TREATMENT OPTION FOR RELAPSED AML AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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Acute myeloid leukemia (AML) is the most common indication worldwide for allogeneic stem cell transplantation either from related or unrelated donor. Despite its high curative potential treatment failure either due to treatment related mortality or relapse remains a problem. While in the more recent years the treatment related mortality has been reduced significantly the incidence of relapse has not been improved in the last 20 years and has become the principal cause of failure after allogeneic stem cell transplantation. The risk of relapse depends on several factors and the most prominent factors are: disease burden at time of transplantation and cytogenetic abnormalities. To improve outcome by lowering the incidence of relapse the definition of relapse after transplantation is likely to change1. While currently the most conventional definition showing less than 5 % blasts on morphological examination is the most commonly used definition for complete remission, it has to be considered that relapse can be monitored by recurrence of initial cytogenetic or molecular (NPM1, DT1, FLT3, etc.) abnormalities or the presence of phenotypically abnormal blast as detected by multicolor flow cytometry. Especially, given the relation between disease burden and outcome these newer definitions of recurrence are likely to have better prognoses than morphological relapse.

Currently several options are available to treat relapse:

Withdrawal of immunosuppression

No systemic study about withdrawal of immunosuppression after occurrence of morphological relapse for AML after allogeneic stem cell transplantation has been performed. Only some small case reports reported about short lasting remission duration, but overall it is very unlikely that by withdrawal of immunosuppression a long term control of the disease can be achieved. Responses are more likely achieved in patients with low tumor burden or only molecular or cytogenetic relapse2.

Donor Lymphocyte Infusion

The response to donor lymphocyte infusion various in the literature between 0 and 60 % depending on the tumor burden, the use of chemotherapy prior to DLI or the remission duration achieved by the allo transplant procedure. However, the majority of the obtained responses do not translate into long term survival. An important factor for more improved outcome of donor lymphocyte infusion is the remission duration achieved by the allo transplant procedure. To improve the result of donor lymphocyte infusion some investigators used prior chemotherapy to reduce the number of blasts. The European Group for Blood and Marrow Transplantation (EBMT) reported on AML patient with first hematological relapse and compared patient who received donor lymphocyte infusion (n = 171) to patients who did not receive donor lymphocyte infusion (n = 228). For those who received DLI the probability of a 2-year-survival was significantly improved with 21 % versus only 9 %. Major risk factors for improved survival were younger age and duration of remission after allo transplantation. In those series the patient who had chemotherapy prior DLI have an 2-year-survival greater than 50 %3. In other trials which combined chemotherapy and donor lymphocyte infusion the 1-year-suvival was only 10 %, if relapse occurred within 6 months after transplant versus

44 %, if relapse occurred later. To reduce the risk of severe myeloid suppression induced by chemotherapy more recently less toxic agents like hypomethylating agents (5-azacytidine) has been used to treat patients with relapse after allo transplant. With this approach combined with donor lymphocyte infusion 23 % of the patients achieved a complete remission, which lasted for a median of 20 months without any additional treatment.

Second allogeneic transplant

A further option which is more valid for younger patients is a second allo transplant. Larger retrospective studies from transplant registry reported a high treatment related mortality of about 30 % and a relapse incidence of about 42 %. Favourable factors for outcome were age of the patients < 20 years and a complete remission duration of at least 6 months after the first allogeneic transplantation. The value of choosing a different donor for the second transplant has not been shown conclusively. Since more patients received a dose reduced conditioning as first transplant, the option for a second transplantation is steadily increasing. However, it is currently unknown, which preparative regimen should be used and if an alternative donor would be of benefit for the patient. Other options to treat relapse are cell-based either NK-cells, different F-cell subsets or vaccine studies.

Conclusions: Overall, the current therapeutical modalities are limited for relapse patients after AML. More clinical studies are needed and further research should focus also in strategies to prevent clinical relapse by monitor those patients closely with molecular markers which may guide for immunotherapeutical or drug base strategies to avoid clinical relapse.

References

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