30,31} while three others have shown no benefit.^{11,32,33} Meanwhile, as discussed above, IFN maintenance has been shown to prolong remission after autologous BMT. At present, it is not clear whether survival is prolonged by IFN maintenance, since a significant survival benefit has not been shown even in those studies where remission duration was prolonged (possibly because when relapse did occur it was more difficult to treat).

IFN has also been used in combination with induction chemotherapy, in varying dosages and schedules, and with various types of chemotherapy; again the results are conflicting. Some, but not all, studies have shown an improvement in the number of patients who achieve objective response, but a survival benefit has not been clearly established.^{30,33–37} In one recently published large study comparing MP alone with MP plus IFN, there was a survival benefit in patients with IgA or Bence-Jones only myeloma but not in the group as a whole.³⁷ At present the available evidence does not justify the routine use of IFN during induction. However, IFN alone, or in conjunction with dexamethasone, can induce responses in a proportion of patients who are resistant to initial chemotherapy.^{11,38}

Further trials are currently being carried out

looking at interferon in combination with, or as maintenance following, various different chemotherapy schedules or after autologous BMT. If IFN prolongs remission with acceptable side effects, then its use can be recommended even if survival is not clearly prolonged. The most widely used dose is 3 mU three times weekly.

New treatment approaches

Modulation of drug resistance

Resistance to chemotherapy in refractory myeloma is often associated with expression of the gene for multi-drug resistance (mdr-1). This gene encodes a membrane glycoprotein (p-glycoprotein: PgP), which acts as an efflux pump to expel drugs from the cell. The drugs affected by mdr include the anthracyclines and vincristine. Only 5% of patients with myeloma express PgP at diagnosis but this rises to 70–80% in previously treated patients who show clinical resistance to treatment with the VAD regimen. The extent of PgP expression seems to correlate with the degree of resistance to chemotherapy.

There are a number of drugs which can block the action of PgP, and so reverse drug resistance. Verapamil and other calcium-channel blockers are active *in vitro*, as is quinidine, but *in vivo* the doses needed for efficacy are too toxic for routine use. Cyclosporin has more recently been found to inhibit PgP, unrelated to its immunosuppressive actions, and has been effectively used clinically to reverse drug resistance in patients with myeloma. Sonneveld *et al.*³⁹ reported a study in which 21 patients with refractory disease were treated with VAD given together with a continuous infusion of cyclosporin (5–10 mg/kg/day). Fifteen of the patients were previously resistant to VAD alone. The overall response rate was 48%, and there were seven responses in the 15 patients who were previously VAD resistant. Toxicity was minimal. These are encouraging results. New analogues of cyclosporin are also being evaluated.

Cytokines and anti-cytokines

Most interest has centred on the role of alpha-IFN, as discussed above. Gamma-IFN is very active against myeloma cells *in vitro*, but limited clinical studies have been disappointing, possibly because of secondary effects of other cytokines released by gamma-IFN.

The role of interleukin-6 (IL-6) as a growth factor for myeloma cells *in vitro* is now well recognized,⁴⁰ while the level of serum IL-6 *in vivo* has been shown to be an important adverse prognostic factor.^{40,41} Based on these observations,

Klein *et al.* used monoclonal antibodies to IL-6 to treat a patient with advanced disease and observed a definite, albeit transient, response.⁴² Interleukin-2 (IL-2) in contrast appears to reduce myeloma growth, probably via the release of inhibitory cytokines (for example, gamma-IFN) from other cells. Gottlieb *et al.* treated four patients with infusions of IL-2 following autologous BMT but the data were insufficient to determine whether this had any benefit.⁴³

Supplementary treatments

Radiotherapy

In contrast to its resistance to chemotherapy, myeloma is very radiosensitive, and relapse at a site which has been treated with radiotherapy is unusual. However, the use of radiotherapy is of necessity limited by the need to spare the marrow. Radiotherapy is useful as an adjunct to chemotherapy when a specific area needs rapid treatment to reduce pain (it is usually effective within days of starting treatment), to treat cord compression, or to prevent fracture through a large lytic lesion (pinning may also be needed).

Because of the radiosensitivity of the disease, total body irradiation forms an integral part of many of the high-dose regimens used in BMT. Here the effect on the marrow is irrelevant but dosage is limited by effect on other tissues so that the dosage is less than can be given for a localized lesion.

Another way of using radiotherapy is as sequential hemi-body irradiation, which is an alternative to chemotherapy in relapsed or refractory patients. One half of the body is treated first, and after recovery from myelosuppression the other half is treated.^{44,45} This can provide very effective relief of symptoms in patients with bone disease, but the myelosuppression may delay or prevent the second treatment, and progression can occur in the untreated area during the period between the two treatments.

Erythropoietin

There are numerous causes for anaemia in myeloma, but it is striking that there is often significant anaemia in patients with normal renal function who do not have heavy marrow infiltration, suggesting a cytokine-mediated mechanism of suppression of erythropoiesis by myeloma cells. There are now a number of studies showing that anaemia in myeloma patients will usually respond to erythropoietin therapy, whether or not there is renal impairment.⁴⁶

Bisphosphonates

Bone disease in myeloma is one of the most distressing clinical features. It is now known to be mediated by cytokines including tumour necrosis factor and interleukin-1 which activate osteoclasts, probably indirectly via osteoblasts. The bisphosphonates inhibit the action of osteoclasts on bone resorption and are widely used for the treatment of hypercalcaemia, but also in long-term use can reduce the progression of bone disease in myeloma.⁴⁷ Both pamidronate (intravenous) and clodronate (oral) have been found to be effective.

Specific problems

Renal failure

Renal failure is a common problem in myeloma, and is most often due to hypercalcaemia or tubular damage by Bence-Jones protein (BJP). Amyloid deposition and plasma cell infiltration can also occur. Initial renal failure may be reversible if due to hypercalcaemia and dehydration, but damage due to Bence-Jones protein is usually irreversible. All patients with myeloma should be encouraged to take a high fluid intake, and this is especially important in those with Bence-Jones proteinuria.

The wider availability of dialysis facilities has improved the outlook for patients presenting with renal failure. As discussed above, the VAD regimen is particularly suitable for patients with irreversible renal failure, and can be given in patients with haemodialysis or peritoneal dialysis. Steroids alone are an alternative in elderly patients. IFN can also be safely used. Alkylating agents can be used but, because they are renally excreted, the doses need to be reduced and, in practice, it can be difficult to find the dose which will be effective without causing excessive myelotoxicity. A major problem for younger patients is that renal failure excludes them from high-dose therapy.

Cord compression

Radiotherapy rather than surgical decompression is the treatment of choice. Since multiple levels may be involved, the use of newer imaging techniques, particularly magnetic resonance imaging, improves the localization of involved areas.

Treatment of relapsed and refractory patients

Patients who relapse over one year after stopping their initial treatment may well respond to re-institution of the same therapy. Those who fail to respond to initial treatment, or who relapse while still on treatment or within a year of stopping

treatment will require an alternative approach. Those who previously had simple alkylating agents may respond to standard combination chemotherapy, but the VAD regimen remains the most effective treatment for such patients. Relapsed or refractory patients who do not respond to VAD pose a difficult problem. They often express the *mdr* phenotype and so may respond to VAD with cyclosporin.

Alternative new approaches for patients who are refractory to VAD and who are fit for intensive treatment approaches are EDAP, a combination of etoposide, dexamethasone, cytosine arabinoside and cisplatin,⁴⁸ or high-dose cyclophosphamide and etoposide with GM-CSF.⁴⁹ These both produce responses in about 40% of patients but the

responses are of fairly short duration unless followed by further intensive therapy. For those not suitable for intensive treatment, steroids with or without IFN are a useful alternative.

Conclusion

There are a number of promising new approaches for patients with myeloma, including high-dose therapy, interferon and cyclosporin. It is important that these are now carefully evaluated in the context of large randomized clinical trials, which are currently continuing at regional, national and international levels, and that patients are entered into these studies wherever possible.

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