Case for More Autologous Transplants in Myeloma in Resource-Constrained Settings

Suvir Singh[1] Rintu Sharma[1]

[1] Department of Clinical Hematology and Stem Cell Transplantation, Dayanand Medical College, Ludhiana, Punjab, India

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Address for correspondence Suvir Singh, MD, DM, Department of Clinical Hematology and Bone Marrow Transplantation, Dayanand Medical College and Hospital, Ludhiana, Punjab 141001, India (e-mail: suvirs@gmail.com).

Abstract

Multiple myeloma is characterized by a near universal risk of relapse. Autologous stem cell transplantation provides a significant progression free survival benefit but is under utilized worldwide. We provide a small snapshot of why ASCT assumes greater importance in resource-constrained settings.

Keywords

- hematology
- medical oncology
- myeloma
- transplant

Multiple myeloma is a malignant plasma cell disorder that has witnessed a steady improvement in survival over the past two decades. The overall survival (OS) in the past 20 years has nearly doubled due to the progress in supportive care, drug therapy, and the increasing use of autologous stem cell transplantation (ASCT).[1,2] Although ASCT alone has directly not led to an increase in OS, for all eligible patients, the choice of first-line of treatment includes induction therapy, followed by high-dose melphalan and ASCT.[3]

However, the role of ASCT as first-line therapy has been questioned with advances in drug therapy for myeloma. Novel agents are associated with unprecedented response rates, including very good partial response (VGPR) or better responses in over 70% of patients on bortezomib/lenalidomide-based triplets.[4] Newer agents, including carfilzomib and daratumumab, have enabled minimal residual disease negativity as a viable target in a significant majority of patients, questioning the need for upfront transplantation.[5–8]

We provide a snapshot of data affirming the utility of ASCT in the current era and highlight how the importance of ASCT is further amplified in resource-constrained settings.

A few randomized trials have compared ASCT with chemotherapy alone for eligible patients. The randomized IFM2009 trial published in 2017 compared lenalidomide–bortezomib–dexamethasone (RVD) alone versus RVD with autoSCT and found significantly better progression-free survival (PFS) and measurable residual disease (MRD) negativity in the autoSCT arm.[9] The phase 3 HO95 study also found an improvement in the 3-year PFS with autoSCT compared with chemotherapy alone.[10] Randomized control trials (RCTs) comparing *newer* novel agents (daratumumab, carfilzomib, pomalidomide) with ASCT are expected in the near future. Randomized data comparing ASCT with chemotherapy alone has been evaluated by two meta-analyses, both of which included similar studies. The first study from China included four RCTs of ASCT versus novel agents and found a significant improvement in the PFS (hazard ratio [HR]: 0.56, 95% confidence interval [CI]: 0.44 to 0.73) with no significant change in OS.[11] A meta-analysis published in JAMA in 2019 found similar results and concluded that even in the absence of an OS benefit, autoSCT in the first remission should be preferred due to high rates of deeper responses including MRD negativity, low treatment-related mortality (TRM), and PFS benefit.[12] As of now, no treatment option has shown enough benefits to replace ASCT as the standard of care, which must be used for all eligible newly diagnosed patients.[13]

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Nevertheless, the utilization of ASCT for myeloma worldwide has been less than ideal but is slowly increasing with time. Data from the USA over 1995 to 2010 indicate the utilization rates of less than 15%, being higher for younger patients.[14] Current data, derived from the SEER database, indicate a slight increase in the utilization rate to ~30% (8,371 transplants out of 30,000 newly diagnosed patients in 2018). The Worldwide Network for Blood & Marrow Transplantation (WBMT) registry also recorded a 107% increase in worldwide transplant activity for myeloma during this period.[15] Increasing the use of first-line ASCT, even in settings with easy access to newer drugs, indicates ongoing clinical benefits in the eligible patients. Additionally, safety and reducing TRM with ASCT for myeloma over the past two decades has allowed easier adoption of this treatment modality. The TRM in most centers in India is less than 5% and typically averages 2 to 3%.[16]

In the absence of direct studies evaluating the utilization of ASCT for myeloma in India, it is easy to realize that very few eligible patients proceed to transplant. However, in resource-constrained settings, proceeding to transplant rather than continuing on newer drugs has several tangible benefits.

Economic concerns and access to newer drugs play a significant role in treatment decisions in low- and middle-income countries (LMICs). Compared with continued administration of newer novel agents, ASCT is more cost-effective in the long run. ASCT has been found to incur a cost of approximately Rs. 334,433 per QALY gained in India, and data from India have demonstrated that it can be made more cost-effective with early initiation of treatment.[18] Bortezomib and lenalidomide are now available as generics and available at a cost of approximately USD 90 and USD 30 for a month of therapy, respectively.

However, the cost of newer agents such as carfilzomib and daratumumab is still formidable. For instance, autoSCT in a public-sector hospital in India has been documented to cost approximately INR 395,527 (USD 6,085), compared with approximately USD 33,000 for 16 doses of daratumumab and USD 9,333 for 6 months of carfilzomib alone (communication with the drug company). The introduction of biosimilars or generic formulations may make newer agents more cost-effective in the future but would need a detailed cost-effectiveness analysis to guide the same.

Therefore, the best option for most patients is an early ASCT, with an aim to stall a relapse for as long as possible. Eliminating a very effective treatment option such as an ASCT is not a viable option for a resource-constrained setting such as India.

Another novel approach includes the use of outpatient transplantation, which now demonstrates results similar to conventional transplants with a careful patient and site selection.[19] Various models of outpatient transplant, including total outpatient, mixed inpatient–outpatient, or delayed admission can be adopted in an attempt to markedly reduce costs by reducing the duration of hospital admission.

ASCT utilization is expected to be lower than Western data in India due to a multitude of reasons including concurrent medical illness, lack of expertise or infrastructure for ASCT at various centers, and financial factors, which can lead to withholding this useful and cost-effective treatment for many patients. Inferring from daily practice, several patients do not undergo this effective treatment due to the fear of complications or after being advised against by family members and primary physicians.

Therefore, it is essential to compile collaborative data illustrating the rates of the utilization of ASCT for myeloma and delineation of underlying reasons for the same so that this efficacious and cost-effective therapy is provided to as many eligible patients as possible.

Conflict of Interest
None declared.

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