

# High-Dose Therapy and Stem Cell Transplantation in Myeloma

*D. Joshua and J. Gibson*

Multiple myeloma remains an incurable disease with little improvement in survival being achieved despite more than three decades of trials with conventional chemotherapy protocols. Multi-agent protocols have not been definitively demonstrated

to be superior to melphalan alone, and whilst alpha interferon may play a role in prolonging plateau phase it is of relatively minor importance. Very few "new drugs" are on the therapeutic horizon with the exception of the anti-angiogenic agents such as thalidomide.

In contrast, great strides have been made in supportive care. These include better management of hypercalcaemia and anemia, the detection and therapy of skeletal disease, better pain relief, and the establishment of protocols for the management of renal disease. Thus tumour refractoriness is now the major therapeutic problem.

The failure of conventional-dose therapy to prolong survival has spurred interest in high-dose therapy. The rationale for the use of high-dose therapy, however, relates not to the failure of conventional therapy but to the demonstration of a drug dose-response relationship in myeloma such that increased dose will lead to cure or prolonged remission. In addition, in patients undergoing allogeneic transplantation a graft-versus-myeloma effect is now well recognised and believed to be a contributor to the response.

The major problem in myeloma, however, remains drug resistance, and this is not necessarily overcome by high-dose therapy programmes. Drug resistance is due to multiple causes, including drug transport proteins such as MDR1, enhanced drug metabolism, the inhibition of drug-induced apoptosis, and alterations in drug targets by random mutation or reduced levels of the enzymes that are the targets for the drugs, e.g. topoisomerase and doxorubicin. For all these reasons simply increasing drug levels as occurs in high-dose therapies remains unlikely to be curative in myeloma.

Historically, the development of high-dose protocols in myeloma rests on two observations. These were the early reports of syngeneic transplants and the use of high-dose melphalan leading to complete responses. Long survivors after syngeneic transplantation have been reported, although many still have paraproteins in their blood and their urine. The other major development was the introduction of high dose melphalan therapy protocols by McIlwain at the Royal Marsden Hospital in England. Initially, melphalan was used at a dose of 140 mg/m<sup>2</sup> unsupported by stem cell rescue. Dramatic responses were seen in some cases, including some complete clinical remissions. The use of bone marrow and subsequent blood stem cell rescue has enabled further dose escalations and the use of additional agents in an attempt to increase the efficacy of high-dose therapy by overcoming drug resistance. An additional significant development has been the virtual replacement, over the last ten years, of bone marrow by peripheral blood derived stem cells as a source

of haemopoietic stem cells.

Currently, the ratio of patients undergoing autologous as opposed to allogeneic transplantation for myeloma is approximately 3:1 (IBMTR data). The high toxicity of allogeneic transplantation in this setting has to date limited its use. Data from the EBMTR long-term follow-up study of allogeneic transplantation in myeloma suggests that at 9 years less than 20% of patients are alive and many of these still have residual disease. A recent matched pair analysis performed by the EBMTR also demonstrated a superior survival for patients undergoing autologous transplants compared to those undergoing allogeneic transplants. A re-awakening interest in allogeneic transplantation has, however, occurred with the development of "mini transplant" protocols as well as a re-awakening of interest in T-cell depletion as a mechanism of reducing graft-versus-host disease, and such a study utilising a fludarabine and melphalan based conditioning is currently in place by the Australian Transplant Cooperative Group.

A variety of protocols have been used in the autologous setting including double transplant protocols (for example, total therapy from Arkansas) and CD34 selection procedures. Pivotal to autologous transplantation development in myeloma was the Attal study, which demonstrated that a single (bone marrow) transplant was superior to conventional multi-agent chemotherapy both in terms of overall survival and disease-free survival. Long-term follow-up of this study has confirmed the initial reports. Subsequent randomised studies (mainly from France) have looked at the issues of one versus two transplants and early versus late transplantation. As yet both studies show no difference in overall survival although follow up is still relatively short.

A large randomised study of CD34-selected versus CD34-unselected single autologous transplants has been recently completed in the USA and preliminary results recently published. Median tumour depletion was greater than three logs in a CD34-selected group, and the kinetics of haemopoietic engraftment were equivalent. With short follow up disease-free and overall survival are still equal. A European study of CD34 selection is also in progress. An Australian study that involved both double transplant and *in vivo* purging with *in vitro* CD34 selection has also been performed and, although this was not randomised, remission rates do not appear to be different from that obtained by single transplants.

Attention has also been focused on attempting to identify those patients who are likely to benefit most from transplantation. Poor prognostic features such as a high beta 2 microglobulin and chromosome 13 abnormalities have been

advocated as markers of early rather than late transplantation. The prognostic factors for response to transplantation are, however, similar to those for overall disease responsiveness no matter what treatment modality has been used. In addition post-remission therapy with alpha interferon has also been advocated. A small randomised study from the Royal Marsden Hospital in England initially appeared to show an advantage for post-transplant interferon in those patients who obtained a complete remission following transplantation. Subsequent follow-up has unfortunately, how-

ever, not confirmed these results.

Growing interest in immunotherapy such as idiotypic vaccination and dendritic cell manipulation has also been pursued in the transplant field, and the combination of vaccination and stem cell transplantation protocols to support high dose therapy is being evaluated in many centres.