Treatment of myeloma

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Introduction

Myeloma is a malignant disease characterized by the clonal proliferation of plasma cells within the bone marrow. It has an annual incidence of 2–4 per 100 000 population, with 2000–3000 new cases per year in the UK, and accounts for 1% of all malignancies. The majority are over 55, with a median age at diagnosis of 70. Myeloma can manifest itself in a variety of ways—bone marrow failure, susceptibility to infection, hypercalcaemia, bony destruction resulting in pain or pathological fracture, renal failure and amyloidosis. It is an incurable illness, with a median survival for all patients of 3 years. Less than 3% survive more than 10 years and the clinical history is usually one of multiple relapses.

Chemotherapy

Since myeloma is usually a disseminated disease at presentation, chemotherapy is the main treatment modality. Some asymptomatic patients with low tumour mass need no treatment; however, those patients with extensive bone disease, bone marrow failure, renal failure or a rapidly rising M-protein need treatment. Chemotherapy is continued only until plateau phase is reached, i.e. clinically and biochemically unchanged for 3 months with a stable paraprotein, as there is no evidence that maintenance chemotherapy prolongs survival in patients with myeloma. There is some suggestion, however, that interferon may prolong relapse-free survival.

Single-agent chemotherapy

In 1958, melphalan was introduced for this condition, producing clinical responses in 40% of patients. It has since been used extensively, alone and in combination. Remissions last a median of 2 years and median survival is improved from under 1 year to between 19 and 39 months. Intermittent treatment is favoured, as it induces remission sooner and increases the response rate with less marrow suppression. This modality is limited by the development of drug resistance, with inevitable relapse. There is also a small risk of the development of a secondary myeloblastic leukaemia or myelodysplasia. Steroids are also effective anti-myeloma agents, reducing bone resorption and lowering M-protein levels. Prednisolone alone is ineffective, although, the addition of prednisolone to oral melphalan improves the response rate by 20% and extends survival by about 5 months.

Combination chemotherapy

The limited success of monotherapy and steroids in myeloma, stimulated the development of combinations of non-cross-reactive agents. Investigators have looked at a variety of alkylating agents, nitrosoureas (BCNU or CCNU), vincristine and Adriamycin in the regimen, as well as routes of administration, schedules of drug dose and treatment interval. Several trials have compared a variety of combination chemotherapy regimens with melphalan and prednisolone (MP). Despite a clear advantage in terms of remission induction, no clear benefit for either survival or remission duration has been shown for the newer regimens over single-agent alkylating agent plus steroid. The 5th MRC Myelomatosis Study showed that ABCM (doxorubicin, carmustine, cyclophosphamide and melphalan) was superior to melphalan alone, although there was only a modest
increase in median survival from 24 to 32 months. In a recent meta-analysis reviewing 18 trials comparing treatment with MP to combination chemotherapy, over 3800 patients were assessed, and no significant difference was seen in the 2-year survival of either group of patients. However, two studies were omitted where a benefit was found in favour of combination chemotherapy. The South Western Oncology Group and the Cancer and Leukaemia Group B have both found that combination chemotherapy in patients with advanced disease produced improved survival and response rates. The consensus seems to be that patients with good prognostic features and an expected survival >2 years have a better outcome with melphalan and prednisolone, whereas those with poor-risk features and an expected survival <2 years may do better with combination alkylating agent chemotherapy.

### Myelo-ablative therapies

#### Autologous/peripheral blood stem cell transplantation

This treatment option is available to patients aged <65 with no other significant co-existing illnesses. Marrow rescue allows significant melphalan dose escalation with a marked reduction in the treatment-associated mortality to <10% compared to high-dose melphalan alone. Peripheral blood stem-cells are increasingly being used as marrow rescue and can allow high-dose therapy in those whose marrow is too heavily contaminated for autologous transplantation. Comparing the two sources of marrow progenitor cells reveals no significant difference in survival or relapse rates. Over 30% of patients autografted will enter complete remission and, although the relapse rate is high, 80% will survive more than 3 years. Autografting appears to be most effective when performed early in the disease but no survival plateau has been identified, suggesting that this procedure is not curative. Some are now beginning to show a survival advantage for autografting over conventional chemotherapy. The French IFM90 trial comparing these two treatment modalities in previously untreated patients showed that both event-free survival and overall survival were improved by the use of autologous bone-marrow transplantation. The MRC’s Myeloma VII trial currently underway is also addressing this issue. Trials of purged autologous marrow, either through positive or negative selection, have shown no reduction in the frequency of relapse. Double autografts have little benefit over single autografts, and are currently associated with considerable toxicity.

#### Allogeneic bone-marrow transplantation

This is a therapeutic option open to only 4% of patients with myeloma, as it is limited by the availability of an HLA-compatible donor and patient age. The upper age limit for allogeneic bone-marrow transplantation is 55, therefore 75% of patients with myeloma are excluded. Despite this, over 500 allografts have been performed in patients with multiple myeloma since the first carried out in the early 1980s using a syngeneic donor. The European Bone Marrow Transplant Group report 162 matched related allografts, 66% of patients engrafting achieved complete remission, with a 4-year survival rate of 32%. Treatment-related mortality was very high at 40%. Factors predictive of survival included only one previous line of treatment, female sex of patient, and presence of CR prior to transplant. Most patients appear to relapse with time, although the survival curve tends to plateau at 5 years post-transplant, suggesting that a proportion may achieve ‘cure’. There is much interest in the possibility of a graft-versus-myeloma effect following allografting, supported by the demonstration of responses to donor leucocyte infusions in patients who have relapsed after allogeneic transplantation.

#### Interferon-alpha

Interferon-alpha (IFN) has primarily been studied as a maintenance treatment aimed at prolonging the plateau phase. An Italian group compared IFN maintenance with no treatment, and the relapse rate after 33 months of follow-up was reduced from 56% to 24%. A recent MRC study found no survival benefit of IFN use in the first plateau phase, although opinion is divided on this issue, and a recent meta-analysis of 24 randomized trials involving 4000 patients showed that IFN produced a moderate improvement in relapse-free survival and a minor improvement in survival.

#### Relapsed and refractory disease

The majority of patients with myeloma will relapse following their initial treatment. Once disease relapse occurs, a second course of first-line treatment should be given, and 50% of patients will respond again. However, 30–50% of patients will not achieve a response on first-line therapy (refractory) or will progress on first-line therapy (relapsing) and should be considered for second-line therapies such as VAD (high-dose dexamethasone and an infusion of vincristine and Adriamycin). This is the treatment of choice for relapsing disease, unless used as part of an initial protocol, producing remission in around 55% of
patients with relapsing disease and 30% of those with primary resistant disease. Poor prognostic factors are serum $\beta_2$ microglobulin $>4 \text{ mcg/ml}$, previous anthracycline therapy, hyperdiploidy or a high plasma-cell labelling index% (a marker of plasma cell turnover). For patients that are VAD-resistant, there are few therapeutic avenues left. VAD resistance is thought to arise from upregulation of the MDR-1 gene, leading to enhanced expression of P-glycoprotein (P-gp). Trials of P-gp-blocking drugs such as verapamil, cyclosporin A and PSC-833 in combination with VAD are underway. Other treatment modalities being investigated for these patients include high-dose interferon and cytokine/growth factor manipulation. Clinical responses to anti-IL-6 monoclonal antibodies have been substantial but transient. Inhibition of TNF alpha and IL-1$\beta$ may slow plasma cell and osteoclast development, and all trans-retinoic acid (ATRA) inhibits myeloma growth by down-regulating IL-6R. Studies are currently underway to evaluate their clinical importance.

Supportive measures

In a disease that affects a predominantly elderly patient group and with a high treatment failure rate, supportive measures are as important as primary therapy. Bone pain requires adequate analgesia, although care should be taken with the use of non-steroidal anti-inflammatory drugs, as they may precipitate renal failure in patients with mild renal impairment. Lytic lesions occurring in critical structural sites need orthopaedic intervention, and isolated painful lesions may require local radiotherapy. Bisphosphonates have been shown to slow the progression of bone disease and reduce the rate of pathological fracture even in those without overt lytic disease. Acute renal failure is usually irreversible; therefore, prophylactic allopurinol, adequate hydration, treatment of urinary infection or hypercalcaemia and the avoidance of nephrotoxins such as non-steroidal anti-inflammatory drugs or iv contrast in patients with mild renal impairment should be ensured. Hypercalcaemia needs vigorous treatment with intravenous hydration, frusemide, steroids and bisphosphonates. Infection in these patients should be aggressively treated with broad-spectrum antibiotics, however, prophylactic immunoglobulin therapy is not of benefit. Myeloma-associated anaemia may respond to recombinant erythropoietin (Epo).

Summary

Survival for myeloma has improved from a median of 7 months in the 1950s to about 30 months today. Progress in chemotherapy has contributed a great deal to this improvement, although it may also, in part, reflect the improved treatment of infections, renal failure and hypercalcaemia as well as earlier diagnosis. For over 30 years, the gold standard of treatment has been oral melphalan and prednisolone, producing a clinical response in approximately 60% of patients and a median survival of around 36 months. Relapse is unfortunately inevitable in all but a handful and, for the majority, treatment can only hope to produce significant periods of remission with minimal treatment-related morbidity and mortality. Recently, improved results have been seen with the introduction of aggressive chemotherapy and bone-marrow transplantation. Marrow ablative therapies produce remissions in virtually all patients, with complete remissions in approximately 1/3. The best response is seen in those with a lower tumour burden, which will reduce the development of secondary resistance. Current treatment is moving towards an approach using sequential therapy. This involves induction chemotherapy with VAD or a similar regimen such as VAMP (vincristine, adriamycin and methylprednisolone), proceeding to high-dose therapy, often with some form of stem-cell rescue. This ensures minimal tumour burden prior to high-dose treatment as well as reducing graft infiltration, improving general performance status and allowing recovery of renal function. Relapse remains a problem, although the use of IFN may reduce this by prolonging the plateau phase. High-dose therapy should be given early, before prolonged use of alkylating agents induces stem-cell dysplasia, before significant complications arise from the myeloma, and before drug resistance is significant. Unfortunately, these treatments come at a price, in terms of increased treatment-related toxicity. There also remains uncertainty as to the extra benefits of high-dose treatment with marrow rescue over high-dose chemotherapy alone. We await the current MRC trial with interest. For a very few, there is the tantalising possibility of cure with allografting. For those in complete remission after first-line induction therapy, allogeneic bone-marrow transplantation offers the best hope of survival, but comes at a greatly increased risk of toxicity, and it is uncertain if it is superior to autografting for the majority of patients. It may soon be possible to identify those poor prognosis patients in whom an allogeneic transplant should be offered at an early stage. Candidate biochemical markers include serum $\beta_2$ microglobulin, neopterin, IL-6, plasma cell labelling index, CRP or LDH and prognostic clinical features include IgD myeloma or stage III disease at presentation. Many patients will have primary refractory or relapsing disease in whom survival is short despite...
all current therapeutic modalities. They should therefore be considered for trials of newer agents, drug combinations and therapeutic interventions such as cytokine manipulation or gene therapy. The lack of effective, curative treatment options for patients with myeloma places great importance on effective palliation. While improving survival duration remains elusive in this condition, all possible efforts must be made to ensure quality of life is maximized.

References


