

REVIEW

The evolving background for high-dose treatment for myeloma

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In the constantly evolving field of myeloma, this special issue is slanted towards how the newer targeted treatments fit in with various transplantation strategies. High-dose treatment for myeloma with autologous stem cell transplantation started 25 years ago, with the consequence of producing complete remissions and a doubling of survival. Since then, its role has been refined and it has been accepted as standard treatment. The current challenge is to optimize its use into a background of the development, availability and regulatory approval of newer targeted therapies such as Thalidomide, Revlimid (Lenalidomide) and Velcade (Bortezomib). This special issue addresses these problems, and gives particular emphasis on the attainment of very long-term survival, with normal quality of life for patients with myeloma who do not necessarily need to be cured of their molecular disease, that is, they are ‘operationally cured.’ It is hoped that the reader will find the information in this issue useful in the day-to-day management of patients and we hope that this will also inspire new research directions designed to improve the outcome of patients with myeloma.

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Introduction

Our understanding of multiple myeloma (MM) has evolved significantly in the last decade, hence this myeloma special issue. We have attempted to deal with all aspects of MM and its treatment, focusing around high-dose therapy and stem cell transplantation (SCT). The chapters in this special edition cover the sequential treatment strategy that is now the basis of treating patients with MM. This sequence is as follows. Once patients have attained maximum response to induction therapy, they are considered for either a single

or double autologous peripheral blood SCT, or sibling or matched unrelated donor allogeneic SCT, or a reduced intensity conditioning (RIC) allo-SCT, either post auto-transplant or post induction. When relapse occurs, this treatment can be repeated, or other treatments sequenced into the programme. These treatment sequences have prolonged the survival of some MM patients into decades.^{1–5} We are very grateful to the distinguished panel of experts who have addressed these issues in this special issue and hope that this would help in promoting further research in this field. We are very thankful to John Goldman for facilitating this project.

High-dose therapy

Historically, it has been known for a quarter of a century that a single high-dose of melphalan can produce a profound anti-myeloma effect including complete remission (CR) in about a third of new patients and these patients will stay in CR for a median of 3 years.^{6,7} It was logical that combining this strategy with induction treatments produced an additive effect. The Table 1 shows the evolution of various high-dose strategies in patients with MM.^{4,7–12} According to the current healthcare purchasers needs for approval of treatment advances, high-dose auto-SCT has fulfilled these requirements for evidence based medicine in two major multicentre randomized trials.^{1,13} Current standard practice in patients younger than 65 years is to consolidate the response attained with induction therapy with melphalan 200 mg/m² followed by the peripheral blood stem cells. To this end, our second chapter relates to how we define the current position of high-dose chemotherapy and auto-SCT for patients under the age of 65 years and we follow this with a chapter on the importance of treating patients over the age of 65 years who constitute more than half the patients with MM. Issues relating to maintaining quality of life are crucial in this patient group. The transplant-related mortality (TRM) of an auto-SCT is currently less than 1% and this can be undertaken in community care settings.¹⁴ In patients with advanced disease and adverse prognostic factors, such as cytogenetic abnormalities, an auto-SCT followed by an allogeneic SCT is currently being evaluated in clinical trials. The introduction of RIC regimens has decreased TRM considerably. The allogeneic dilemma is the basis of the

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Table 1 Various high-dose strategies over the years

Year of publication	Modality of treatment
1983	McElwain and Powles ⁷ Melphalan 140 mg/m ²
1986	Barlogie <i>et al.</i> ⁸ Dose escalation of melphalan to 200 mg/m ² with autologous bone marrow rescue
1991	Gahrton <i>et al.</i> (EBMT) ⁹ Allogeneic stem cell transplant
1997	Powles <i>et al.</i> ¹⁰ Use of autologous peripheral blood stem cells versus marrow
1999	Barlogie <i>et al.</i> ¹¹ Tandem autologous stem cell transplant
1999	Storb <i>et al.</i> ¹² Reduced intensity conditioning (RIC) allogeneic transplant
2003	Maloney <i>et al.</i> ⁴ Autotransplant followed by RIC allogeneic transplant

fourth chapter. It is clear that although in some instances the so-called allogeneic effect can be curative, the indications for a full allogeneic SCT are rare and the RIC allo-SCT are still very much being investigated for potential usage with no standard defined criteria. It is into the setting of SCT that our chapters on targeted treatments define how to improve SCT outcomes. An overview on the results of Thalidomide, Lenalidomide and Bortezomib trials is provided by the Dana Faber group, which underlines major advances that have been made in the understanding of the newer biological agents and how they can be interdigitated into the SCT programmes. But the cost of these new drugs is high, and although no price can argue against the value of a very effective drug, the exponential increased cost for treating myeloma is due to patients living longer because of expensive drugs, giving more time to receive other expensive treatments.

What lessons have we learnt in optimising stem cell transplants?

Evidence-based medicine confirms that long-term survival benefit can be achieved with high-dose chemotherapy followed by autologous peripheral blood SCT. Following are some of the optimizing principles that have so far evolved, and are the basis for the discussion in chapters in this issue that follow.

- (1) Patients should whenever possible be approached for entry into a clinical trial if eligible.
- (2) For patients with asymptomatic stage I myeloma or smouldering myeloma with no end-organ damage, a watch and wait strategy must be adopted.
- (3) If a patient is considered eligible for SCT, then stem cell sparing agents are to be used for induction therapy (avoid melphalan and high-doses of cyclophosphamide).
- (4) For induction therapy prior to a SCT, it is not possible at present to recommend any of the regimens as superior, but infusional chemotherapy may be favoured for rapidly progressing aggressive myeloma (that is, with severe, destructive vertebral disease or renal dysfunction) to attain a quick response. Speed of response of cyclophosphamide-thalidomide—dexamethasone versus CVAMP is currently being assessed in the MRC Myeloma IX trial. Lenalidomide with dexamethasone may be considered within a trial setting but long-term outcome is unknown.

- (5) For patients ineligible for SCT, melphalan-prednisolone with thalidomide (MPT) should be considered for 12 cycles.¹⁵
- (6) Early auto-SCT up to six weeks after induction therapy is recommended.
- (7) However, auto-SCT is not sacrosanct. A recent meta-analysis has postulated that it is not unreasonable to consider other treatment options in patients fit for an auto-SCT but this included published data, not individual patient data.¹⁶
- (8) Also, currently there is no long-term data available on the use of novel agents in new patients with myeloma; hence, it is not possible to make any statement at present on the time tested strategy of attaining at least some long-term survival (about 30%).
- (9) Tandem or double auto-SCT may be considered in some high-risk patients though, with the availability of novel drugs, the second auto-SCT may be reserved salvage setting when other options for treatment have been used up. Indeed, a second transplant may be considered for those patients who do not attain CR with the first SCT to maximize the chances of 'operational cure'.
- (10) Use of interferon maintenance has been abandoned in most centres but with the availability of pegylated interferon which is better tolerable with better compliance and less toxicity, this may possibly be revisited in a trial setting.¹⁷
- (11) No long-term data is currently available for maintenance therapy with novel drugs. There are randomized trials comparing thalidomide versus placebo and although short-term benefit is seen, the long-term results are awaited.¹⁸
- (12) Regarding full allo-SCT, high TRM and significant toxicities related to graft versus host disease (particularly with the age group involved) have dramatically limited the role of this strategy.^{9,19}
- (13) RIC allo-SCT have become more in vogue.⁴ However, RIC allo-SCT should only be offered to patients within a clinical trial setting as there is still no consensus on the type of conditioning regimen, immunosuppressive therapy post transplantation, dose of infused stem cells, schedule of donor lymphocyte infusion and the ideal place for this in the patients treatment pathway. Should this be used immediately after an autologous SCT or reserved for later?
- (14) Data on cumulative risk of myelodysplastic syndrome and acute leukaemia must be collected prospectively in trials. Patients on clinical trials should be followed-up life-long.

Some additional issues are discussed in the chapters that follow.

Quality of life (QoL) issues

If patients are going to have sequences of packages of therapy, and there is going to be a high proportion of

them surviving for more than 10 years, then it is crucial that they have optimized QoL; hence, we have included two chapters that relate to this, namely treatment strategies for bone disease and the use of haematopoietic growth factors.

To this end, there have been some pivotal QoL decisions, driven on the political forum, mainly by bodies such as the International Myeloma working Group, International Myeloma foundation, Multiple Myeloma Research foundation, Myeloma Euronet and similar international groups that have brought together the huge number of people working in this field into some consensus decisions relating to the day-to-day care of these patients, and how regulators and politicians can be lobbied for change. These bodies are to be congratulated for their efforts.

Throughout this special edition, QoL is a constant theme and this is best achieved as a balance between treating the disease initially as intensively as possible, thereby inducing very long-term remission (operational cure), and transferring the disease into an indolent course with a higher level of disease activity (chronic condition). Time without symptoms, treatment or toxicity (TWIST) favours early transplant, but targeted therapies may change this.

We feel that in future research studies, treatment developments in the patient's treatment pathway should be considered with at least some attempt at a surrogate assessment of the impact of such treatments upon the QoL of the individual patient.

Staging system

In this special issue, we do not have a specific topic on staging but it is central to all the work described. Although the Durie-Salmon staging system has divided patients predominantly by tumour burden and renal function,²⁰ it has been superseded by the more reproducible and simple International Staging System (ISS) which incorporates albumin and β_2 -microglobulin, resulting in low-, intermediate- and high-risk groups of patients with median overall survival (OS) times of 62, 45 and 29 months, respectively.²¹ Apart from this, several molecular classification systems have been proposed on the basis of gene expression profiling, cytogenetics and proliferation-based models but these are still being evaluated.

Concept of CR and response criteria

It is difficult to realize that 25 years ago MM was regarded as a chronic progressive disease, and the concept of CR was unknown. It was first documented in MM patients in early 1980s⁷ and is now pivotal to our understanding of response. Subsequent studies have shown a clear survival benefit for patients achieving CR.^{11,22} Gore *et al.*²³ described CR as disappearance of serum or urine paraprotein (immunoelectrophoreses), absence of abnormal plasma cells from the bone marrow and normal bones. CR was the stepping stone to the advances made in understanding how to treat acute leukaemia in the 1960s and 1970s and is a very clear end-point. However, studies involving CR in MM have been

criticized because of the variability seen in CR rates between established centres often using the same sort of treatment programmes because MM with its heterogeneity of subclasses of protein had variable criteria for CR. This applies particularly to Bence-Jones and nonsecretory myeloma. Therefore, Blade *et al.*²⁴ in 1998 made an excellent attempt at coming up with the EBMT response criteria for patients with myeloma treated with high-dose therapy and SCT. These included disappearance of paraprotein and urine Bence-Jones by immunofixation to document CR. These have been supplanted by the 'International uniform response criteria for multiple myeloma' published in 2006 which the authors believe is a more comprehensive system.²⁵ These criteria include the use of free light chain assay which itself has not yet been standardized.

Operational cure

In acute leukaemias and lymphomas it is well established that the first step towards cure is the achievement of CR, and for those with, for example, AML, obtaining morphological and cytogenetic CR is associated with a high proportion being cured. For patients with MM, it is not the same and the chances of true cure, that is, eradication of the last myeloma cell, are very low. The isolated secondary metastasis that occurs, for example, in hypernephroma or seminoma 20 years after removal of the primary, illustrates a small group of patients with cancer who live in symbiosis with micrometastasis for decades and some myeloma patients appear to do the same, that is, they are able to live a normal life span with micro disease and for many, they die with the disease rather than due to the disease.

We have been using high-dose melphalan in patients with myeloma for over 25 years now, and have seen prolonged disease free survival with excellent performance status in a number of patients and some of these patients even have quiescent or healing bone disease. In a recent paper published amongst a group of 451 patients who underwent an autologous SCT almost 30% of the patients are projected to be alive a decade after the transplant.⁵ These patients with long lasting CRs with essentially normal quality of life are 'operationally cured'. Increasing numbers of myeloma patients are living a normal life span and dying of unrelated causes. Quantitative longitudinal molecular studies in these patients should provide further insight into the dynamics of 'nonmolecular long-term CR' and its association with better prognosis, and understanding this could be the basis for controlling disease in others.

These observations thus pose the question of how and why some patients live in symbiosis with their disease, and why their disease appears to be switched off. This should be the focus of intensive future research to find new drug targets that can be exploited.

Conclusion

Even with the targeted therapies currently in clinics and SCTs, the current prospects of being cured of myeloma remain

small. But, it is equally clear that if the sequence of combinations of treatment such as (1) CTD or thalidomide + dexamethasone, (2) Bortezomib ± Dexamethasone, (3) infusional chemotherapy (VAMP/VAD), (4) Lenalidomide ± dexamethasone and (5) SCT is put together for the individual patient to obtain the best in terms of survival from each treatment package, then we can begin to dream of up to 50% of patients selected with good presentation criteria to be alive at 10 years and may be 'operationally cured'. It is into this background that new classes of drugs such as chaperone protein inhibitors can be considered and studies need to be coordinated so that we do not lose ground that we have already gained.

In addition, success will depend not only when to give treatment but also when not to treat, and how to switch the disease off. We need to redefine the rules of obtaining prolonged periods without symptoms, treatment or toxicity, that for the patient is truly normal life.

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