High efficacy of combinaison of HMA + Mylotarg® to treat LMA relapse after alloSCT.

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We report three AML patients relapsing after alloSCT and succesfully treated by the association of Decitabine® and Mylotarg®.

A 61-year-old man, with CML controlled by Imatinib, developed 7 months later an unrelated NPM1+/ FLT3-ITD AML (high allelic load). Cytological remission was obtained after treatment (HOVON132- like). Before unrelated alloSCT, marrow control showed a molecular relapse. He developed an overt relapse 3 months after the transplant, treated by Decitabine® 20mg/m² (d1-d5) + Mylotarg® (5mg at day 8) allowing complete remission with MRD persistence (NPM1 quant.=0.00840). Then, he received 3 additional courses of Decitabine® followed by Nexavar® 200mg/d and two infusions of donor lymphocytes (DLI). Eighteen months after relapse, the patient is still in molecular complete remission.

A 68-year-old woman with NPM1+/FLT3-ITD AML included in the QUANTUM FIRST protocol (intensive chemo +/- quizartanib). She underwent a MUD allograft in CR1 and maintained a positive NPM1-MRD post-transplant despite administration of Nexavar® 200 to 400mg/j and manifestations of alloreactivity. She developed an overt relapse 2,5 years post-transplant which was salvaged by the combination of Decitabine® (20mg/m² d1-d5), Mylotarg® (5mg at day 8) and three DLIs, allowing complete remission to be achieved with NPM1-MRD negativity.

A 65-year-old woman, with a M1-AML, normal karyotype and mono-allelic CBPα mutation obtained remission after standard 3+7 and 2 courses of HD Ara-C and underwent a related alloSCT. One year later, she developed a cytogenetic relapse, with gain of a +8 followed by an overt relapse. She didn't respond to two courses of Azacitidine alone but obtained CR after 2 courses of Decitabine®+Mylotarg®. Unfortunately she presented a second relapse 6 months later.

The use of Mylotarg® to treat a post-allograft relapse is particularly relevant since the target is restricted to the myeloid compartment and preserves the lymphoid compartment which remains available to exercise alloreactivity and allows the use of DLI.

There is a rationale for combining a hypomethylating agent (HMA) with Mylotarg®. The first agent increases the expression of CD33[(1)] on the surface of blast cells making them more sensitive to the action of the second.

Post-allograft HMA has many advantages. Acting on the proliferation of the leukemic clone, promoting alloreactivity by increasing the expression of specific antigens on the leukemia cell surface[(2)] and mitigate the risk of GVHD by polarizing the lymphocytes (including DLIs) towards a regulatory profile by inducing FOXP3 expression[(3)].

Finally, this series demonstrates the effectiveness of the HMA+Mylotarg® combination in advanced and chemo-resistant disease. It allows this combination to be considered in older or unfit de novo AML patients for whom response to HMA alone remains insufficient.

Bibliography

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