**Impact of varying maintenance strategies post- Autologous stem cell transplantation in standard and high-risk multiple myeloma patients: a single-centre Canadian retrospective study**

**Background and rationale:**

Over the past decade, there have been significant advances in the treatment strategy of newly diagnosed patients with multiple myeloma (NDMM) with the introduction of proteasome inhibitors (PI), immunomodulatory drugs (Imid) and monoclonal antibodies (MoA) resulting in improvement of survival rates, however treatment of patients with high risk subsets of disease remains to be challenging. Studies have also demonstrated that multiple myeloma (MM) is not only a clinically but also genetically complex and heterogeneous disease (1). Cytogenetic alterations are considered to have an important prognostic value in MM, helping to identify high-risk patients (2,3). Fluorescence in situ hybridization (FISH) analysis identifies chromosomal in the bone marrow plasma cells in about 90% of MM patients at initial diagnosis (4). Several abnormalities have been identified as independent negative prognostic markers for survival of MM patients and were used by consensus panels to categorize risk groups, including presence of del(17p), t(4;14), t(14;16), t(14;20), gain(1q), amp (1q) and del(1p) and ISS stage 3 disease (5,6). Furthermore, although autologous stem cell transplantation (ASCT) and the development of new agents have considerably increased the median survival of MM patients, data suggesting specific treatment options for different cytogenetic risk groups in newly diagnosed MM are few (7).

In the 2019, the STaMINA trial by Stadtmauer et al (8) , demonstrated that in patients with high-risk cytogenetics there was a benefit with tandem ASCT compared with a single ASCT (3-year progression-free survival (PFS), 65% *v* 41%, respectively; *P* = .05). In their 6-year follow up publication, the Stamina group confirmed the benefit of tandem ASCT followed by lenalidomide maintenance compare to single ASCT and lenalidomide (PFS 49.4% vs. 39%, p=0.01) for high risk patients (Parameswaran H, JCO, 2020). In the study by Gagelmann et al (7) , the multivariate analysis suggested that high-risk cytogenetics was associated with worse survival (hazard ratio (HR) 2.00; P=.003) but tandem ASCT mathematically improved outcomes (HR,.46 and.64; P=.02 and P=.03).

Maintenance treatment following ASCT has become the standard of care in patients with myeloma to deepen responses and prolong treatment response duration. A recent meta-analysis of the largest clinical trials investigated the role of maintenance Lenalidomide post- ASCT and confirmed significant improvement in both PFS and OS in all post-ASCT patients. In the subgroup analysis of small number of patients with poor risk cytogenetics, PFS benefit was seen but this was not translated into improvement in OS (14). Despite the fact that lenalidomide has become the standard of care in maintenance therapy, its efficacy in patients with high risk features remains conflicting (10-13, 20).

The Myeloma XI trial assessed lenalidomide maintenance versus observation in patients with NDMM including cytogenetic high risk subgroup analysis. Although not able to completely overcome the negative impact of high-risk cytogenetics, the PFS benefit was present regardless of cytogenetic risk and the hazard ratio for improvement in PFS for lenalidomide over observation was similar for the high-risk and ultra-high-risk populations to that of the standard risk group (hazard ratios, 0.38 for standard [95% CI 0.28-0.50]; 0.45 for high [95% CI 0.33-0.62]; and 0.42 for ultra-high [95% CI 0.24-0.75]). However, the subgroup analysis was not powered enough to draw a conclusive interpretation (10).

Proteasome inhibitors (PI) are another class of agents that have also been used as single agent or in combination with lenalidomide for maintenance therapy. The HOVON-65/GMMG-HD4 trial compared bortezomib-based induction and maintenance with non bortezomib- based approach. Bortezomib during induction and maintenance significantly improved PFS and OS in all newly diagnosed patients with MM. The subgroup analysis showed that the adverse impact of del(17p) on PFS and OS could be significantly reduced by bortezomib treatment (median PFS, 12 v 22 months; HR, 0.47; 95% CI, 0.26 to 0.86; P .01; median OS, 24 months v not reached at 54 months; HR, 0.36; 95% CI, 0.18 to 0.74; P .003). (15,16).

The Tourmaline-MM3 clinical trial compared an oral PI, ixazomib, to placebo as maintenance therapy post ASCT. The use of ixazomib resulted in 28% reduction in the risk of progression versus placebo with median PFS of 27 months compared to 21 months (median PFS 26·5 months [95% CI 23·7–33·8] vs 21·3 months [18·0–24·7]; hazard ratio 0·72, 95% CI 0·58–0·89; p=0·0023). The PFS benefit with ixazomib was consistent in patients with poorer prognosis, including ISS stage III disease and presence of high-risk cytogenetics (17).

Currently, data validating the effects of tandem ASCT and maintenance treatment in the real world setting in patients with high risk features is scarce. To address this knowledge gap, we sought to conduct a retrospective cohort study of all evaluable transplant eligible (TE) NDMM patients followed at the London Regional Cancer Program (LRCP) in London, Canada to assess the impact of tandem ASCT and the various potential maintenance strategies on long-term outcomes of patients with high risk MM.

**Research Question**

Does dual maintenance strategy with a Pi and lenalidomide positively impact on long-term outcomes of patients with high risk MM post-ASCT?

**Hypothesis**

We hypothesize that patients on dual maintenance therapy post- ASCT have improved PFS compared to patients on single agent or no maintenance therapy

**Study Design and Methodology:**

This is a single centre retrospective cohort study of NDMM patients followed at the LRCP in London, Canada from January 2007 to January 2021. Data collection will be retrieved using our local multiple myeloma database with de-identified data. This study will be assessed and approved by our local research ethics board. We will collect data pertaining to all patients who received at least 1 ASCT, regardless of their cytogenetic status. Patients considered to have standard risk cytogenetics will serve as our comparator arm. However, our target population in the study is patients with high risk features.

Patients who meet the inclusion criteria will be identified from the database and the following data will be collected: Baseline demographics including age, sex and medical history, date of MM diagnosis, type of multiple myeloma, presence of plasmacytoma or extramedullary disease, ISS and R-ISS staging, High risk cytogenetics type (FISH analysis); Treatment details: type of induction treatment, disease response prior and post ASCT as detailed below, number of transplantation and dates, dose of conditioning regimen, date of initiation of maintenance treatment, type of maintenance treatment, dose of maintenance treatment at initiation, changes in the dose of maintenance treatment with reason, best/deepest response to maintenance treatment as specified below, Date of achieving best response to maintenance treatment, Date of disease relapse and type of relapse (biochemical versus clinical), treatment at the time of first relapse, time on second line therapy, in order to assess PFS2. Baseline blood work including CBC, Creatinine, calcium, LDH, albumin, beta 2 microglobulin.

As part of this endeavour, we will also perform a sub-study of ASCT to assess the impacts of single ASCT versus tandem ASCT in high risk patients. Our main objective in the sub-study is to understand if there is a significant difference in ORR and median PFS and OS for patients who undergo each one of the procedures. In addition, we will perform a sensitivity analysis of tandem ASCT versus single ASCT undergoing maintenance therapy with lenalidomide ± PI and evaluate the impact of ASCT type and maintenance type on PFS and OS.

**Study Objectives and outcomes**

*Primary objective*: The primary objective of this study is to compare the median PFS for patients with TE high risk multiple myeloma receiving maintenance treatment post ASCT with Lenalidomide + PI versus single agent maintenance/no maintenance.

*Primary outcome measure*: The primary outcome is the median PFS in high risk patients post-ASCT receiving maintenance treatment with Lenalidomide + PI versus other strategies (no maintenance, single agent maintenance).

*Secondary objectives*: The secondary objectives include evaluating the outcomes of lenalidomide maintenance with and without protease inhibitor, evaluating the outcomes of different doses of Lenalidomide maintenance and effects of tandem versus single ASCT as detailed below:

*i)* Median OS

*ii)* The ORR and depth of response based on international myeloma working group criteria (IMWG) in the following pre-specified periods: Post induction, 1 to 3 months post ASCT (if tandem, 1 to 3 months post tandem as well), 12 months post ASCT ( for those who did not receive maintenance therapy); or 12 months after initiation of maintenance therapy.

*iii)* Subgroup analysis to assess ORR, median OS and median PFS in high risk patients according to their maintenance strategy.

*iv)* To assess the median lenalidomide maintenance dose

*v)* To assess the rate of lenalidomide dose reduction and discontinuation.

*vi)* To assess Impact of lenalidomide maintenance treatment at full doses versus reduced doses in OS.

*vii)* To assessImpact of maintenance approach in PFS2

*viii)* To assess impact of single versus tandem ASCT on ORR, PFS and OS in patients with high risk multiple myeloma.

**Inclusion and Exclusion Criteria and description of study patients:**

*Inclusion Criteria:*

-We will include all patients ≥18 years old diagnosed with Multiple myeloma based on the IMWG criteria with high risk disease, who were treated with upfront induction followed by ASCT (single or tandem) and received maintenance treatment with lenalidomide and/or protease inhibitor post ASCT or no maintenance treatment.

*Exclusion Criteria:*

- We will exclude patients who did not proceed to transplantation following upfront induction treatment secondary to ineligibility or progression.

- Patients who received thalidomide maintenance

- We will exclude patients with very early relapse post ASCT (less than 12 weeks) who required to start second line treatment prior to initiation of maintenance treatment.

**Data analysis:**

The meta-analysis published by McCarthy *et al.* evaluated 1208 myeloma patients enrolled in 3 RCTS for first line therapy with ASCT and maintenance or no maintenance with lenalidomide. The analysis demonstrated a significant PFS difference of 53% versus 24% in 4 years, confirming the benefit of maintenance. In addition, Duggan et al. recently demonstrated a very similar number: 52% versus 22% of PFS in 3 years for high risk patients in a real-world Canadian data study (REF). Of those, 22 % received dual maintenance therapy. However, no sub-group analysis was performed to assess a difference in PFS related to maintenance strategy. We currently have in our local database a total of 175 ASCT patients including both high and standard risk patients. As far as we know, there is currently no data available on the impact of dual maintenance therapy in the high risk population. Therefore, we will need to extrapolate what the current literature shows regarding the benefits of maintenance versus no maintenance, keeping in mind that high risk patients encompass around 15 to 25% of newly diagnosed myeloma patients. Therefore, for an 80% power and 2-sided alpha of 0.05, we require a total of 170 patients to show the benefit of maintenance versus no maintenance similar to what is described in the literature. We will analyse baseline data by means of descriptive statistics. We will use chi-square or fisher exact as appropriate for categorical variables and student- t test for continuous variables. OS and PFS will be assessed visually using Kaplan-Meier curves and multivariate Cox proportional hazards. Time-to-event end points will be analyzed by means of the Kaplan–Meier method, with the use of a two-sided stratified log-rank test to compare the treatment groups and a multivariate Cox proportional-hazards model adjusted for stratification factors to estimate adjusted hazard ratios and 95% confidence intervals. A competing-risk analysis will be performed to assess the effect of censoring events on progression-free survival.

Progression-free survival is defined as the time from diagnosis until either the first documentation of disease progression or death from any cause. Censoring rules for progression-free survival followed the Food and Drug Administration guidance on end points in cancer trials (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry; U.S. Department of Health and Human Services FDA, Onc.Center of Excellence,Center for Drug Evaluation and Research, 2018). Overall survival is defined as the time from diagnosis until death from any cause. PFS2 is defined as time from diagnosis to disease progression or death from any cause after the second line therapy.

**Duration of study**

Data will be captured for 7 years from MM diagnosis until second relapse, or death from any cause or last follow-up, whichever comes first.

**Definitions:**

-High risk MM: Defined as presence of one of t(4;14), t(14;16), t(14;20), del(17/17p), (1q) amplification identified by fluorescence in situ hybridization (FISH) and patients will ISS stage 3 disease (5,6)

-Disease response and progression: disease response and progression criteria is based on IMWG uniform response criteria (21)

-PFS- time from transplant to disease progression.

-OS- time between transplant and death from any cause or last follow up.

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