Biologic and Clinical Advances in Multiple Myeloma

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Recent advances in our understanding of the cellular and molecular derangements involved in multiple myeloma are beginning to be translated into novel therapeutic approaches. Growth factors, specifically interleukin-6,

Introduction

Myeloma is a neoplastic disease of cells in the B-lymphocyte lineage, with a peak incidence in individuals 70 to 80 years old. Although the median age at diagnosis is 70 years [1], it is not uncommon for the disease to be diagnosed in much younger patients. An estimated 13,500 new cases of multiple myeloma were diagnosed in the United States in 1992. Little improvement in 5-year survival rates has occurred since the mid-1970s.

Myeloma has a distinct racial distribution, with incidence and death rates in American blacks nearly double those in whites [2]. In fact, myeloma represents the most common (30%) of all lymphoreticular malignancies in the American black population [3]. The etiology of myeloma has remained obscure. Hereditary factors, radiation exposure, agricultural exposure, and antigenic stimulation have all been implicated to some extent. Support for the theory of antigenic stimulation has come from the discovery that some myeloma paraproteins show antibody activity against specific antigens [4]. Also supporting this theory is the fact that, in murine models, the ability to induce peritoneal plasmacytomas is vastly reduced when the mice are raised in a germ-free environment [5].

Recent research has begun to elucidate the cellular and molecular derangements involved in the pathogenesis of multiple myeloma. These advances, in turn, have suggested novel approaches to treatment.

Biology

Renewable "Stem-Cell" Compartment

Although the terminally differentiated B-lymphocyte, the plasma cell, is the morphologically identifiable cell in myeloma, it represents the end-stage, nonproliferating cell compartment. It has been well documented that there are also monoclonal, early-stage B-cells circulating in the peripheral blood, and that these cells bear the same unique idioype (clonally rearranged immunoglobulin genes) as the malignant plasma cells [6]. Accumulating evidence suggests that the clonal B-cells may represent the renewable "stem-cell" compartment in myeloma.

Myeloma tumor cells have been well characterized by extensive phenotypic analysis. The cells in the circulating "stem-cell" pool express the B-cell markers CD19, CD20, and CD24. They also express the pre-B-cell markers CD10 (CALLA) and CD9 (an activated lymphocyte marker), as well as the plasma cell marker PCA-1. A subset express CD5 (an activation marker expressed on T-cells). This profile is consistent with differentiating, late-stage B-cells.

Aside from the fact that they are monoclonal, these "stem cells" differ from normal B-cells in that they express adhesion molecules, as well as other molecules known to play a role in cell motility, extravasation, and invasion, such as CD11b. These data are consistent with the hypothesis that myeloma originates with the transformation of a B-cell precursor in an extramedullary site, with subsequent migration of late-stage B-cells through the peripheral blood to the bone marrow, where the terminal stages of maturation to the plasma cell occur. The bone marrow microenvironment, with its collection of stromal cells, extracellular matrix glycoproteins, and many cytokines, is apparently very conducive for the maturation of malignant B-cells to plasma cells, leading to further disease expansion and progression.

Assays have been developed that take advantage of the fact that the "stem-cell" compartment in myeloma is identifiable by the unique immunoglobulin gene rearrangement of the malignant clone. Bird et al described their findings using a polymerase chain reaction (PCR)-based technique that
employs consensus primers to amplify the rearranged locus of the immunoglobulin heavy-chain gene [7]. They followed six myeloma patients in clinical complete remission after allogeneic bone marrow transplantation. All patients were PCR positive within the first year after bone marrow transplantation. One patient became PCR negative at 1 year after transplantation, and two others at 2 and 4.5 years post-transplantation, respectively. These investigators concluded that PCR positivity up to 1 year after marrow transplantation is common, and is not necessarily predictive of relapse. The significance of residual clonally rearranged cells is not completely understood at this time. Elucidation of this phenomenon will require further study of more cases with longer follow-up. The goal of such efforts is to identify patients who may benefit from additional therapeutic intervention after bone marrow transplantation.

T-Cell Abnormalities
There appear to be both qualitative and quantitative abnormalities in immunoregulatory T-cells in myeloma patients. The ratio of CD4 to CD8 cells is decreased on presentation and continues to decline with disease progression. T-cells with membrane receptors specific for both the idiotype and isotype of the immunoglobulin have been found in myeloma patients. These T-cells can bind to and suppress human myeloma cell lines in vitro. Sensitive molecular techniques have revealed clonal T-cell populations in myeloma patients [8]. However, the relevance of these clonal T-cells is unknown. Recently, Massaia et al demonstrated anti-plasma-cell activity in bone marrow mononuclear cells from myeloma patients stimulated with the anti-CD3 monoclonal antibody OKT3 [9]. A greater understanding of the role of immunoregulatory cells in myeloma should set the stage for targeted therapeutic interventions.

Dysregulation of Interleukin-6
The progression of myeloma depends greatly on growth factors, specifically, interleukin-6 (IL-6). In murine model systems, dysregulated IL-6 production can lead to various plasma-cell proliferative disorders, including plasmacytomas and Castleman's disease [10]. An overproduction of IL-6 is found in 37% of myeloma patients at diagnosis, and is associated with a poor prognosis. Initial work suggested that IL-6 was an autocrine growth factor, produced by the myeloma tumor cells themselves [12]. However, more recent data suggest that marrow stromal overproduction of IL-6 is more important in myeloma [13]. The study of critical paracrine and autocrine loops in disease progression can help identify targets for novel therapeutic approaches. A recent case report from France described a patient with refractory myeloma in whom monoclonal anti-IL-6 antibodies produced an impressive, albeit transitory, response [14]. It has also been demonstrated that IL-6 antisense oligonucleotides can inhibit the growth of human myeloma cell lines [15]. Very recent work has shown that gamma-interferon can inhibit several IL-6-dependent biologic processes by downregulating IL-6 receptor expression, and can completely inhibit four human myeloma cell lines that are dependent on exogenous IL-6 for growth [16].

Preneoplastic Syndromes
Isolated monoclonal gammopathy, the so-called monoclonal gammopathy of undetermined significance (MGUS), is a preneoplastic syndrome that has been extensively studied. However, because of the asymptomatic nature of MGUS, it is unknown whether this syndrome always precedes myeloma. Natural history studies by Kyle have demonstrated that after a median follow-up of 22 years, approximately 25% of patients with MGUS will develop myeloma, amyloidosis, or another lymphoproliferative disease [17]. Extramedullary plasmacytomas and solitary plasmacytomas of bone are two other syndromes that have the propensity to develop into myeloma. The further study of preneoplastic lesions should help elucidate factors necessary for tumor progression, as well as potential targets for intervention.

Cytogenetics
When determined by standard culture techniques, cytogenetic abnormalities have been detected in the tumor cells of 20% to 30% of newly diagnosed myeloma patients. The percentage approaches 50% when analysis is performed after long-term culture and cytokine stimulation[18]. The most common abnormality is a structural change in the long arm of chromosome 14 at the site of the immunoglobulin heavy-chain gene. The 14q+ abnormality is found in a number of lymphoproliferative disorders, and is not specific for myeloma. In fact, there are no specific chromosomal abnormalities in myeloma.
Sequential cytogenetic changes have been noted with serial follow-up. Very complex karyotypes have been seen in patients with advanced and relapsed myeloma.

Molecular Biology

Studies at the molecular level have revealed alterations in proto-oncogenes, tumor-suppressor genes, and, most recently, cell-survival genes in patients with multiple myeloma.

Proto-oncogene Alterations

Myc Proto-Oncogenes---The myc proto-oncogenes encode nuclear phosphoproteins involved in the control of cellular proliferation and differentiation. The c-myc gene (on chromosome 8q24) plays a role in the pathogenesis of a number of B-cell malignancies and also in the 8;14 translocation found in Burkitt’s lymphoma.

In myeloma, gross structural changes involving chromosome 8 are rarely seen. However, molecular analyses have revealed c-myc gene rearrangements and abnormal c-myc transcript size in a majority of patients studied [19]. Inappropriately high levels of c-myc messenger RNA have also been seen in myeloma tumor cells [20]. These findings suggest that other mechanisms besides translocation can result in c-myc gene dysregulation in myeloma. It is interesting to note that the vast majority of murine peritoneal plasmacytomas harbor a translocation that disrupts the c-myc gene by replacing 5’ regulatory sequences with immunoglobulin gene sequences, resulting in overexpression of the c-myc gene.

Ras Oncogenes---The ras oncogenes are among the most commonly activated oncogenes found in human cancer. The ras genes encode for a protein (p21) that is located on the inner surface of the plasma membrane, have guanosine triphosphatase activity, and participate in signal transduction. Dalla-Favera et al demonstrated that insertion of H- or N-ras into human lymphoblasts immortalized by Epstein-Barr virus resulted in increased clonogenicity and tumorigenicity, as well as differentiation into plasma cells [21]. In a large study that looked at DNA from 56 myeloma tumor biopsies, mutations involving the N- or K-ras genes were detected in 27% of cases at diagnosis and 46% of cases after treatment [22]. Codon 61 of N-ras was preferentially involved in the activating mutations. Furthermore, there was a correlation between the presence of a ras oncogene mutation and a lack of response to therapy.

Tumor-Suppressor Gene Alterations

p53 Gene Mutations---The p53 tumor-suppressor gene encodes a nuclear DNA-binding protein that is active in cell-cycle regulation. Alterations in the p53 gene have been implicated in the pathogenesis of a wide variety of malignancies, and germ-line p53 mutations have been demonstrated in the familial cancer, or Li-Fraumeni, syndrome.

The role of p53 gene mutations in myeloma patients has recently been explored [23,24]. Point mutations were detected in tumor cells from 13 of 82 myeloma patients. The mutations occurred within highly conserved domains of the p53 coding sequence and were associated with more advanced stages of disease. Furthermore, several cases were described in which a p53 mutation was detected at disease progression but not at diagnosis. This finding suggests that the p53 mutation is a late event in myeloma, and that myeloma progression is a multistep process. Eventually, a myeloma tumor progression model consisting of sequential genetic alterations, similar to those seen in colon cancer, may be elucidated.

Retinoblastoma Gene Deletion---The retinoblastoma gene (Rb-1) is the prototype tumor-suppressor gene [25]. An inherited germ-line mutation is associated with an 85% chance of tumor formation in the developing retina during childhood. Mutations in the Rb-1 gene have now been studied extensively in many tumor types, and are described most frequently in small-cell lung cancer.

Investigators have recently reported on the incidence of Rb-1 gene deletions in myeloma. Using a very sensitive technique of fluorescence in-situ hybridization, Tricot et detected Rb-1 gene deletions in tumor cells from 12 of 23 myeloma patients studied [26]. Since the majority of patients harboring Rb-1 deletions were previously untreated, these investigators proposed that this gene deletion may be an early event in myeloma pathogenesis.

Alterations in Cell-Survival Genes

Most recently, the bcl-2 gene on chromosome 18, which encodes a mitochondrial membrane protein known to play an important role in cell survival, was shown to be expressed in eight of eight human myeloma cell lines at levels comparable with those observed in a follicular lymphoma cell line carrying a 14;18 translocation involving the bcl-2 gene [27].

The role of bcl-2 in promoting cell survival in follicular lymphomas, which can then go on to acquire
second "genetic hits," has been a rapidly evolving and fascinating hypothesis, and represents a new mechanism of tumorigenesis [28]. Korsmeyer et al, in elegant experiments, demonstrated the oncogenic potential of the \textit{bcl}-2-immunoglobulin fusion gene found in follicular lymphomas in transgenic mice [29]. Mice bearing the fusion gene initially display a polyclonal expansion of small B-lymphocytes. After a long latency period, there is progression to a monoclonal high-grade lymphoproliferative malignancy, which is associated with secondary genetic abnormalities, most often a \textit{c-myc} translocation.

The roles of \textit{bcl}-2, apoptosis, and unchecked cell survival are just beginning to be explored in myeloma. The role of oncogene expression is not yet as clearly defined as it is for some of the other lymphoid malignancies.

**Standard Therapy**

The clinical picture of multiple myeloma, although varied, has a number of characteristic features primarily attributable to the accumulation of paraprotein-producing cells. Complications include osteoporosis, lytic bone lesions, pathologic fractures, repeated infections, progressive pancytopenia, hypercalcemia, proteinuria, and renal failure. Although there have been anecdotal reports of pathologic cures after conventional chemotherapy [30], myeloma remains an incurable disease. Median survival duration ranges from 6 to 64 months, depending on the stage at presentation. Treatment does prolong survival, however, and can be very effective in palliating symptoms.

**Melphalan plus Steroids**

Melphalan was first used to treat myeloma patients three decades ago. Up to 70% of patients show a significant decrease in tumor burden with this alkylating agent. Despite attempts to intensify the initial treatment of myeloma using multidrug, non-cross-resistant regimens, a recent meta-analysis suggests that the mainstay of therapy remains single-agent alkylator therapy in conjunction with steroids [31]. Oral melphalan, in combination with monthly prednisone, is well tolerated, and has remained the standard treatment for multiple myeloma. Most responding patients reach a response plateau after 6 to 12 cycles of therapy. Prolonged maintenance therapy has not been shown to be useful and is associated with a high incidence of secondary leukemias.

**Regimens for Relapsed and Refractory Disease**

There has been progress in treating relapsed and refractory disease. In 1984, Barlogie et al first reported on the effectiveness of continuous-infusion vincristine plus Adriamycin and oral dexamethasone (VAD regimen) in patients with refractory myeloma [32]. The rationale, in the VAD regimen, for the protracted administration of vincristine and doxorubicin by continuous infusion over 4 days, rather than by bolus injection, was to expose the tumor cells with low growth fractions to these cytotoxic agents over a longer period. Also, a continuous infusion of doxorubicin appears to reduce the risk of anthracycline-associated cardiomyopathy.

Barlogie et al subsequently compared high-dose dexamethasone alone with VAD in patients with resistant myeloma [33]. In previously unresponsive patients, dexamethasone and VAD had similar response rates. In relapsed patients, the response rate was higher in those treated with VAD. These results suggested an inherent difference between primary and acquired drug resistance.

**Drug Resistance**

Although myeloma is initially very sensitive to cytotoxic agents, eventual development of drug resistance is a major problem.

**Multidrug Resistance**

Acquisition of the multidrug resistance phenotype results from overexpression of the membrane-associated efflux pump, \textit{p}-glycoprotein. Overexpression of \textit{p}-glycoprotein confers resistance to multiple, natural product drugs and plays an important role in myeloma drug resistance.

A growing body of evidence indicates that \textit{p}-glycoprotein expression in myeloma correlates with prior chemotherapy [34]. Grogan et al examined 106 bone marrow samples from myeloma patients with an immunocytochemical assay for \textit{p}-glycoprotein. Patients with no prior therapy had a low incidence of \textit{p}-glycoprotein expression (6%), whereas those who had received prior chemotherapy had a much higher incidence (43%). In the prior-chemotherapy group, the incidence of \textit{p}-glycoprotein positivity was associated with the total doses of vincristine and doxorubicin (drugs both known to be affected by the \textit{p}-glycoprotein efflux pump).
The landmark observation that the calcium-channel blocker verapamil could overcome multidrug resistance in mouse leukemia [35] set the stage for clinical studies of p-glycoprotein pump blockers in myeloma. Dalton et al [36] showed that administration of verapamil along with VAD chemotherapy partially circumvented drug resistance in patients whose tumors overexpressed p-glycoprotein. High-dose verapamil is associated with severe cardiovascular side effects, and therefore, other p-glycoprotein blockers have been studied, most notably quinine. The Southwest Oncology Group is currently sponsoring a phase III trial that is randomizing myeloma patients to induction therapy with VAD vs VAD plus quinine in an attempt to prevent the acquisition of multidrug resistance.

**Glucocorticoid Resistance**

Less data are available on the mechanisms of glucocorticoid resistance in myeloma. Rosen et al recently detected high levels of a variant glucocorticoid receptor messenger RNA with a deletion in its 3' end in a hormone-resistant human myeloma cell line [37]. This cell line had no detectable abnormalities in the glucocorticoid receptor gene, suggesting transcriptional or post-transcriptional events as the cause of this phenotype.

**High-Dose Therapy**

**With Allogeneic Bone Marrow Transplantation**

Studies of attempts to cure myeloma with high-dose chemoradiotherapy and allogeneic bone marrow transplantation are ongoing. Unfortunately, only 5% of myeloma patients are eligible for such studies. The most common reasons for ineligibility are advanced age and the lack of a suitable donor. Recently, the European Group for Bone Marrow Transplantation reported their results with allogeneic transplantation in 90 multiple myeloma patients [38]. The median age of patients who underwent transplantation was 42 years. Transplant-related mortality was 38%, and the rate of disease-free survival at 3 years was 31%. These findings, as well as similar data from the Seattle Bone Marrow Transplant Team [39] and the University of Arkansas [40] (on 27 and 19 patients, respectively), suggest a plateau in disease-free survival at 3 years post-transplantation. All three studies show a trend toward longer survival among patients with chemosensitive disease, and among patients who have received only one first-line treatment regimen prior to transplantation. The fact that grade 1 graft-vs-host disease predicted better long-term survival in the European study is suggestive evidence for a graft-vs-tumor effect. Clearly, at present, there are no clear guidelines for referral of myeloma patients for allogeneic bone marrow transplantation. However, any patient less than 55 years of age who has an HLA-matched sibling should be considered a candidate, given the fact that no other treatment regimen has proven to be curative.

**With Autologous Bone Marrow Transplantation**

A growing body of experience with the use of autologous bone marrow support to facilitate the administration of very-high-dose chemotherapy in myeloma has emerged. Alkylating agents have a steep dose-response curve in lymphoid malignancies, and the use of autologous stem-cell rescue can increase tolerated doses by several-fold. High response rates to single-agent melphalan at doses of 80 to 140 mg/m² have been reported even in patients with refractory disease [41]. A significant increase in response and survival rates is seen as the melphalan dose is increased from 100 to 200 mg/m², or to 140 mg/m² with total-body irradiation [42]. Unlike allogeneic transplantation, protocols for autologous transplantation are well tolerated by patients up to 65 years of age. Initial studies were carried out in patients with advanced or refractory disease. Even in these two groups unlikely to derive maximal benefit from autologous marrow transplantation, 50% of patients exhibited a 75% decrease in tumor burden [43]. Because the duration of response was generally short lived in such patients, focus shifted to performing transplants at an earlier stage of disease. A British study reported an unprecedented, 50% complete remission rate (defined as complete absence of any M-component and < 5% bone marrow plasma cells) when patients with previously untreated, advanced stage myeloma were treated with three cycles of standard chemotherapy followed immediately by high-dose melphalan (200 mg/m²) and bone marrow rescue [44]. The vast majority of myeloma patients undergoing autologous transplantation have been conditioned with melphalan alone or in combination with total-body irradiation. No other regimens have been studied as extensively. In the past, rates of morbidity and mortality associated with these high-dose regimens were prohibitive, ie, more than 30%. However, by shortening the time to marrow recovery with the use of peripheral blood stem cells and cytokines, this figure has been markedly
Timing of High-Dose Therapy--The timing of high-dose therapy for myeloma is critical. It is reasonable to employ high-dose therapy early, since there is concern for stem-cell damage secondary to the protracted use of alkylating agents. Aside from the acute risks of repeated myelosuppression, protracted alkylating agent therapy also increases the risk of secondary leukemia and myelodysplastic disease [45].

A trial at the University of Arkansas looked at the feasibility and efficacy of marrow-ablative chemoradiotherapy supported by unpurged autologous bone marrow grafts and sought to define prognostic variables [46]. Multivariate analysis showed that responsive disease, low tumor burden, and less than 2 years of prior therapy predicted higher complete remission rate in patients undergoing autologous transplantation.

The only randomized study of high- vs conventional-dose therapy in multiple myeloma was recently reported by French researchers [47]. An interim analysis of the first 100 patients with follow-up of 1 year or more from diagnosis revealed that the response rate, duration of response, and progression-free survival rate were improved by autologous transplantation, as compared with conventional chemotherapy. Data on overall survival are not yet available.

Contamination of Autologous Grafts--The possibility of reinfusion of marrow or peripheral blood myeloma tumor cells during autologous transplantation has been a theoretical hurdle to the use of this technique. The vast majority of myeloma patients receiving autologous marrow transplants have had gross contamination of marrow with monoclonal plasma cells at the time of harvest. However, when a multivariate analysis was done to assess the impact of various pretransplant characteristics on outcome, the marrow plasma cell percentage (below 30%) at the time of harvest had no effect on remission rate or median survival [46].

Studies evaluating monoclonal antibody, 4-hydroxycyclophosphamide, and immunotoxin purging are ongoing, but so far show no survival advantage. It seems more likely that myeloma patients who relapse after autologous transplantation do so because of failure of the preparative regimen to eradicate all clonogenic tumor cells. The high frequency of relapse after allogeneic transplantation supports this theory.

Gene marker studies currently underway at the National Heart, Blood and Lung Institute and elsewhere should answer the question of whether contaminated autografts contribute to relapse in myeloma. The problem is compounded by our inability to clearly define the myeloma "stem cell" phenotypically, which makes the choice of purging agents and assessment of purging efficacy much more difficult.

Newer approaches to defining the "stem cell" genotypically are more promising for the detection of minimal residual disease. Recently, it has been reported that purified CD34+ progenitor cells can serve as effective, tumor-free hematopoietic support in myeloma patients undergoing myeloablative therapy [48].

Potential Benefits of Peripheral Stem-Cell Rescue

There are many reasons to consider the use of peripheral blood stem cells rather than autologous bone marrow to rescue patients receiving high-dose therapy. First, peripheral blood stem cell harvests can be performed on an outpatient basis, bypassing the potential morbidity of marrow harvesting and anesthesia. Also, stem cell harvesting may be performed in situations where marrow harvesting is not possible, for example, after pelvic irradiation. It is also believed that peripheral blood stem cells are contaminated with malignant cells to a lesser extent than are harvested bone marrow cells.

Another reason for considering the use of peripheral blood stem cells is that they clearly increase the speed of engraftment, compared with autologous bone marrow. This is expected to result in decreases in morbidity, time in hospital, and cost.

Stem cells can be collected under several conditions, including steady-state, following cytokine stimulation, and following hematopoietic recovery from chemotherapy, with or without cytokine stimulation. It should be noted, however, that the shortened engraftment time achieved with peripheral blood stem cell transplantation has been observed only when stem cell collections were mobilized by a combination of chemotherapy and cytokines. Multiple investigators have achieved powerful mobilization of peripheral blood stem cells with high-dose cyclophosphamide (Cytoxan, Neosar) plus hematopoietic growth factors [49].

Lastly, it has been suggested that peripheral blood stem cell transplantation may provide a more rapid immune reconstitution, since a majority of the mononuclear cell population in the peripheral blood are T-cells [50]. The peripheral blood also contains a larger number of natural killer cells than does the bone marrow. This may provide an opportunity to selectively amplify cells responsible for...
antitumor or autologous graft-vs-disease effects.

High-dose chemotherapy and peripheral blood stem cell transplantation have been used most frequently for the treatment of multiple myeloma in Europe. Fermand et al treated 63 myeloma patients with stage 2 and 3 disease, half of whom were previously untreated [51]. These investigators used a high-dose CHOP (cyclophosphamide, Adriamycin, Oncovin, and prednisone) regimen without growth factors for peripheral blood stem-cell mobilization. Previous exposure to chemotherapy was the main factor that negatively affected stem-cell harvest.

Patients were then treated with monthly VAD for an average of three cycles before receiving myeloablative therapy (carmustine [BiCNU], etoposide [VePesid], melphalan, cyclophosphamide, and 1,200 cGy of total-body irradiation) and peripheral blood stem-cell transplantation. There were seven early deaths, but by 6 months post-transplantation all remaining 56 patients were in remission by standard criteria (71% of whom either were in complete remission or had minimal residual disease). Median survival duration in these patients has reached 5 years. All peripheral blood stem-cell grafts resulted in sustained trilineage hematopoiesis. This is certainly impressive data given the expected poor prognosis of the patients studied.

**Ex Vivo Hematopoietic Cell Expansion**

Most recently, work has focused on ex vivo expansion of hematopoietic cells. Koller et al have reported that human stem and progenitor cells can be expanded tenfold from bone marrow mononuclear cell populations over 14 days in a continuously perfused culture system (bioreactor system) [52]. Prolonged culture appears to give normal progenitor cells a selective advantage over leukemic progenitors [53].

Ex vivo expansion may be expected to reduce harvest time and decrease the infusion dose required for bone marrow reconstitution. The ability to expand early progenitor stem cells in culture could lead to profound improvements in our ability to support patients through high-dose chemotherapy. Also, in the future, ex vivo expansion may permit transplantation in situations in which adequate numbers of either bone marrow progenitors or peripheral blood stem cells cannot be collected.

**Biologics**

In vitro and in vivo studies have demonstrated that the biologic response modifier alpha-interferon is effective against multiple myeloma. In clinical studies, alpha-interferon has been used as a single induction agent or in combination with conventional chemotherapy for previously untreated or relapsed myeloma patients and patients with refractory or resistant disease.

When used alone for induction therapy, alpha-interferon achieves response rates somewhat lower than those seen with chemotherapy. However, survival is comparable. The combination of alpha-interferon and conventional induction therapy produced a significantly higher response rate and response and survival durations than conventional therapy alone [54]. The impressive overall response rate of 20% observed with alpha-interferon in refractory and resistant myeloma makes this agent one of the most effective second-line treatments for myeloma [55,56].

Mandelli et al demonstrated that the duration of remission was prolonged in patients who were randomized to maintenance treatment with alpha-interferon after induction chemotherapy and disease stabilization [57]. The rationale is that the patient's own antitumor defenses, bolstered by biomodulators such as interferon, will have the best chance of working in the setting of minimal disease.

The major side effects of chronic alpha-interferon administration are a self-limited flu-like syndrome, mild myelosuppression, weight loss, headaches, and mental depression. The dose employed for maintenance therapy in myeloma is generally well tolerated; however, the optimal dose and schedule remain to be established.

**Conclusion**

Although much has been learned about the biology of the B-cell malignancies, little improvement in the 5-year survival rate for multiple myeloma has been seen since the mid-1970s. Multiple myeloma remains a uniformly fatal disease, with a median survival from diagnosis of no more than 30 months. High-dose cytotoxic chemoradiotherapy with stem-cell support offers the possibility of long-term eradication of the disease. The use of biologic response modifiers can be expected to prolong the remissions achieved with such therapies.

Ongoing studies are exploring mechanisms of drug resistance in myeloma, and how they may be averted. One focus of such studies is the potential to reverse or inhibit expression of p-glycoprotein.
In addition, new interventions directed at the complex cytokine networks that are involved in the pathogenesis of myeloma, such as interleukin-6, may yield potential targets for novel therapies.

**References:**


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