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THERAPY FOR MULTIPLE MYELOMA - HISTORICAL PERSPECTIVE: REVIEW OF LITERATURE

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ABSTRACT

The current therapeutic strategy for multiple myeloma has witnessed a dramatic improvement when compared with the rhubarb pill and infusion of orange peel that were used in 1844. It is still an incurable disease but the introduction of novel therapies have altered the natural course of the disease, transforming it into a chronic disease from a terminal illness. Recently an increased understanding of the interaction between the malignant plasma cells and the bone marrow microenvironment, cell-receptor ligand interactions and intracellular signalling pathways, have provided multiple opportunities to disrupt the development and progress of multiple myeloma. Following the success of thalidomide, lenalidomide, and bortezomib in multiple myeloma, a number of novel agents are currently investigation. These targeted therapies may enable personalization of therapy for individuals with myeloma in future.

INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell malignancy, characterized by the proliferation of neoplastic plasma cells. It's the most important of the class of diseases included under the plasma cell dyscrasias. Multiple myeloma is a clonal plasma cell neoplasm characterized by the proliferation of plasma cells in the bone marrow, monoclonal protein, osteolytic bone lesions, renal disease, and immunodeficiency. Delineation of the mechanisms mediating plasma cell proliferation, survival and migration in the bone marrow microenvironment may enhance the understanding of pathogenesis, and a better understanding of the molecular pathogenesis is fundamental to developing more effective prognostic, therapeutic and preventive approaches. Recent therapeutic options for multiple myeloma have witnessed a dramatic improvement when compared with the previous rhubarb pill and infusion of orange peels that was used in 1844 (Table - 1).[1] Although multiple myeloma still remains an incurable disease, incremental advances have altered the natural course of the disease, improving survival and for a sizeable proportion transforming it from a terminal illness into a chronic disease.[2] The principal determinant for therapeutic intervention in patients with myeloma is the presence or absence of clinical signs and symptoms. Asymptomatic patients with multiple myeloma (known as smoldering myeloma) are not indicated for treatment because of the absence of clear benefit with currently available antimyeloma therapies and some patients remain stable without treatment over extended periods of time.[3]

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INDUCTION CHEMOTHERAPEUTIC REGIMENS

Melphalan and Prednisone (MP) Chemotherapy

In old days without therapy, the median survival of a patient with active myeloma was approximately five to six months. In the history, Blokhin et al. first reported the usefulness of scarolysin (a racemic mixture of the d- and l-isomers of phenylalanine mustard) in three of six patients with multiple myeloma.[4] The d- and l-isomers were later separated and the antimyeloma activity was found to reside in the l-isomer, which was known as melphalan. Subsequently, Bergsagel et al. demonstrated the efficacy of melphalan in 14 out of 24 patients with multiple myeloma, [5] which was further confirmed by others.

Table 1. Multiple myeloma—a historical overview of myeloma from its first description in 1844 to the present

Rhubarb and orange	1844	First documented case
Steel and quinine	1845	Abnormal urine protein deleted
Plasma cell deleted	1895	
	1928	First large myeloma case series
Serum protein spike identified	1939	
	1956	Identification of light chains
Melphalan	1958	
	1962	Corticosteroids
Cyclophosphamide	1964	
	1974	VBMCP
Durie –Salmon staging	1975	
	1979	Interferon
High dose melphalan	1983	ASCT
VAD	1984	
	1999	Thalidomide
Bortezomib	2002	Lenalidomide
International stage system	2005	Cytogenetic classification

VBMCP: Vincristine, Carmustine, Melphalan, Cydophosphamide, and prednisone, VAD: Vincristine, Doxorubicin, and Dexamathasone, ASCT: Autologous stem cell transplantation

The melphalan and prednisone (MP) regimen has shown a partial response in 50-60% of multiple myeloma patients, while 3-5% of patients achieving a complete response. The median response duration is approximately 18 months and overall survival is 24 to 36 months. Because of the wide variability in gastrointestinal tract absorption and the high risk of cytopenia with increased doses, intravenous formulations of melphalan along with oral prednisone and dexamethasone have been tried with improved response rates.[6] Moreover, MP regimen should not be used as induction therapy in patients eligible for high-dose therapy and stem cell transplantation because the ability to mobilize adequate numbers of stem cells decreases with prolonged use of this combination.[6,7]

Vincristine-Doxorubicin (Adriamycin)-Dexamethasone (VAD)

Chemotherapy

After its introduction in the year 1980, the VAD regimen quickly became one of the most commonly used treatments for myeloma in the process of preparation for stem cell transplantation. Here, newly diagnosed patients with myeloma, eligible for transplant were given VAD for 4 to 6 cycles and then proceeded to transplantation. Infusional VAD when given as initial therapy produced overall and complete response rates higher than that reported for MP, but median survival was still approximately 36 months.[8] For many decades, VAD stood the test of time and became the standard induction regimen for multiple myeloma in major randomized trials. Despite its efficacy, the administration of VAD chemotherapy required a central venous line and continuous intravenous infusion for four days in every 3 to 4 weeks. Unfortunately, this resulted in a risk for catheter-related sepsis and thrombosis and led to exploration of other modified regimens including replacement of conventional doxorubicin with pegylated liposomal doxorubicin. Pegylated liposomal doxorubicin has several pharmacologic and safety advantages over conventional doxorubicin, including an extended circulation time and a significantly lower risk of cardiotoxicity, myelosuppression, GI problems and alopecia.[9]

In a phase II trial of pegylated liposomal doxorubicin, vincristine and reduced-dose dexamethasone [DVd) in 33 patients with newly diagnosed multiple myeloma, a response rate of 88% (12% complete responses, 76% partial responses) was demonstrated.[10] Several study groups have investigated the efficacy and safety of DVd regimen in multiple myeloma and have demonstrated that this regimen is well tolerated and produces response rates similar to those produced by the conventional VAD regimen.[9] DVd is associated with relatively less myelosuppression and fewer Grade 3/4 neutropenic events and fever, results in less cardiotoxicity, and does not require a central line or continuous infusion. However, the common side effects like neurotoxicity and cardiotoxicity associated with the use of vincristine and doxorubicin respectively, led some to question the use of VAD regimen in which two drugs (vincristine and doxorubicin) were perceived to have negligible single-agent activity.[11] Hence, the use of these regimens as initial therapy has declined substantially since the introduction of induction regimens combining Proteasome inhibitors and immunomodulatory drugs.[12]

Corticosteroids as Induction Therapy

With the use of single-agent high-dose dexamethasone therapy in myeloma, approximately 43% of newly diagnosed patients had a response, which is similar to that achieved with MP.[13] Even a retrospective study evaluated if single agent dexamethasone would be an effective induction therapy prior to high dose chemotherapy.[14] Including minimal responses, the overall response rate for dexamethasone and VAD was 74% and 86%, respectively ($p = 0.13$). No significant differences were observed in the progression-free and overall survival (OS) at one year post transplant. A recent study compared melphalan and dexamethasone (MD) with MP.[15] Although, the proportion of complete responses were higher in the MD arm, there was no significant difference in event-free survival and median overall survival (OS). The Intergroupe Francophone du Myélome (IFM) randomized 488 previously untreated myeloma patients, in between 65-75 years of age, to receive MP, MD, dexamethasone alone, or dexamethasone and interferon-α.[16] Although none of these regimens induced a significant number of complete responses, patients receiving Melphalan-Dexamethasone (MD) had a 70% overall response rate, which was significantly higher than that seen with any of the other three regimens. However, the MD regimen was associated with a higher risk of severe toxicity, most notably severe pyogenic infections (including pulmonary infections and septicaemia). Moreover, the higher response rate observed with MD regimen did not translate into either a significantly superior median time to disease progression or median overall survival.

Interferon

Interferon as a single antimyeloma agent has been reported to produce response rates of 15-20%.[6] However, in a non-randomized study of previously untreated patients with multiple myeloma, similar response rates were observed for patients treated with interferon-dexamethasone regimen (57%), and for those treated with dexamethasone alone (48%).[17] Moreover, Interferon also failed to achieve meaningful benefit after high- dose chemotherapy (HDCT).[18] It is associated with flu—like symptoms, weight loss,

impotence, depression, mental status changes, GI disturbances and cytopenia. Unfortunately, the lack of convincing efficacy and substantial toxicity has reduced the enthusiasm for this therapeutic agent.

Other Regimens

Several other combinations of chemotherapeutic antimyeloma agents have been tried in last few decades in an attempt to improve patient survival. Among these include the M2 [vincristine, carmustine, bis-chloronitrosourea (BCNU), melphalan, cyclophosphamide and prednisone] and the ABCM regimen (adriamycin, BCNU, cyclophosphamide and melphalan) among others.[19-21] However, a meta-analysis by the Myeloma Trialists' Collaborative Group failed to demonstrate any benefit of these combination chemotherapy regimens over MP regimen.[22]

ADVENT OF STEM CELL TRANSPLANTATION

McElwain and Powles pioneered the use of autologous bone marrow transplantation in a patient with plasma cell leukemia following high-dose melphalan (140 mg/m^2).[23] Later Barlogie et al. used a regimen combining melphalan 140 mg/m^2 and total body irradiation (850 cGy) followed immediately by autologous or allogeneic bone marrow transplantation in six myeloma patients refractory to chemotherapy.[24] Now autologous peripheral blood stem cell transplantation has replaced autologous bone marrow transplantation, as it avoids the need for patient anaesthesia and engraftment is more rapid.[6]

Determining Transplant Eligibility

One of the first steps in evaluating patients with multiple myeloma is to determine whether or not they would be considered a candidate for high-dose therapy or not.[25] Here, although age is the parameter most commonly used to determine transplant eligibility in clinical trials with most patients enrolled in randomized clinical trials studying autologous stem cell transplant (ASCT) being less than 65 years of age, in day to day practice the physiologic age, functional status and presence of co-morbidities are factors taken into consideration while determining candidacy for HDCT.[25,26] Even, studies have pointed out that age and even renal dysfunction are not absolute contraindications to transplantation.[27,28]

INDUCTION THERAPY FOR TRANSPLANT-ELIGIBLE PATIENTS

At present, if a newly diagnosed myeloma patient is considered a potential candidate for ASCT, initial therapy is aimed at maximizing disease control with the least stem cell toxicity. Classically, this includes 4 to 6 months of therapy with one or more commonly used chemotherapeutic regimens, followed by high—dose therapy and ASCT.[29] Induction therapy for transplant eligible patients has evolved a lot in the past decade. Although several induction regimen have been studied in such patients, till recently, comparative trials have been limited.[30] Until recently, the most commonly used induction chemotherapeutic regimen was a combination of VAD. At present, regimen involving bortezomib and immunomodulatory agents that have demonstrated activity in patients after disease progression following ASCT (recurrent or relapsed disease) have now been moved to frontline therapy as induction.[31] Current view that, stem cell toxins, such, as nitrosourea or alkylating agents may compromise stem cell reserve and regimens with these agents (notably melphalan) should be avoided in patients who are potential candidates for transplant. Moreover, myeloma patients refractory to initial therapy may show similar benefit to those who respond to induction therapy.[32]

HDCT WITH STEM CELL SUPPORT VERSUS CONVENTIONAL THERAPY

Currently, the role of high—dose chemotherapy (HDCT) with stem cell support in improving the outcome of patients with multiple myeloma has been evaluated in several clinical trials. In the IFM94[33] and The Medical Research Council Myeloma VII Trial[34], previously untreated multiple myeloma patients were randomly assigned to receive either conventional chemotherapy or HDCT followed by ASCT. The results of the IFM94 trial have demonstrated a significantly higher response rate in patients receiving intensive therapy (81%) than in those who received conventional chemotherapy (57%; $p < 0.001$). The probabilities of event—free survival and overall survival (OS) at five years were 28% and 52% in the intensive therapy group and 10% and 12% in the conventional-dose group ($p = 0.01$). Similar impressive response rates were also observed in the Myeloma VII Trial. The rates of complete response (CR) were higher in the intensive therapy group than in the conventional therapy group (44% vs 8%; $p < 0.001$). Moreover, intention-to-treat analysis showed a higher rate of progression-free survival (31.6 months vs 19.6 months; $p < 0.001$) in the intensive therapy group than in the conventional therapy group. Also, as compared with conventional therapy, intensive treatment increased median survival by almost one year; 54.1 months versus 42.3 months (p : 0.04). In contrast, the long-term results of a randomized control trial from the Group Myelome-Autogreffe confirmed a benefit of HDCT with stem cell support in terms of event-free survival and time without symptoms, treatment and treatment toxicity (TwiSTT), but could not provide evidence for superiority of HDCT over conventional chemotherapy in the overall survival of patients aged 55 to 65 years with symptomatic newly diagnosed myeloma.[35]

The Intergroupe study S9321 also yielded comparable response rates, and progression-free survival and overall survival (OS) in patients randomly assigned to either HDCT supported with ASCT or standard dose therapy.[18] The results of the Spanish Cooperative Group "PETHEMA" showed that HDCT intensification, when given to multiple myeloma patients who had responded to initial chemotherapy, significantly increased the complete remission rate but had no significant impact on progression-free survival and overall survival (OS).[36] Unfortunately, The contradictory conclusions reached in some of these trials may be as a result of prolonged courses of very intensive chemotherapy given as conventional treatment in those trials and high rates of cross-over negating potential survival benefits. Hence, the role of HDCT in the treatment of multiple myeloma needs reassessment in the era of novel agents. Currently, the high response rates seen with

the regimens incorporating novel agents have challenged the value of ASCT in multiple myeloma. Whether HDCT can be replaced by additional cycles of novel agents, still needs to be determined.[32]

Timing of first ASCT

Autologous ASCT may be performed early in the course of the disease (early transplant), immediately after 4 to 6 cycles of induction chemotherapy. However, it is also possible to adopt a strategy of induction to plateau stage followed by close observation with plans to transplant at the time of relapse (delayed transplant).[37] In a multicenter, prospective randomized trial designed to assess the optimal timing of ASCT, similar median overall survival times were noted in two groups, whether ASCT was performed early as a part of first-line therapy, or at first progression.[38] With a median follow-up of 58 months, estimated median overall survival (OS) was 64.6 months in the early HDCT group and 64 months in the late group (p = 0.92). Median event-free survival was 39 months in the early HDCT group whereas median time between randomization and failure of conventional treatment was 13 months in the late group. Average time without symptoms (TwiSTT) were 27.8 months and 22.3 months in the two groups, respectively. So, early HDCT may also be preferred because it is associated with a shorter period of chemotherapy. At present, the choice between the two approaches are based on patient preference, other clinical conditions, and risk factors.[25,37]

Role of Tandem Transplant

In view of the survival benefits observed with ASCT, it has been postulated that an additional ASCT (tandem ASCT) may offer even better outcomes. In a study evaluating previously untreated patients < 60 years of age, randomly assigned to either single or double transplant, there was significantly improved seven- year event-free survival (20 vs 10%; p = 0.03) and overall survival (42 vs 21%; p = 0.01) in recipients of double versus single transplant.[39] However, the beneficial effect of the second transplant on overall survival differed according to the response to the first transplant. In general Patients who achieved a complete response or very good partial response with the first ASCT did not benefit significantly from the second transplant. Also, by comparison, patients who did not have at least a very good partial response to the first transplant had a significant benefit from the second transplant. In the Bolonga 96 trial, the second ASCT significantly increased the probability to attain at least a near complete response (nCR; 33% vs 47%, respectively; p = 0.008), prolonged relapse- free survival (RFS) duration of 18 months (median, 24 vs 42 months, respectively; p < 0.001) and significantly extended event-free survival (EFS; median, 23 vs 35 months, respectively; p = 0.001).[40] Also as seen previously, benefits offered by double ASCT were particularly evident among patients who failed at least nCR after one auto transplantation.

A meta-analysis of six randomized controlled trials (RCT) enrolling 1,803 patients found that double ASCT is associated with improved response rates but at risk of clinically significant increase in treatment-related mortality.[41] Moreover, there was no difference in overall survival. Recent evidence suggests that a tandem ASCT can improve overall survival by about 10% compared with single ASCT. This effect is small because patients who relapse after a single ASCT can receive salvage ASCT, although there is controversy regarding the benefits of salvage transplant[42] The National Comprehensive Cancer Network (NCCN) Multiple Myeloma guidelines has recommend that a tandem transplant could be a valuable option in myeloma patients with less than a very good partial response after the first ASCT.[25]

Conditioning Regimens for ASCT

The goal of the conditioning regimen in myeloma patients undergoing stem cell transplant is to achieve the best response rate with minimum toxicity. Initial studies of ASCT included total body irradiation (TBI) as a component of the preparativeregimens.[25] The results of the Intergroupe Francophone du Myelome [IFM] 9502 trial concluded that 200 mg/m^2 melphalan is a less toxic and at least as effective conditioning regimen when compared with 8 Gy total body irradiation TBI with 140 mg/m2 melphalan.[43] The melphalan and total body irradiation (TBI) regimen was associated with more mucositis, longer hospitalization, and worse overall survival. Therefore, 200 mg/m^2 of melphalan should be considered as the standard of care for ASCT in multiple myeloma patients. Moreover, conditioning with melphalan plus TBI or melphalan plus cyclophos- phamide for second autotransplants within one year in patients responding to first autotransplant is feasible, but does not improve complete remission rates and may lead to an inferior outcome when compared to melphalan 200 mg/m^2, which is the conditioning regimen of choice for both first and second auto- transplants in responding patients.[44]

ALLOGENEIC TRANSPLANTATION

Currently, allogeneic hematopoietic Stem cell transplant is considered by several experts to be the only curative treatment for multiple myeloma. The presence of a graft-vs-myeloma effect mediated by immune competent donor lymphocytes is supported by the induction of sustained remissions following donor lymphocyte infusions after allogeneic stem cell transplant.1 Historically, the first successful syngeneic bone marrow transplantation for myeloma was reported in two physician brothers.[45] Subsequently, some small case series were reported in patients with multiple myeloma who received myeloablative allogeneic bone marrow transplant from an HLA-compatible sibling donor.[46,47]An analysis by the European Blood and Marrow Transplant Registry compared myeloma patients treated with allogeneic bone marrow transplant to those who received ASCT.[48] The median overall survival (OS) was significantly better in the autologous group (34 vs 18 months). The poorer survival rates in the allogeneic transplant group were explained by the higher treatment related mortality (41% vs 13%). Recently, nonmyeloablative transplant strategies designed to reduce treatment related mortality by depending more on the anti-tumor effect of the graft than on the initial cytoreduction achieved by the conditioning regimen have begun to be explored.[32]

Conclusion

The outcome of patients with multiple myeloma treated with conventional approaches, with or without high—dose

therapy/ASCT has resulted in a median survival of approximately 2 to 3 years and 5 to 8 years, respectively. However, the management of multiple myeloma is rapidly changing. With a better under- standing of the pathophysiology of the disease, novel agents designed to interrupt myeloma growth and survival pathways have come into clinical practice with unprecedented speed. With the introduction of novel agents such as thalidomide, lenalidomide, and bortezomib in the last decade, further improvements in long- term outcome for patients with multiple myeloma are expected. This improvement can result from better initial therapy for patients eligible and not eligible for stem cell transplant, from more effective salvage regimens for patients with relapsed/ refractory disease and finally from better supportive measures and general management.[49,50]

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