

## ABOUT THE AUTHOR



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## TO TRANSPLANT OR NOT TO TRANSPLANT IN MULTIPLE MYELOMA

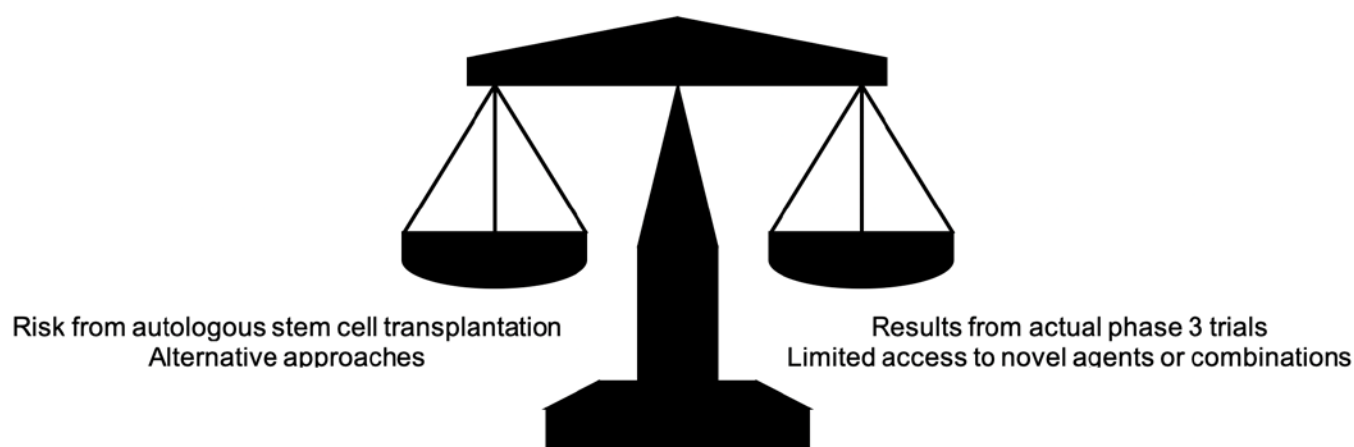
### Introduction and benefits of autologous stem cell transplantation

Multiple myeloma (MM) is the second most common hematologic cancer resulting from proliferation and accumulation of abnormal plasma cells (myeloma cells) with a preferential homing in the bone marrow. It causes significant morbidity including lytic bone lesions, renal insufficiency, anemia and infections to name just a few.<sup>1</sup> Although MM remains largely incurable, it is a chemo-sensitive disease. The use of high-dose intravenous melphalan (100-140 mg/m<sup>2</sup>) in the treatment of MM was first studied almost 4 decades ago.<sup>2</sup> Subsequently, the dose of melphalan was increased and was followed by autologous hematopoietic stem cell to decrease the aplasia-associated toxicity.<sup>3,4</sup> Results from phase 3 studies comparing chemotherapy alone to chemotherapy followed by high-dose melphalan and autologous stem cell transplantation appeared in the mid-90s with the publication of the IFM-90 study<sup>5</sup> demonstrating significant clinical benefits on response rate, event-free survival and even overall survival in a cohort of two hundred previously untreated patients under the age of 65 years. This landmark study was followed by confirmatory studies in the early 2000's.<sup>6-8</sup> Within the last 2 decades, although improvement in the treatment of transplant-eligible patients is mostly the result of better induction regimens<sup>9,10</sup> and due to the addition of maintenance therapies,<sup>11-13</sup> autologous stem cell transplantation remains a cornerstone treatment for MM patients. Indeed, despite novel and more effective treatments for MM, autologous stem cell transplantation continues to demonstrate clinical benefits (**Table 1**).<sup>9,10,14-17</sup> Moreover, tandem autologous transplantation has demonstrated progression-free survival and overall survival benefits for some patients with poor risk cytogenetics.<sup>17</sup>

In 2022, with better knowledge of MM, awareness of potential consequences of high-dose melphalan and with novel and more effective treatment modalities, the role of autologous stem cell transplantation is certainly becoming a question for debate. The purpose of this article is to present the pros and cons of autologous stem cell transplantation in our Canadian reality (**Figure 1**). This article aims to better assess its role as a therapeutic option considering our health system's limited resources in which many novel drugs will not be available/accessible in Canada for several more years to come.

### Risk of high-dose melphalan

High-dose melphalan is well known for significant risk of adverse effects such as severe bone marrow suppression which can result in infection or bleeding, severe gastrointestinal toxicity such as nausea, vomiting, diarrhea and mucositis with ulceration that further increase the risk of infection via bacterial translocation, among other risks.<sup>18</sup> The risk of early mortality within the first few months after autologous stem cell transplantation is approximately 1-2%<sup>5</sup> and predominantly the result of infectious complications.



**Figure 1.** Weighing the pros and cons of autologous stem cell transplantation; courtesy of Richard LeBlanc, MD

Beyond the risk of complications and mortality associated with high-dose melphalan is the risk of second primary malignancy. In a retrospective cohort study looking at 841 consecutive MM patients who underwent autologous stem cell transplantation between 1989 and 2009, the overall cumulative incidence of second primary malignancies was found to be 5.3% at 5 years and 11.2% at 10 years when nonmelanoma skin cancers were excluded from the final analysis.<sup>19</sup> In addition, this risk is further increased with the use of lenalidomide in maintenance therapy.<sup>19,20</sup> Melphalan as an alkylating agent that induces DNA damage and high-dose melphalan exposure increases mutational burden detected between diagnosis and relapse by 10-20%.<sup>21</sup> Clinically, melphalan has been shown to increase the relative risk of acute myeloid leukemia by 10-50 fold and the risk of myelodysplastic syndrome by 100 fold in a database analysis of over 9,000 recipients of hematopoietic cell autotransplants between 1995 and 2010 for Hodgkin lymphoma (n = 916), non-Hodgkin lymphoma (n = 3546) and MM (n = 4566), reported to the Center for International Blood and Marrow Transplant Research.<sup>22</sup> This is particularly important since overall survival of myeloma patients

is improving. In a recent analysis of 14,532 myeloma patients, the 10-year survival rate favored patients who did not receive transplant.<sup>23</sup> In addition, for long term survivors after autologous stem cell transplantation, the 10-year cumulative incidence of severe and/or life-threatening chronic health conditions is approaching 60%, representing a significant morbidity burden for these patients.<sup>24</sup> As non-transplant regimens become more effective, autologous stem cell transplantation might eventually be regarded as unnecessary and may require a re-examination of its risk-benefit profile.

#### **Alternative approaches**

The combination of immunomodulatory drugs and proteasome inhibitors in addition to dexamethasone have been shown to have substantial activity against MM.<sup>25,26</sup> These observed benefits from the combination raise questions about the role of autologous stem cell transplantation. The IFM 2009 study compared the bortezomib-lenalidomide-dexamethasone (VRD) combination in induction and consolidation with or without autologous stem cell transplantation, followed by lenalidomide maintenance as a first line treatment for transplant-eligible patients. Although median

progression-free survival was significantly longer in the transplant group (50 months vs 36 months; HR 0.65;  $p < 0.001$ ),<sup>9</sup> a long-term follow-up analysis at 95 months, demonstrated median PFS2 to be similar (HR 0.96;  $p = 0.751$ ) between the two groups as well as the rate of overall survival at 60.2% in the VRD arm compared with 62.2% in the transplant arm (HR 1.03;  $p = 0.815$ ).<sup>27</sup> However, 77% of patients randomized in the non-transplant group in first line treatment received autologous stem cell transplantation at time of relapse.<sup>27</sup> Similarly, the FORTE trial compared the carfilzomib-lenalidomide-dexamethasone (KRd) combination in induction and consolidation with or without autologous stem cell transplantation followed by maintenance therapy in first line treatment for transplant-eligible patients with newly-diagnosed MM and who were aged 65 years or younger. Although the overall response rate was similar in both groups, sustained minimal residual disease negativity rate and progression-free survival were in favor of the transplantation group.<sup>10</sup> These trials still suggest a potential role for autologous stem cell transplantation, although, perhaps, not as first-line treatment (Table 1).

| Studies<br>References      | n    | Induction                                    | Intensification                 | Consolidation                          | Maintenance                      | ≥PR               | ≥VGPR             | ≥CR               | MRD                  | PFS<br>(months)           | OS<br>(%)                        |
|----------------------------|------|----------------------------------------------|---------------------------------|----------------------------------------|----------------------------------|-------------------|-------------------|-------------------|----------------------|---------------------------|----------------------------------|
| RV-MM-PI-209 <sup>14</sup> | 273  | Rd x 4                                       | ASCT x 2 vs<br>MPR x 6          | None                                   | <b>Len vs none</b>               | -<br>-            | -<br>-            | 36%<br>34%        | NE<br>NE             | m: 43.0<br>m: 22.4        | @4y: 81.6%<br>@4y: 65.3%         |
| EMN-441 <sup>15</sup>      | 389  | Rd x 4                                       | ASCT x 2 vs<br>RCd x 6          | None                                   | <b>Len+pred vs<br/>Len alone</b> | -<br>-            | -<br>-            | 33-37%<br>23-27%  | NE<br>NE             | m: 43.3<br>m: 28.6        | @4y: 86%<br>@4y: 73%             |
| EMN02 <sup>17</sup>        | 1197 | VCD x 3-4                                    | ASCT x 1-2 vs<br>VMP x 4        | <b>VRD x 2 vs<br/>none</b>             | Len                              | 95%<br>95%        | 84%<br>77%        | 44%<br>40%        | NA<br>NA             | m: 56.7<br>m: 41.9        | @5y: 75.1%<br>@5y: 71.6%         |
| IFM2009 <sup>9</sup>       | 700  | VRD x 3                                      | ASCT x 1 vs<br>VRD x 3          | VRD x 2                                | Len x 1y                         | 99%<br>97%        | 88%<br>77%        | 59%<br>48%        | 79%*<br>65%*         | m: 50<br>m: 36            | @4y: 81%<br>@4y: 82%             |
| FORTE <sup>10</sup>        | 474  | <b>KRd x 4 vs<br/>KRd x 4 vs<br/>KCd x 4</b> | ASCT x 1<br>KRd x 4<br>ASCT x 1 | <b>KRd x 4<br/>KRd x 4<br/>KCd x 4</b> | <b>K-Len vs<br/>Len alone</b>    | 97%<br>94%<br>91% | 89%<br>87%<br>76% | 54%<br>57%<br>42% | 80%#<br>69%#<br>73%# | m: NR<br>m: 55.3<br>m: 53 | @4y: 86%<br>@4y: 85%<br>@4y: 76% |
| MANHATTAN <sup>140</sup>   | 41   | DKRd x 8                                     | As per SoC                      | -                                      | As per SoC                       | 100%              | 95%               | 95%               | 71% <sup>∞</sup>     | @1y:98%                   | @1y: 100%                        |

**Table 1.** Studies influencing the decision for autologous stem cell transplantation; courtesy of Richard LeBlanc, MD

\* Performed for patients achieving ≥VGPR after consolidation and maintenance (sensitivity level of 10<sup>4</sup>)

# Performed for patients achieving ≥VGPR before maintenance and every 6 months during maintenance (sensitivity level of 10<sup>5</sup>)

∞ Performed after DKRd for 8 28-day cycles (sensitivity level of 10<sup>5</sup>)

**Abbreviation:** ASCT, autologous stem cell transplantation; CR, complete response; DKRd, daratumumab-carfilzomib-lenalidomide-dexamethasone; K, carfilzomib; KCd, carfilzomib-cyclophosphamide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; Len, lenalidomide; m, median; MPR, melphalan-prednisone-lenalidomide; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PR, partial response; pred, prednisone; RCd, lenalidomide-cyclophosphamide-dexamethasone; Rd, lenalidomide-dexamethasone; SoC, standard of care; VCD, bortezomib-cyclophosphamide-dexamethasone; VGPR, very good partial response; VMP, bortezomib-melphalan-prednisone; VRD, bortezomib-lenalidomide-dexamethasone; y, year; @, at.

Characters **in bold** represent part of randomization for these studies

Aside from immunomodulatory drugs and proteasome inhibitors, monoclonal antibodies against CD38 have emerged as very effective therapeutic options available to clinicians. In randomized phase 3 trials, daratumumab has been shown to significantly improve progression-free survival and overall survival, both in first-line treatment<sup>28-31</sup> and in a relapsed setting.<sup>32-38</sup> Specifically in transplant-eligible patients, the randomized phase 2 GRIFFIN trial comparing lenalidomide, bortezomib, and dexamethasone (RVd) with or without daratumumab (quadruplet) in induction and consolidation treatment in addition to autologous stem cell transplantation and maintenance therapy, demonstrated an impressive 99% overall response rate of daratumumab-based treatment. The daratumumab arm (D-RVd) also achieved a  $\geq$ CR of 51.5% compared to the RVd arm at 42.3%, a  $\geq$ VGPR of 90.9% compared with 73.2% for the RVd arm and a significantly higher minimal residual disease negativity rate of 51% compared to 20.4% in the RVd arm ( $P < 0.0001$ ).<sup>39</sup> After a median follow-up of 22.1 months, the estimated 24-month progression-free survival was 95.8% (95% CI, 89.2-98.4) in the D-RVd group and 89.8% (95% CI, 77.1-95.7) in the RVd group. Based on these promising results, the phase 2 MANHATTAN nonrandomized clinical trial evaluated the efficacy of the quadruplet treatment daratumumab-KRd in newly-diagnosed transplant-eligible myeloma patients in the absence of high-dose melphalan and autologous stem cell transplantation. Treatment was administered for eight 28-day cycles and resulted in a minimal residual disease negativity rate of 71%, (29 of 41 patients) with a 1-year progression-free survival rate and overall survival rate of 98% and 100%, respectively (**Table 1**).<sup>40</sup>

## Discussion

Over the last few decades, myeloma patients have achieved longer survival

rates as a result of the discovery and approval of novel therapies and combinations.<sup>41</sup> However, in Canada, accessibility to many of these treatments are limited and varies from one province to another. For example, most centers still use cyclophosphamide-bortezomib-dexamethasone (CyBorD) as an induction treatment for transplant-eligible myeloma patients instead of the more effective RVd or KRd combinations.<sup>42</sup> Also, daratumumab-based therapies as first line treatment options, such as those used in the CASSIOPEIA<sup>31</sup>, GRIFFIN<sup>39</sup> and MANHATTAN<sup>40</sup> trials, are not available in Canada, nor are the use of quadruplet treatments. In the context of these access limitations and considering the literature showing randomized trials with currently-available agents in Canada still demonstrating clinical benefit with the use of autologous stem cell transplantation, it is prudent to continue the use of transplantation for transplant-eligible myeloma patients as part of the therapeutic armamentarium.

However, impressive results from the MANHATTAN trial with the absence of high-dose melphalan followed by autologous stem cell transplantation are certainly noteworthy. Based on these results, a large randomized, multicenter, 3-arm, phase 2 (ADVANCE) study (NCT04268498) comparing initial treatment with VRd vs KRd vs daratumumab-KRd is presently recruiting. After 8 cycles, patients achieving minimal residual disease negativity will receive maintenance therapy with lenalidomide for up to 2 years. Those with minimal residual disease positivity will have the option to receive an autologous stem cell transplant if available, before initiating the same maintenance therapy. To better evaluate the role of autologous stem cell transplantation, a similar minimal residual disease adapted strategy will be used in the

phase 3 MIDAS IFM 2020-02 trial (NCT04934475). After induction treatment with isatuximab-KRd for 6 cycles, patients who achieve minimal residual disease negativity will be randomized to the same treatment as a consolidation for 6 cycles vs high-dose melphalan and autologous stem cell transplantation followed by isatuximab-KRd consolidation for 2 cycles. All patients will receive 3 years of maintenance therapy with lenalidomide. The results of this study may eventually elucidate a sub-population for whom autologous stem cell transplantation can be avoided.

Numerous novel therapies are also emerging with certain immunotherapeutic modalities demonstrating particularly promising results, such as chimeric antigen receptor (CAR)-T and bispecific antibodies. Although still early in their development lifecycle, these therapeutic modalities have shown impressive results in heavily pre-treated relapsed/refractory MM patients.<sup>43-52</sup> Their benefits in earlier use have yet to be demonstrated in clinical trials which will take several more years, but certainly the clinical efficacy of these new agents will have to be compared with that achieved using autologous stem cell transplantation before they are widely adopted.

## Conclusion

Without doubt, the role of autologous stem cell transplantation will be open for discussion based on the rapid improvement of myeloma therapies. The day may soon arrive when the risks of autologous stem cell transplantation will outweigh its clinical benefits in light of the availability of novel, more effective and safer therapeutic options. Until such time as clinical trials clearly demonstrate that autologous stem cell transplantation can be avoided and alternative therapeutic modalities are fully available for Canadian patients, autologous stem cell transplantation

will remain the standard of care in Canada despite the associated morbidity, mortality and second primary malignancy risks. The eligibility criteria for patients who may be candidates for transplantation are more stringent than those criteria for patients undergoing chemo-immunotherapy alone and, as such, autologous stem cell transplantation as first line treatment should be considered in eligible patients to avoid subsequent ineligibility.

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