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Short Communication OMICS International

Favourable/Intermediate ELN-Risk Acute Myeloid Leukemia to Transplant or Not to Transplant First-Line?

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Short Communication

Favourable/intermediate ELN-risk acute myeloid leukemias (AMLs) (e.g. those harboring t(8;21) or inv(16) or NPM1A mutations or CEBP-alpha bi-allelic mutations) account for 30% to 50% of all newly diagnosed AMLs [1,2]. In this setting, conventional induction treatments may induce complete remission (CR) in up to 70% to 80%, but relapses still occur in 40% to 50% of cases and, at the end, no more than 30% to 40% of patients can be cured [1,2]. Therefore, the optimization of post- remission therapy represents the greatest challenge in the treatment of favourable/intermediate-I ELN-risk AML.

Nowadays, there is general agreement in offering allogeneic stem cell transplantation (allo-SCT) in first remission to AML patients falling into the category of unfavourable/intermediate-II ELN-risk AMLs, but whose relapse risk significantly exceeds 50% of the cases [1,2].

For the favourable/Int-I ELN risk AMLs the post-remission treatment is more problematic due to their heterogeneity and to the difficulty in precisely defining their prognosis. Currently, the approach commonly followed is based on the use of one or two intensive chemotherapeutic regimens, including intermediate/high-dose cytarabine, with or without autologous (auto)-SCT [1,2]. Indeed, the actual rates of allo-SCT transplant-related mortality (TRM) are considered not acceptable for those patients whose relapse risk is below 35% to 40% with standard consolidation/intensification treatment [3]. Once these patients relapse, it is commonly thought that a 2nd CR may be obtained in the great majority of patients and that allo-SCT may be offered at this time [4].

These indications are certainly embraceable but, at the same time, it has to be considered that the achievement of a 2nd CR should not be assumed as certain and that a number of major complications (e.g. infections or organ damage) may occur, thus enhancing the morbidity and mortality (that is to say the TRM) of allo-SCT as second-line treatment. Furthermore, and this is even more important, it may be questionable whether allo-SCT in 2nd CR is as curative as in 1st CR. Several data suggest that allo-SCT in 2nd CR shows less potent anti-leukemic activity and much higher toxicity [4]. In other words, for advanced-phase diseases, if the clinical patients' conditions may be worse, the burden and the drug resistance of leukemia may be higher and negatively influence the relapse after transplant. From the clinical point of view, patients in 2nd CR undergoing allo-SCT may be considered comparable to high-risk-risk AML submitted to allo-SCT first-line. Nevertheless, this is probably not completely true, because the biological characteristics of leukemias at relapse are probably different compared to those present at diagnosis.

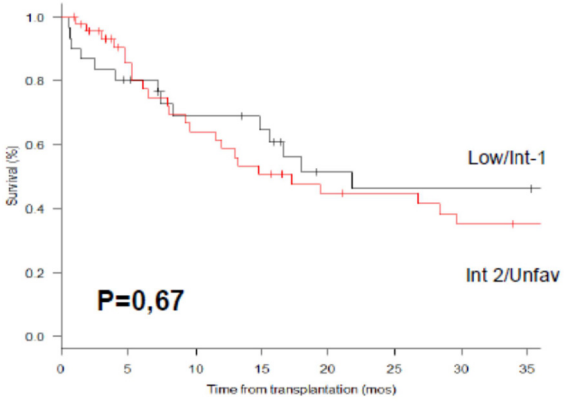

Figure 1A: Overall smTival of the 8 AML patients according to ELN-risk group.

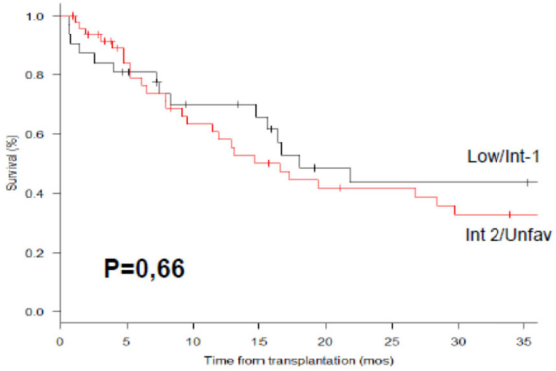

Figure IB: Disease free srnYiYal of the 8 AML patient according to EL-risk group.

Different clinical (e.g. age, secondary AML, extramedullary involvement) and laboratory (e.g. white blood cell count, LDH serum levels) factors at diagnosis have been identified and correlated with prognosis, but none of them, neither alone nor in combination, has been universally recognized and systematically applied to guide a risk-adapted therapeutic strategy, especially in the case of favourable ELN-risk AMLs.

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Recently, many groups remarked the importance of the application of next generation sequencing (NGS) in the mutational screening of AML, both at diagnosis and during the follow up of the patients. The opportunity to screen mutational hotspots in different target genes by target re-sequencing is biologically meaningful and reveals new evidences regarding the risk stratification of the patients. In this regard, it was observed that the genomic profile of leukemic clones may significantly change from diagnosis to relapse showing the emergence of clones that are more difficult to eradicate [5-7]. In the next future, these technologies will be commonly available, but currently the great majority of hematological centers do not have the opportunity of adopting them into clinical practice.

Minimal residual disease (MRD) monitoring by multiparametric flow cytometry (MFC) on leukemia associated immunophenotype (LAIP) and/or quantitative polymerase chain reactions (Q-PCR) on target genes (Flt3-ITD, NPM1A, WT1), are techniques which are currently used to evaluate the quality of response during treatment and may help to allocate patients to different treatment strategies [8-10]. The predictive power of each technique and the identification of the most accurate time-point for MRD assessment are not well defined and thus it is still a matter of debate how and when MRD data should be used in the context of the AML treatment program.

Analyzing the data of 78 AML patients consecutively submitted to allo-SCT in our Center over a 6 years period (2010-2015) [11], we have seen no differences in terms of long term outcome (overall survival -OS- and disease-free survival -DFS), with respect to ELN risk category at diagnosis. In particular, patients had a median age of 53 years (range 20-68); 40% and 60% were grouped in the ELN favourable/intermediate-I, and intermediate-II/unfavourable risk category, respectively and 47% of them were in advanced disease-phase at the time of transplant, that means beyond 1st CR. The clinical and transplant characteristics of the patients according to the ELN-risk group were well balanced. Half of the patients received a sibling HLA compatible donor, 76% of the cases received peripheral blood stem cells and half of the patients received a myeloablative conditioning regimen. With a median follow up of 20 months (range 8 to 58 months), the projected 2 years OS and DFS of the entire cohort was 45% (95%CI: 32% to 57%) and 43% (95%CI: 30% to 54%). The relapse rate (RR) and the TRM at two years were 38% (95%CI: 26% to 50%), and 15% (95%CI: 8% to 26%), respectively. Interestingly, the median OS and DFS in favourable/intermediate-I *vs* intermediate-II/unfavourable was 21.8 and 14.8 months (Figure 1A; p=0.67) *vs* 18 and 14.8 months (Figure 1B; p=0.66). Indeed, no differences were observed comparing the 2 years RR and TRM of patients in the favourable/intermediate-I *vs* unfavourable/ intermediate-II ELN risk group (36% *vs* 40%; p=0.66 and 16% *vs* 18%; p=0.95). When we considered the status of the disease at the time of transplant, we observed that the percentage of patients allotransplanted in advanced phase of the disease (beyond 1st CR) was higher in those included in favourable/intermediate-I with respect to unfavourable/intermediate-II ELN-risk group (73% vs 43%; p=0.001).

Our data clearly show that allo-SCT can cure approximately 50% of AML patients, with no difference between favourable and unfavourable ELN risk groups, because the long-term outcome of favourable patients allotransplanted in advanced phase (beyond 1st CR) is very similar to that of unfavourable patients transplanted first-line. This confirms that the biggest obstacle to the success of transplantation is the biological aggressiveness of the disease, that affects the post-transplant outcome and suggests that there is no advantage from allo-SCT if favourable disease at diagnosis are transplanted when the disease acquires unfavourable biological features, such as those associated with advanced phase.

To improve the results of transplantation we can act on those factors which can reduce the TRM, while we have no effective therapeutic arms on biological aggressiveness of leukemia, with the exception of the early use of allo-SCT, before a low-risk disease become a high-risk disease by relapsing after conventional chemotherapy. Therefore, it's reasonable to offer allo-SCT "early" (1st CR) to patients with worse biological characteristics at diagnosis (high-risk ELN patients), but it is not reasonable to offer allo-SCT "late" (beyond 1st CR) to patients with more favourable biological characteristics at diagnosis (favourable/intermediate ELN risk), but with advanced disease at the time of transplant.

How can we overcome the limits of this treatment strategy for these AML patients? By monitoring the MRD by MFC on LAIP and WT1, we have seen that WT1 levels as well as LAIP were independently associated with long-term outcome. In particular, WT1 levels from bone marrow ≥ 121/10^4 ABL copies (p=0.02) and LAIP>0.2% (p=0.0001) after 1st consolidation, as well as WT1 levels from peripheral blood ≥ 16/10^4 ABL copies (p=0.0001) after 1st intensification was associated with a relapse risk from 25% to 80% [10]. These data strongly highlight the importance of MRD monitoring in post-induction phase, and suggest that this could be a useful parameter to guide the decision for allo-SCT and to rapidly address to allo-SCT those patients with a persistent MRD positivity.

Conclusion

In conclusion to transplant or not to transplant favourable/intermediate-I ELN-risk AML first-line? Favourable/intermediate ELN-risk AML should not be excluded, a priori, from a front-line allo-SCT program. In this setting, the rate of relapses, although less than 40% to 50%, is not abolished, and it is clear that, with the cytogenetics and molecular biology at diagnosis, we are currently unable to identify the risk of the disease in a satisfactory manner. Thus, the risk of the disease evaluated at diagnosis should be integrated with a prospective and dynamic monitoring of MRD, that is able to give us an *in vivo* measure of disease chemosensitivity and can guide to address a proportion of favourable/intermediate risk AMLs to intensification with allo-SCT [10,11].

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