How can different therapeutic strategies and financial resources impact on outcomes after Autologous Stem Cell Transplantation in Myeloma? Study in France and Algeria

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soho2023 ELEVENTH ANNUAL MEETING

INTRODUCTION

The actual international standard care for eligible Multiple Myeloma patients remains an intensive induction, followed by high-dose melphalan and autologous stem cell transplantation (ASCT). However, access to the last-generation therapeutic arsenal and advanced biological tools are not homogeneous worldwide. Our study involved two groups of newly diagnosed MM patients who received a first line treatment consisting of double or triple induction, ASCT, with or without consolidation and maintenance. The patients received ASCT at the *Centre Léon Bérard* in Lyon, France or at the *Etablissement Hospitalier et Universitaire* in Oran, Algeria.

OBJECTIVES

The principal aim of this study was to evaluate the long-term outcome after ASCT in these 2 countries and to assess any potential effect of drugs access and difference in management on the patients' outcomes.

METHOD

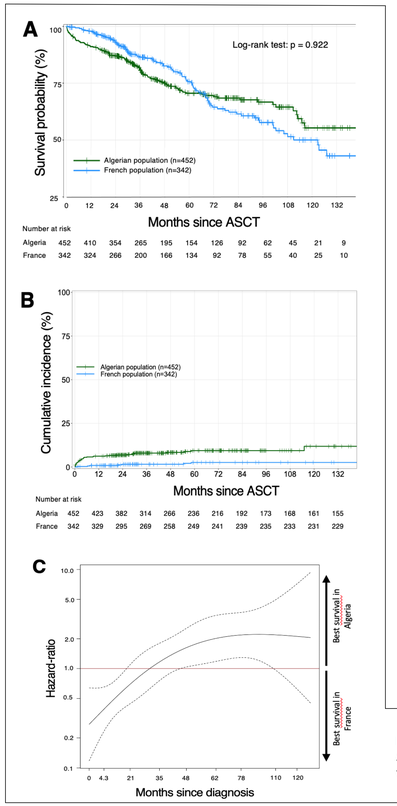
Data from all Algerian and French MM patients who underwent ASCT were reported in the PROMISE database of the European blood and marrow transplantation (EBMT) registry. Quantitative and qualitative variables were compared using the Student T test or the non-parametric Mann-Whitney U test and the Pearson's Chi-square test. Overall survival (OS) and progression-free survival (PFS) were presented and estimated using the Kaplan-Meier method. Time to next treatment or death (TTNT) incorporated the period of treatment delivery. Log-rank tests were performed to compare survival curves. Non-relapse mortality (NRM) was illustrated. Comparative study between both countries was possible for OS and TTNT. Proportional Hazards Assumption was also tested, using Schoenfeld's residuals. Univariate and multivariate analyzes were computed using Cox regressions. To generate the multivariate Cox regressions comparing both groups, confounding factors were selected from the comparative descriptive analyses between the two cohorts and then added as adjustment variables. As the proportional hazard assumption between Algerian and French populations was violated according to the Schoenfeld's residuals representation (p<0.001), we had to face the problematic of this time-varying effect. Therefore, according to the Schoenfeld graph, the time since ASCT was split into three periods: 0 to 12 months, 12 to 48 months, and beyond 48 months for OS, and 0 to 5 months, 5 to 12 months, and beyond 12 months for TTNT.

RESULTS

A total of 342 patients were included in the French group and 452 patients in the Algerian group.
The age at diagnosis was 60 (30-74) years in France and 54 (29-79) in Algeria. At diagnosis, there were more stage III myeloma according to the Salmon and Durie classification in Algeria (96.7%) than in France (89.4%). In France, most patients (92.5%) had a PS (Karnofsky) of 0 or 1, while in Algeria, patients seemed to display worst conditions as 55.6% of patients had a PS status of 1 and 20.9% had a PS of 2 and a more important proportion of patients presented kidney failure, hypercalcemia and bone lesions.

The median PFS from diagnosis was 39.35 months in France and 84.7 months in Algeria.
In the French multivariate analysis on PFS, the only parameter that was associated with a significantly better PFS was maintenance (HR 0.47 [95% CI: 0.23; 0.97], p=0.04), while in the Algerian analysis the parameters associated with a better PFS were consolidation (HR 0.39 [95% CI: 0.25; 0.61], p<0.001) and aplasia duration (HR 1.08 [95% CI: 1.02; 1.15], p=0.011).
The median OS was 122.8 [95% CI: 100.9; NA] months from ASCT in France and was not reached in Algeria. In both countries, regarding the impact of consolidation and maintenance on OS, the median OS from ASCT was not reached for patients receiving both consolidation and maintenance treatments and no death was reported in France. In the Algerian group, the median OS was 100.86 [95% CI: 49.87; NA] months for patients receiving either consolidation or maintenance treatment. In the French group, multivariate analysis on OS showed that shorter aplasia duration and combination of consolidation and maintenance were significantly associated with a better OS. In the Algerian group, factors of interest for survival in multivariate analysis were age at transplantation, number of lines of induction therapy, hypercalcemia at diagnosis, and having received consolidation and maintenance treatments.

Despite important differences between the 2 countries, thanks to an adjustment of variables, we showed a similar Overall Survival (OS) for the total population (Figure 1), and for patients who did not relapse and did not receive any chemotherapy after ASCT. Surprisingly, these latter patients concerned 2/3 of Algerian patients and only 1/3 of French patients. For relapsing patients, we found a better OS in France for patients who received ≤3 lines of treatment after ASCT, and no difference between French patients who received ≥4 therapeutic lines and Algerian patients receiving 1 or 2 lines (Figure 2). We also performed survival analysis using the instant ratio and found a better survival in France between 0-12 months after ASCT. Furthermore, we showed a better survival in Algeria after 48 months. This last result was enhanced by a significant difference in the time to next treatment (TTNT) (Figure 3).



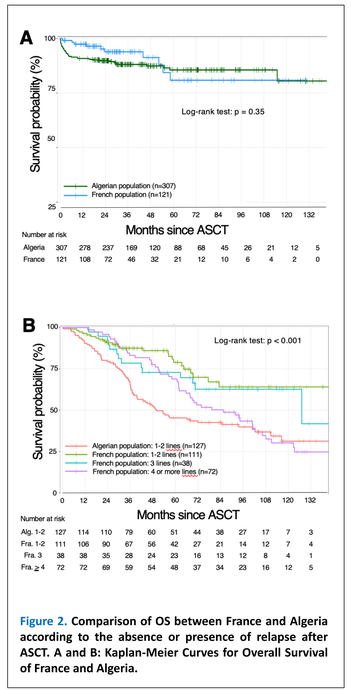


Figure 2. Comparison of OS between France and Algeria according to the absence or presence of relapse after ASCT. A and B: Kaplan-Meier Curves for Overall Survival of France and Algeria.

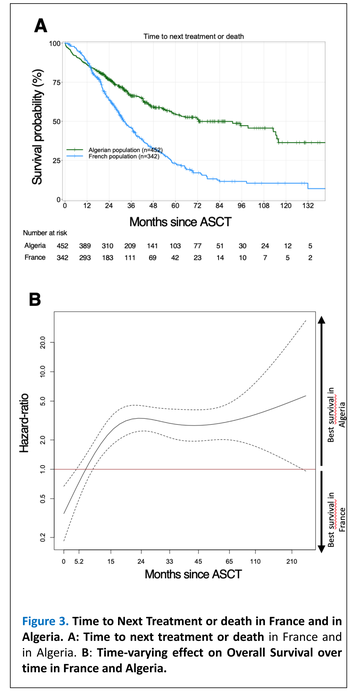


Figure 3. Time to Next Treatment or death in France and in Algeria. A: Time to next treatment or death in France and in Algeria. **B: Time-varying effect on Overall Survival over time in France and Algeria.**

Figure 1. Comparison between France and Algeria. A: Kaplan-Meier Curves for Overall Survival of France and Algeria since ASCT. B: Cumulative incidence of Non Relapse Mortality (NRM) in France and in Algeria. C: Time-varying effect on Overall Survival over time in France and Algeria.

CONCLUSIONS

Waiting to re-treat MM patients in Algeria, correlated with delayed TTNT, could argue to the hypothesis of lower healthcare costs and perhaps therapeutic saving when comparing France and Algeria, strengthened by a similar global long-term OS.

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Acknowledgements: to Bekadja Mohamed Amine and his team for the data from center of Oran in Algeria and Stephane Morisset for the statistical analyses

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