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Commentary

Progress in multiple myeloma

Multiple myeloma is a disease of malignant plasma cells and is often diagnosed at late stages with anaemia, hypercalcemia, advanced osteolytic lesions or fractures. Other complications include infections, hyperviscosity and renal failure. In many cases, multiple myeloma is preceded by a stage of monoclonal gammopathy which may have progressed over many years. The ultimate prognosis and progression of both conditions is determined by genetic abnormalities such as translocations, loss of genes or inactivation of tumour suppressor genes[1]. The first description of multiple myeloma dates back into the 1850s[2]. Much later, with the development of immunoelectrophoresis in the 1950s, clonal plasma cells secreting monoclonal proteins were discovered as the inherent cause[2]. Melphalan accompanied by prednisone was the first effective systemic treatment (introduced in the 1960s)[3]. Oral melphalan rarely leads to complete remission, but in some patients, it controls the disease for many years. In the 1980s, the question was asked, if low-dose chemotherapy works, would high-dose chemotherapy induce durable remissions? With the advancement of technologies (myeloid growth factors and collection of mobilized stem cells), around 1998, high-dose melphalan followed by infusion of mobilized peripheral blood stem cells, had become a standard treatment in many high-income countries. High-dose melphalan (if used early in the course of disease) increased the median survival from 2-3 yr to 3-5 years[4]. Over the next 20 years, new drugs were introduced (proteasome inhibitors, immunomodulatory drugs and bisphosphonates)[5]. Taken together, in Western countries, the prognosis of multiple myeloma has significantly improved over the last 25 years. Part of this improvement is due to the utilization of novel therapies including high-dose chemotherapy followed by autologous stem transplantation[4-7].

In this issue, Kumar *et al*[8] have shown that autologous stem cell transplantation can be safely performed in India and is effective in bringing patients with multiple myeloma into remission, thereby extending their survival. The authors have reported on 349 patients with multiple myeloma who underwent autologous transplantation between 1995 and 2016. The median age of patients at the time of transplant was 52 years. Following transplant, 61 per cent came into complete remission and 17.8 per cent obtained a very good partial response. The median overall survival of all patients was 7.5 years. These results were comparable to Western countries[6,7]. The authors need to be congratulated not only on their outcomes but also for their careful patient selection and long-term follow up. Yet, room for improvement remains, as mortality by day 100 is still higher than in most reported series. Use of molecular cytogenetics may facilitate the choice of treatment[9]. Countries with limited resources face special challenges, including cost of medication, health literacy, access to new treatments, infrastructure, training of physicians and nurses[10]. It has been argued that autologous stem cell transplant is not cost-effective in terms of quality-adjusted life years[11]. How much is an additional year of life in perfect health worth to individuals or to society? The answer to this question can only be given by society. New treatments or new drugs are usually more expensive than the previous standard treatments. The allotment of new treatments should be fair, based on need and resources available.

Multiple myeloma is a fascinating disease with many open questions. The incidence in different ethnic groups varies. For example, people from Africa have a higher incidence of multiple myeloma than people from Central Europe or Asia[12]. The genetic basis for this is not entirely clear. Monoclonal gammopathy of undetermined significance has some of the same genetic lesions as multiple myeloma. Why does not every person with monoclonal gammopathy develop multiple myeloma? The answer may be in the microbiome[13] or other environmental or inherited factors. Allogeneic transplantation for

multiple myeloma was developed earlier than autologous transplantation and has a potential for cure, but comes with a high toxicity even in younger patients (mostly from graft versus host disease and infections). Therefore, allogeneic transplantation at present has a limited indication[14]. In the age of immunotherapy, the use of allogeneic stem cells (or tumour-specific T-cells) should be reinvestigated.

Several new treatments are under development, some are already in use for relapsed or refractory myeloma. An example is daratumumab (a monoclonal humanized antibody targeting CD38). Daratumumab has shown surprising activity in relapsed multiple myeloma which led to its approval by the U.S. Food and Drug Administration[15]. Nevertheless, autologous transplantation (which is by itself a simple treatment involving only one alkylating agent) has held its place in multiple myeloma[16]. In India, development of the infrastructure for autologous and allogeneic transplantation will for certain benefit many more patients with blood disorders[17,18].

***Conflicts of Interest*:** None.

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