CORRESPONDENCE

Real-world outcomes of tandem ASCT in newly diagnosed multiple myeloma patients with standard risk features: a single-center analysis

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INTRODUCTION

Multiple myeloma (MM) is a clonal neoplastic proliferation of plasma cells that accounts for 1% of all cancers and 10–15% of hematological malignancies.

Cytogenetic aberrations, detected by fluorescent in situ hybridization (FISH), directly impact prognosis and stratify patients into standard-risk and high-risk cytogenetics groups. 85% of newly diagnosed MM patients (NDMM) have standard-risk cytogenetics according to Revised International Staging System (R-ISS).

Although MM remains an incurable disease for most patients, overall survival (OS) has improved significantly largely due to new drugs, including proteasome inhibitors (PI), immunomodulators (IMID) and monoclonal antibodies. Standard treatment of autologous stem cell transplant (ASCT) candidates includes an induction regimen with bortezomib-dexamethasone plus lenalidomide (VRD) or thalidomide (VTD); or quadruplet therapy adding daratumumab to VTD. Responders, then, receive intensification treatment with single or tandem ASCT followed by maintenance with lenalidomide until progression or intolerance [1, 2].

The role of tandem ASCT in patients with standard-risk cytogenetics has been poorly studied. We aimed to investigate whether a tandem ASCT approach is superior to single ASCT in NDMM patients with standard-risk cytogenetic features.

MATERIALS AND METHODS

This was an observational, single center, retrospective study conducted on NDMM with standard-risk cytogenetics who underwent ASCT between September 2014 and October 2022.

Eligibility criteria included receiving induction therapy with VRD or VTD as first line followed by single or tandem ASCT. Primary refractory or high-risk cytogenetics patients were excluded. Standard-risk cytogenetics status was defined as absence of 17p13 deletion, translocation (4;14) or translocation (14;16) analyzed by FISH, according to R-ISS criteria.

Tandem ASCT was defined as two ASCTs within 12 months without relapse or progression in between. Preconditioning regimens included melphalan (200 mg/m^2 or 140 mg/m^2) or busulfan-melphalan combination. Consolidation therapy after ASCT was allowed and lenalidomide maintenance began when its funding was approved in Spain.

Response assessment was based on International Myeloma Working Group criteria. MRD was analyzed by flow cytometry with sensitivity of 1×10^{-5}.

The primary endpoint of our study was to determine whether the proportion of patients achieving MRD negativity was higher in those with standard-risk characteristics undergoing tandem ASCT compared to those receiving single ASCT. The secondary endpoint was to determine if tandem ASCT improves PFS and depth responses (complete response (CR) or greater) after intensification.

Statistical analyses were performed using IBM SPSS Statistics software v.28.0. The Kolmogorov-Smirnov test was used to compare sample distributions, and differences in study variables were analyzed with Chi-squared, Fisher's exact, and Student's t-tests. Progression-free survival (PFS) was calculated from the date of induction therapy initiation until relapse, death from any cause or last follow-up. OS was calculated from date of induction therapy initiation until death from any cause or last follow-up. PFS and OS rates were estimated with the Kaplan-Meier method, median follow-up with the reverse Kaplan-Meier method, and subgroups were compared using the log-rank test. Cox regression models assessed the significance of prognostic variables from univariate and multivariate analyses.

Confidence intervals (CIs) were set at 95%, and a p-value of <0.05 indicated statistical significance.

RESULTS

During the specified period, 66 NDMM patients underwent ASCT in our center. Of these, 11 (16.6%) with high-risk cytogenetic features were excluded. Consequently, 55 patients with standard-risk cytogenetics were analyzed, of whom, 20 (36,4%) received tandem ASCT.

Most demographic and disease characteristics were balanced between groups. Most patients were in lenalidomide maintenance in tandem group (68.5% VS. 5.2%, $P < 0.001$). The mean time between end of induction and the ASCT was 6.5 months (range 4–11) with a 5.2-month interval between transplants in the tandem setting (range 4–8).

By the data cutoff date, 32 events (death or progression) were observed: 10 (50%) in the tandem group and 22 (62.8%) in the single ASCT group.

CR or greater rates improved after the intensification in both the single ASCT [31.4% to 65% ($p = 0.027$)] and the tandem group [15% to 50% ($p = 0.018$)]. Furthermore, MRD negativity rates increased after intensification in the single ASCT [from 31.4% to 65% ($p < 0.001$)] and the tandem group [30% to 65% ($p = 0.02$)].

The primary endpoint of MRD conversion rate was not significantly different within the respective cohorts, 7 and 12

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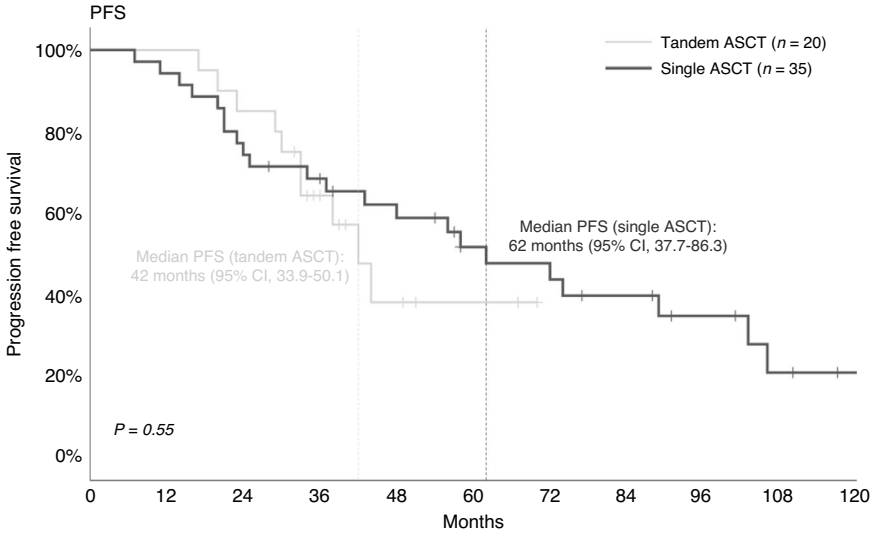

Fig. 1 Outcomes after single versus tandem ASCT. Progression free survival (PFS).

patients in single and tandem arms respectively (50% in both groups, $p = 1$).

After a median follow-up of 55 months (interquartile range, 38.0 to 88.0), median PFS was 42 months (95% CI, 33.9 to 50.1) for tandem group and 62 months (95% CI, 37.7 to 86.3) for single ASCT group ($P = 0.55$) (Fig. 1). The impact of tandem ASCT was similar within different induction treatments. Median PFS was shorter in the VRD- tandem ASCT cohort compared to the VRD plus single group (38 vs. 106 months, $p = 0.17$). The impact was similar within VTD induction subgroup, with a median PFS of 48 and 44 in single and tandem arms respectively ($p = 0.78$). The estimated 5-year OS rate was 85.3% and 66.5% in single ASCT and double ASCT subsets ($p = 0.7$). Univariate analysis found no factors affecting results, although maintenance therapy showed a trend toward improving PFS.

No ASCT-related mortalities or increased incidence of second primary malignancies with tandem were observed ($P = 0.36$). In the tandem cohort, 1 patient (5%) developed 1 solid tumor, while none in the single-ASCT arm did.

DISCUSSION

Our main objective was to provide real-world data on tandem ASCT in NDMM patients with standard-risk cytogenetics receiving triplet therapy, addressing the lack of published data for this subset.

Cavo et al. [3] demonstrated that tandem ASCT could overcome the poor prognosis associated with high-risk cytogenetics, but their study did not include IMID drugs, limiting comparability to current NDMM standards. Recently, the PETHEMA/GEM group presented a series of tandem ASCT, but excluded MM patients with standard-risk cytogenetics [4]. In contrast, STAMINA trial found no benefit for the tandem ASCT cohort, although a significant proportion of patients in the tandem arm did not receive the second ASCT [5].

According to our data, the superiority of tandem ASCT over the single group was not confirmed in standard-risk cytogenetics NDMM patients, even with more patients in the tandem group receiving lenalidomide maintenance, which showed a trend toward improved PFS and OS.

The study's limitations include its retrospective nature, the lack of MRD evaluation after the first transplant in the tandem cohort and differing follow-up durations between cohorts. Moreover, lenalidomide maintenance could be a confounding factor, improving PFS and OS in the tandem ASCT group. Although gain/amplification (1q21) is considered an adverse prognostic factor, we did not examine it, as it is not included in the R-ISS, the prognostic score available when most patients were diagnosed.

Our patients were treated with a three-drug induction regimen without monoclonal antibodies, which may not fully represent current treatment trends. Quadruplet therapy, as demonstrated in the GRIFFIN, PERSEUS, and CASSIOPEIA clinical trials, and supported by real-word evidence, may improve patient prognosis without tandem ASCT approach [6–9]. The ongoing IFM 2020-02 trial is evaluating the benefits of tandem ASCT in MRD-positive patients after a quadruplet induction regimen. The pending results are expected to clarify the potential advantages of tandem ASCT in MRD-positive patients, whose risk of progression is higher [10].

In conclusion, our real-world data suggest that tandem ASCT may not be an effective approach in NDMM patients candidates for ASCT with standard-risk cytogenetic. Further clinical trials are needed to evaluate its effect in the era of quadruplet therapy.

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DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

APG, ERR and VC participated in conception and design of the work and participated in the writing of the manuscript draft. APG, ERR, VC, IEM, AHC, AJSS and AJMM contributed to data collection. APG, ERR and VC performed data analysis and interpretation. MBB, AMGH and IMM were responsible for the collection and infusion of hematopoietic progenitors. VC, MJMB, IEM, JMC, BNA and ASS have conducted patient monitoring. ESF, MCGG and MSV performed the bone marrow biopsy to diagnose and evaluate the response. AMP evaluated MRD by flow cytometry. All authors revised the article and gave approval of the final version to be published.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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