A close-up photograph of a scientist in a white lab coat looking through a microscope. The scientist's face is partially visible, focused on the eyepiece. The microscope is white and black, with the eyepiece and objective lenses clearly visible. The background is softly blurred, suggesting a laboratory setting.

FURTHER PROGRESS IN THE TREATMENT OF MYELOMA
WILL ONLY BE MADE IF WE HAVE A BETTER UNDERSTANDING
OF THE MYELOMA POPULATION THAT SURVIVES EVEN THE
MOST INTENSIVE TREATMENT STRATEGIES.

Autologous stem cell transplantation represents a major step forward in the treatment of myeloma. While most transplant protocols in myeloma call for one round of high-dose chemotherapy and no further treatment thereafter, we now know that a more intensive approach including induction therapy, two cycles of high dose chemotherapy coupled with an autologous stem cell transplant, consolidation therapy, and two years of maintenance therapy is more effective. This is the lesson we have learned as a result of our Total Therapy studies, which consistently have delivered the best treatment results for newly diagnosed myeloma patients. Further improvements will come, for the most part, from a better understanding of myeloma biology and also, to a lesser extent, from some tweaking of the Total Therapy approach to decrease toxicity and further increase survival.

Multiple myeloma (MM) is a differentiated clonal B-cell tumor, consisting in the early stages of the disease of slowly proliferating malignant plasma cells (myeloma cells). It is the second most common hematologic malignancy after non-Hodgkin lymphoma. Normal plasma cells are very hardy cells and usually the only type of cell to survive the effects of myelosuppressive chemotherapy and radiation. The clonal plasma cells have abnormal cytogenetics even at the stage of monoclonal gammopathy of undetermined significance. Before it transforms to an aggressive disease—which is typically associated with extramedullary disease, immature morphology of the myeloma cells, rapid proliferation, and increase in LDH—the disease is entirely bone marrow stroma-dependent and, therefore,

contained within the active hematopoietic bone marrow, although breakout lesions from the bone can be seen. The myeloma cell displays on its membrane a multitude of receptors, the ligands of which are present in the micro-environment. Binding of these receptors by their ligands promotes growth and survival of the myeloma cells and also results in the secretion by the plasma cells of angiogenic factors. In addition to supporting growth and survival, the micro-environment also places most of myeloma cells in a deep G1 phase by up-regulation of p21 and p27. Cells in the G1 phase of the cell cycle are very poor targets for conventional dose chemotherapy.

It is very likely that in myeloma, just as many other cancers, a cancer stem cell population exists. It is estimated that one in 10,000 to one in 20,000 malignant cells is a cancer stem cell. Based on the extensive somatic mutations in the complementarity regions of the gene coding for the heavy chain, it is very likely that this cancer stem cell arises from a B-cell that has had extensive exposure to antigen in the germinal center and therefore most likely is either a memory B-cell or a plasmablast. If there is indeed a myeloma stem cell, such a cell will have many characteristics in common with a hematopoietic stem cell in that it is resistant to conventional doses of chemotherapy and that high doses of chemotherapy will be necessary, which can at least eradicate hematopoietic stem cells and therefore such therapy will require stem cell support. The agents most toxic to hematopoietic stem cells are alkylators, such as melphalan, busulfan, and BCNU, agents found to be very effective in myeloma, while other alkylators, such as cyclophosphamide and platinum compounds

WORKING TOWARD A BETTER UNDERSTANDING AND A BETTER TREATMENT OF MYELOMA

by: Guido Tricot, M.D., Ph.D.

that spare hematopoietic stem cells, are much less effective in myeloma even at higher doses. The difficulty in myeloma is not to eradicate the more differentiated myeloma compartment, which comprises more than 99.9% of the tumor mass, but also to kill the myeloma stem cells. Consequently, achieving a hematologic remission, as currently defined, will have a poor correlation with long-term outcome and should not be used as an early substitute for survival estimates.

It has been more than 25 years since the late Tim McElwain and colleagues introduced high dose melphalan for the treatment of MM. Administration of melphalan 100-140 mg/m² without stem cell support induced biochemical and bone marrow remissions in three (all previously untreated) of the nine myeloma patients, which was much higher than the 3-5% complete response typically seen with conventional therapy. However, high dose melphalan induced prolonged aplasia of five to eight weeks and was therefore associated with high morbidity and mortality rates in a disease with a median age of 67 years. This led other investigators to the concept of stem cell rescue, which allowed further dose escalation of melphalan to 200 mg/m². Stem cell support was initially provided with autologous bone marrow and subsequently with peripheral blood stem cells, containing more CD34 cells/kg and therefore resulting in more prompt bone marrow recovery and less morbidity and mortality. This made application of autologous transplantation feasible in patients 60 to 75 years old, who were in otherwise good clinical condition, and it reduced procedure-related mortality to 2-5%, which is not higher than that seen with six months of conventional chemotherapy and/or the novel agents, such as bortezomib, thalidomide, and lenalidomide.

In an attempt to minimize toxicity and to maximize myeloma cell kill, the concept of tandem autologous transplantation was introduced in Total Therapy I. The underlying hypothesis was that rather than giving a single very intensive preparative regimen prior to stem cell rescue, providing effective but less toxic high dose chemotherapy twice would be better tolerated in older patients and equally effective. A total of 231 patients

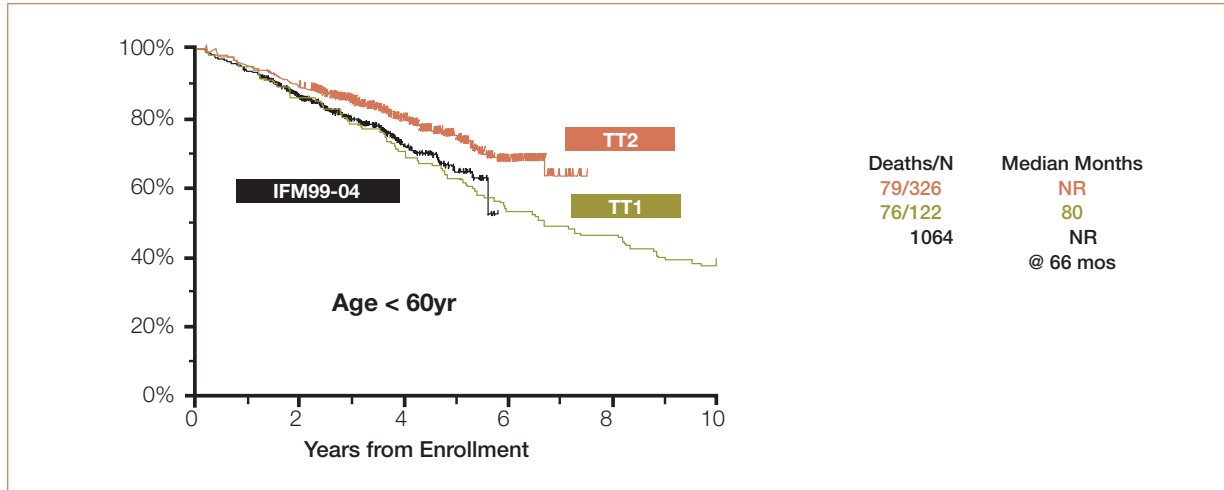
were enrolled from 1990 to 1994. With a median follow-up of 12 years, 62 patients are still alive and 31 have not progressed. The 10 year event-free and overall survivals were 15% and 33%, respectively. In its evidence-based review, the American Society for Blood and Marrow Transplantation concluded that autotransplantation is the preferred treatment modality for myeloma and that its application is recommended as *de novo* rather than as salvage therapy. Yet, less than half of the patients aged 65 or less with myeloma actually proceeds to transplantation.

In Total Therapy II, 668 newly diagnosed myeloma patients were randomized upfront to intensive therapy including tandem autologous transplants with or without thalidomide during the whole treatment. The complete remission rate and the 5-year event-free survival were superior in the thalidomide arm. However, the 5-year overall survival was similar, approximately 65% in both arms ($p = 0.9$), but this may be due to the limited follow-up. The 5-year event-free survival was better on Total Therapy II (43% versus 28%; $p < 0.001$) with also a trend for better overall survival (62% versus 57%; $p = 0.11$). Superior event-free and overall survivals were seen in the two-thirds of patients with normal metaphase cytogenetics. In Total Therapy III, which enrolled 303 patients, not only the myeloma cells were targeted but also the micro-environment to prevent rescue of myeloma cells after transplantation. The latter was achieved by adding thalidomide and bortezomib to the intensive treatment regimen. Approximately 80% of patients achieved a complete remission and with a limited follow-up of 20 months, the two-year event-free and overall survivals were 84% and 86%, respectively. Based on these data, it is reasonable to expect that the 10-year survival of newly diagnosed myeloma patients on Total Therapy II and III will be more than 50%, compared with a median survival of 4 years with the best non-transplant based therapies (See Figure 1).

Although we have made major strides in the treatment of myeloma in the last 15 years, most myeloma patients will still relapse, although much later than it used to be. Further progress in the treatment of myeloma will only be made if we have a better understanding of the myeloma

Figure 1

10 Year Survival is a Reasonable Expectation in Myeloma
Tandem Transplants IFM and Total Therapy



Overall survival of three different tandem autologous transplantation studies are depicted. Total Therapy I, Total Therapy II, and the French IFM study. It should be noted that the French IFM study replicated Total Therapy I and shows exactly the same results. Therefore, it proved possible to independently confirm the results of Total Therapy I.

population that survives even the most intensive treatment strategies. We are now focusing on obtaining gene expression profiles of such cells to see if we can find targets to eliminate those cells. We are also interested in investigating if those cells have the same gene expression profile as the myeloma stem cell. Another area of our research is to find treatment modalities that are non-cross resistant with high dose chemotherapy, and we are especially interested in immunotherapy with natural killer cells (NK cells) to mop up residual myeloma cells.

More than 30 new anti-myeloma drugs are now in early development. Some of those will be winners, but it probably will take another 3 to 4 years before we have identified those. Although the hope is that one day we will be able to treat myeloma without high-dose chemotherapy and transplantation, it appears much more likely that these new drugs will have their best application if used after transplantation when the tumor load is low and the risk of developing resistance has been drastically reduced. The outlook for patients with myeloma will continue to improve, but it will require patients to participate in cutting edge clinical trials to see myeloma becoming a curable disease in a substantial proportion of patients. ■



Guido Tricot, M.D., Ph.D., is the director of the Utah Blood and Marrow Transplant and Myeloma Program at Huntsman Cancer Institute at the University of Utah. He has been researching and treating multiple myeloma for over 20 years. He is working to further refine treatment for recently diagnosed myeloma patients and is studying gene expression profiles of myeloma cells surviving transplantation to investigate how to target these resistant cells with specific therapies.