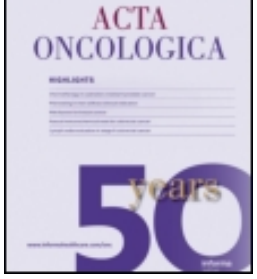

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Treatment Approaches for Relapsing and Refractory Multiple Myeloma

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Relapsing patients with multiple myeloma show a response rate higher than 50% with the resumption of the initial chemotherapy. However, since the duration of second responses are short, HDT/autotransplantation is recommended in patients with sensitive relapse. In patients with primary refractory myeloma the best treatment approach seems to be early HDT/autotransplantation. It is crucial to recognize a subset of patients who do not respond to the initial chemotherapy but who have non-progressive disease in order to avoid the administration of salvage regimens until clinical disease progression occurs. The treatment of patients with refractory relapse is disappointing. The most promising agent in this situation is thalidomide. Patients with late relapse after autologous transplantation can benefit from a second autologous transplant. The results of the allogeneic transplantation after autotransplantation are disappointing. In heavily pretreated resistant patients a conservative approach with alternate day prednisone (30 to 50 mg) along with pulse cyclophosphamide (800 to 1200 mg every 2 to 3 weeks) is recommended.

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Patients with multiple myeloma (MM) who fail to respond, relapse or become refractory to first-line treatment show a low response rate and usually a short survival to subsequent salvage therapies (1–3). The management of these patients with refractory myeloma is truly challenging. First, we briefly review the treatment of patients with relapsing MM. Secondly, we summarize the treatment options for primarily refractory myeloma (progression or no response to initial therapy) and secondarily resistant myeloma (refractory relapse). Finally, we discuss the salvage treatment approaches after relapse from allogeneic or autologous transplantation as well as the treatment recommendations for heavily pretreated patients.

RELAPSE OFF THERAPY

In patients who respond to the initial treatment and relapse once the induction therapy has been completed, the resumption of the same chemotherapy results in a response rate higher than 50% (4, 5). However, the duration of response significantly decreases with successive relapses and the median survival from relapse is about one year. Thus, the Canadian group reported that 36 out of 63 (57%) patients relapsing off therapy (unmaintained remissions) achieved a second response with the resumption of regression analysis showed that the degree of reduction in the M-protein size with the initial treatment and the absence of symptoms at the time of relapse were the factors associated with a significantly higher probability of achieving a second response (4). In the study by Paccagnella et al. (5), 26 out of 38 (69%) patients responded when the M2 protocol (VBMCP) was re-initiated at the time of relapse. This study clearly showed a significant shortening in the median duration of response after the initial therapy, first re-treatment and second re-treatment with the same VBMCP regimen (22 vs. 11 vs. 6 months, respectively).

Taking these results into account, particularly the short duration of second responses, high-dose therapy (HDT) followed by stem cell rescue should be considered whenever possible in patients with sensitive relapse. In fact, in a randomized trial designed to assess the optimal timing of HDT followed by peripheral blood stem cell (PBSC) rescue, patients who underwent a rescue transplant, because of either primary resistance to VCMP or relapse, had a survival identical to that of patients receiving HDT/autotransplantation as part of up-front therapy (6). An interesting finding is that the 2-years' survival after relapse in 45 relapsing patients was 59%. Although there

autotransplantation versus conventional chemotherapy in relapsing patients, there is general agreement in that HDT/PBSC rescue should be considered whenever possible in MM patients with sensitive relapse.

PRIMARY RESISTANCE

The median survival of patients with primary refractory MM is about 15 months (4). Patients with primary resistant disease seem to benefit from early myeloablative therapy followed by autotransplantation, since tumor resistance can be transiently overcome with HDT. In fact, it has been suggested that this subset of patients is the one most likely to benefit from HDT/autotransplantation (7). However, it is crucial to identify patients with primary refractory myeloma early in the course of the disease in order to prevent the emergence of resistant subclones. In the MD Anderson series, 19 out of 27 (70%) patients with primary resistant disease who received a rescue transplant during the first year after diagnosis achieved an objective response (7). Furthermore, patients who were given an early transplant survived significantly longer than 60 patients with primary resistant disease who were continued on conventional chemotherapy. Response rate, progression-free survival and overall survival were also significantly lower in those primary resistant patients treated with rescue transplant later in the course of the disease (7). In a multivariate regression analysis, including 135 patients with resistant MM from the University of Arkansas who were given HDT, the two variables most significantly associated with a longer event-free and overall survival were: 1) a low β2-microglobulin serum level and 2) primary resistance (as opposed to resistant relapse) (8). In this study, the response rate among 72 primary resistant patients was 62%, while the median event-free and overall survival were 21 and 47 months, respectively.

When HDT is not feasible, treatment with VAD or dexamethasone alone produces a 25% response rate in alkylating resistant disease (9). In the PETHEMA experience, the response to VBAD in primary resistant patients was significantly higher than that in patients who became resistant after a prior response—refractory relapse—(48% vs. 24%, respectively) (10).

NON-RESPONDING, NON-PROGRESSIVE MYELOMA

It is important to recognize the subgroup of patients with the so-called 'non-responding, non-progressive' myeloma (4, 11). In our experience, these patients usually present with a high serum M-protein, frequently of IgG type, a high proportion of bone marrow plasma cells, moderate anemia, and symptoms of hyperviscosity or bacterial infections, particularly pneumoccocal pneumonia. However, patients have a high-mass, smoldering disease. The reason for treatment is usually the presence of a certain degree of anemia or recurrent infections. If, for any reason, these patients are treated and no changes in their paraprotein levels and clinical status are observed after 4 to 6 courses of chemotherapy, these patients should not be given salvage chemotherapy regimens unless disease progression occurs. Although these patients are normally classified as 'non-responders', they in fact have a prolonged survival because of the temporarily 'non-progressive' nature of the disease (12, 13). It is likely that the small proportion of long-survivors that appears at the end of survival curves of resistant patients mainly comprises this subset of patients.

REFRACTORY RELAPSE TO ALKYLATING AGENTS

Second-line treatment for refractory myeloma produces disappointing results because of both a low response rate to salvage therapy and the short duration of clinical response. With the combination of vincristine, BCNU, doxorubicin and prednisone (VBAP), response rates of about 25% as well as survival prolongation for responding patients have been reported (13, 14). A modification of the VBAP regimen, in which prednisone was replaced by dexamethasone (VBAD), produced a response in more than one-third of the patients (10). The highest response rate in patients with MM refractory to alkylating agents has been reported with the four-day continuous infusion of vincristine and adriamycin, along with high-dose dexamethasone (VAD) (15). The inconveniences of VAD are that vincristine and doxorubicin have to be given through a central venous catheter and that there is a significant steroid toxicity, particularly infections and miopathy. Another aspect of the VAD treatment that has not received much attention is that the median duration of response is usually less than 9 months (15–17). High-dose glucocorticoids, particularly dexamethasone, produce a response rate of 20 to 25% in refractory patients (9). It is of interest that VAD or dexamethasone alone are equally effective in the treatment of patients with primary refractory myeloma, while VAD is superior to dexamethasone alone for relapsing refractory patients (9). It is our current policy to treat patients with alkylating resistant relapse with courses of VBAD administered every 4 weeks, giving the dexamethasone on days 1–4 and 9–12 of each course.

It has been suggested that the lack of response to VAD in MM is due to the expression of the multidrug-resistant phenotype (MDR). Multidrug resistance is characterized by the expression of glycoprotein p-170 encoded by the MDR-1 gene. Attempts to prevent or overcome the MDR in resistant myeloma with verapamil or quinine have been disappointing (18). It has been reported that clinical resis-

association could be found between response to VAD and MDR-1 expression, which suggests that in MM there are mechanisms of resistance other than MDR (20, 21). The efficacy of the association of VAD with the cyclosporin analog PSC 833, which is a potent chemosensitizer and less nephrotoxic and immunosuppressive than cyclosporin A, is currently being investigated in prospective trials in relapsed and refractory patients.

The combination of etoposide, dexamethasone, cytarabine and cisplatinum (EDAP) produced a 40% response rate in heavily pretreated patients, but this regimen was extremely myelosuppressive and the patients' median survival was short (22). Other recently introduced intensive regimens consisting of cyclophosphamide/etoposide (23), cyclophosphamide/teniposide/dexamethasone (24), or cyclophosphamide/dexamethasone/idarubicin/etoposide (25), usually given with cell growth factors, produce a high response rate. However, the duration of both response and survival is short. In addition, these regimens produce a severe myelosuppression, as well as being costly. When considering the treatment of resistant myeloma, toxicity, which results in a decrease in the quality of life, and cost should be weighed against a doubtful prolongation of survival when compared with more conservative approaches. Probably these regimens should only be indicated to rapidly decrease the tumor burden of patients in whom a subsequent HDT followed by autologous or allogeneic stem cell rescue is planned (23).

The results of monotherapy with a number of different agents (hexamethylmelamine, high-dose cytarabine, chorozotocin, mitoxantrone, vincristine, vindesine, m-AMSA, VM-26, deoxicoformycine, epirubicin, 2-clorodeoxiadenose, retinoic acid, clarithromycin, interferon -IFN-) have been disappointing (1–3). San Miguel et al. (26) treated 51 refractory patients with IFN-alpha2b plus high-dose dexamethasone. Thirty-seven of these patients completed the induction period and 18 (48%) attained an objective or partial response. In contrast, Alexanian et al. (27) reported that the combination of dexamethasone or VAD with IFN-alpha did not improve either the response duration or survival when compared with historical controls using dexamethasone or VAD alone.

Topotecan, a topoisomerase I inhibitor, was administered to 43 patients with relapsing (25 pts) or primary resistant (18 pts) myeloma in a SWOG trial (28). All of these patients had each received only one chemotherapy regimen. The overall response rate was 16%. Responses were observed in both relapsed and refractory patients. The median progression-free survival was 13 months and the median overall survival was 28 months. The major limiting toxicity of topotecan was myelosuppression, particularly grades 3 and 4 granulocytopenia, which occurred in 93% of the patients (28).

patients have shown an encouraging objective response rate of 46% (18/39) plus 31% (12/39) of minimal responses (29). Of the 18 patients who achieved an objective response, 11 were in response at the time of the report with a median duration of response still not reached with a range from 71 to 907+ days. Based on these encouraging results, a large phase III trial comparing vinrelbine/dexamethasone versus dexamethasone alone is currently in progress.

Treatment with anti-interleukin-6 antibodies was administered to 10 patients with advanced MM (30), resulting in the inhibition of C-reactive protein (CRP) production and in a decrease in the plasma cell LI. Unfortunately, no improvements in the patients' clinical status or decreases in the amount of M-protein were observed. It is of interest, however, that one patient with primary plasma cell leukemia, who was producing low amounts of IL-6, had a complete inhibition of C-reactive protein production and achieved a 30% reduction in the M-component size for 2 months, but a relapse occurred after treatment with anti-IL-6-MoAb was stopped (30).Thalidomide, an antiangiogenic agent, was given to 89 high-risk refractory myeloma patients (31). A decrease in M-protein of more than 50% was observed in 20% of the patients, while an additional 14% achieved a reduction in M-protein of between 20 and 50%. Of note, 46% of responders in whom a bone marrow aspiration was carried out showed a disappearance of the bone marrow plasmacytosis. The thalidomide toxicities were: neurologic (75%), gastrointestinal (66%) and constitutional symptoms (60%). At the time of the report, the follow-up was still too short to give a reliable assessment of the duration of response.

The first studies of HDT/autotransplantation in MM were performed in patients with advanced refractory disease. Although the response rate was high (50–85%), the event-free and overall survival were short, ranging from 4 to 6 months and 4 to 15 months, respectively (32–34). In a large, single institution series, including 63 patients with refractory relapse MM, the early death rate after HDT/autotransplantation was 14% and the overall response rate 59% (8). Median event-free and overall survival were 8 and 15 months, respectively. As mentioned above, in the latter series, patients with primary resistant disease had a more favorable outcome than those with a refractory relapse (8). In a recently published cooperative study by the SWOG, including 66 assessable (intent-to-treat) patients with refractory MM (80% refractory relapse, 20% primary resistance), the response rate was 58% and the median progression-free and overall survival periods from initial registration were 11 and 19 months, respectively (35). The actuarial 3-year progression-free and overall survival rates were 25% and 31%, respectively. Although these results are better than those previously published, patients with re-

RELAPSE AFTER TRANSPLANTATION

Relapse after allogeneic transplant

One of the major obstacles to the success of allogeneic transplantation for myeloma is failure to eradicate the disease in the majority of cases. According to the European Registry experience, 40% of evaluable patients do not achieve a complete remission post-transplant. Furthermore, the probability of relapse in those patients who do enter complete remission (CR) is 45% at 5 years and late relapse continues to occur (36). A graft-versus-myeloma effect of donor lymphocyte infusions (DLI) has been demonstrated in patients with MM (37–39). Despite its efficacy, DLI is associated with significant morbidity and mortality. Thus, graft-versus-host disease (GvHD) has been reported in up to 80% and marrow aplasia in up to one-third of patients (40). These complications result in a treatment-related mortality of around 20%. It has been reported that 8 out of 13 patients with relapsed myeloma after allogeneic bone marrow transplantation responded to DLI (41). Acute and chronic GvHD occurred in 66% and 55% of all patients, respectively, and two patients developed fatal marrow aplasia. The factors associated with response to DLI were a T-cell dose $> 1\times 10^8$/Kg and the occurrence of GvHD (41).

Relapse after autologous transplantation

High-dose therapy followed by autologous stem cell rescue is increasingly being performed as part of up-front therapy in MM. However, the majority of patients receiving an autograft will subsequently relapse and will require salvage therapy. Tricot et al. (42) reported the results with salvage therapy in 94 patients who had relapsed after autotransplantation. Salvage treatment consisted of standard chemotherapy in 53 patients and a rescue transplant in the remaining 41 (31 autologous, 10 allogeneic). The projected survival at 18 months after salvage therapy for all 94 patients was 59%. In a multivariate regression analysis, low beta-2M (< 2.5 mg/l) and late relapse (> 12 months) were identified as the independent factors significantly associated with a favorable outcome. Thus, the CR rate and overall survival rate at 18 months for the 51 patients who had at least one favorable variable were 18% and 79%, compared with 2% and 38% for the remaining 43 patients with no favorable parameters. Finally, transplantation performed as salvage therapy was associated with a significantly survival prolongation when compared with standard treatment. Nevertheless, this might simply reflect an unavoidable bias favoring the transplant group (i.e. none of the patients in the transplant group had previously received two transplants versus 43% in the patients given conventional salvage chemotherapy; 61% of patients in the transplant arm had low beta-2M compared with only 32% of those in the chemotherapy group) (42).

The results of salvage therapy with allogeneic transplantation after autologous transplant have been disappointing. Transplant-related mortality within the first 100 days was almost 20%. Although 42% of patients achieved a complete remission, the median event-free and overall survival rates were 19 and 24 months, respectively; 19% of patients had grade 3 or 4 GvHD. One patient died of cytomegalovirus pneumonia and six from invasive aspergillosis (43). In our opinion, the high transplant-related morbidity/mortality precludes allogeneic transplantation as a rescue option after relapse from HDT/autologous stem cell rescue.

HEAVILY PRETREATED MYELOMA

Unfortunately, all patients with MM will become refractory to therapy during the course of their disease. A conservative approach is recommended for the management of patients resistant to current treatment strategies (i.e. alkylating agents, dexamethasone-based regimens—VAD or VBAD—and HDT/stem cell rescue) as well as in those in whom the above treatments are not feasible (elderly patients, poor performance status, severe pancytopenia). Appropriate supportive care with antibiotics, transfusions, analgesics and local radiation is required. Along with these general measures we are using a gently chemotherapy approach with alternate-day prednisone (30–50 mg) combined with a pulse dose of intravenous cyclophosphamide (800–1 200 mg) every 2 to 3 weeks. Although this treatment produces objective responses in very few resistant patients, it is a palliative regimen that can temporarily control the disease, and with a very low toxicity (44). While it is true that intensive chemotherapy can transiently overcome drug resistance, the responses are usually brief and these approaches are costly and life-threatening, resulting in prolonged hospitalization in patients with a short life span.

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