Efficacy of decitabine as salvage therapy for chronic neutrophilic leukemia (CNL) relapsing early after second allogeneic stem-cell transplantation.

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Objectives

CNL is a rare disease usually characterized by a CSF3R-T618I mutation. Except allogeneic stem cell transplantation (alloSCT), no treatment has been shown to improve survival. Studies show inconsistent results with hydroxycarbamide, ruxolitinib, dasatinib or agents such as interferon-α, hypomethylating agents, thalidomide and cladribine.

Methods

Second allogeneic transplantation remains a curative option after first relapse if the patient is still eligible. No current guideline actually exists for the management of relapse after second alloSCT. We report here the case of early relapse after a second alloSCT.

Results

A 65 years-old man was diagnosed with CNL harboring the classical CSF3R-T618I mutation and a ASXL1 mutation. He suffered from night sweats, pruritus, weight loss and large splenomegaly. He sequentially received hydroxycarbamide, ruxolitinib and dasatinib without improvement. We therefore decided to offer to the patient the opportunity to proceed to alloSCT after splenectomy. Given the proliferative nature of the disease, he underwent an HLA 12/12 MUD alloSCT after bridging with aracytine followed by a fludarabine and melphalan containing reduced-intensity conditioning (RIC). Graft versus host disease (GvHD) prophylaxis comprised thymoglobulin, ciclosporin and MMF. Donor blood and medullar global chimerism at 3 months were 100% but 82% for T lymphocyte. In the absence of GvHD, immunosuppression (IS) was progressively decreased. At 9 months, T lymphocyte chimerism continued to decrease and global chimerism was falling to 77%. Donor lymphocyte infusion (DLI) was administered 3 times without any sign of alloreactivity. Ruxolitinib was reintroduced to try to contain the leukemic clone but hyperleucocytosis appeared. Hydroxycarbamide was restarted. At 15 months, blood chimerism was lost. Dasatinib and mercaptopurine were ineffective. A second HLA 12/12 unrelated alloSCT after bridging with aracytine and a RIC (fludarabine, cyclophosphamide and TBI 2 grays) was performed. Despite acute GvHD (generalized erythrodermia requiring methylprednisolone), relapse occurred after 3 months with donor medullary chimerism rapidly decreasing from 92% to 37%. IS was interrupted. Decitabine was started in hope of controlling the leukemic clone parallel to the administration of DLI to restore alloreactivity. After 3 cycles of decitabine (8 months after second alloSCT), medullary chimerism was complete. The patient developed chronic GvHD with oral, genital and eyes impairment. Tacrolimus and methylprednisolone were started with progressive clinical improvement. 1 year after second HSCT, there is no sign of CNL and GvHD is under control.

Conclusion

Given the rarity of CNL, there is very little data on the outcome after alloSCT, particularly after second allogeneic transplant. It therefore seemed interesting to relate the story of this patient by insisting on

the incredible sensitivity of the disease to decitabine. This made it possible to restore a useful alloreactivity towards a perfectly controlled disease as evidenced by the recovery of complete donor chimerism after only 3 courses of decitabine. It also highlights the usefulness of hypomethylating agents in managing the relapse of myeloid disease after alloSCT.