

The sobering reality of fertility preservation in young female patients with acute leukemia

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“Rachel envied her sister, and said unto Jacob, ‘Give me children, or else I die’ ” (Genesis 30:1). The desire of parenthood is deeply embedded in humans, with religious, cultural and psychological elements. Allogeneic bone marrow transplantation (alloSCT), which is the best post-remission therapy for patients with acute leukemia exhibiting high-risk genetics or with suboptimal response to initial treatment, is likely to result in ovarian failure among female survivors,¹ particularly if preceded by myeloablative conditioning.² There is no standard procedure for fertility preservation in females with acute leukemia. Ovarian protection during chemotherapy with gonadotropin-releasing hormone agonists has not been proven to be beneficial in patients with hematologic malignancies,³ while other promising hormonal therapies, such as müllerian inhibiting substances, are at a pre-clinical stage of research. The cryopreservation of oocytes, which might be the best option for post-pubertal patients with cancer, often requires several weeks for ovarian stimulation and oocyte retrieval⁴ whereas, in most cases, the treatment of acute leukemia cannot be delayed for so long a time. Furthermore, the coagulopathy that accompanies the diagnosis of acute leukemia, as well as the attendant neutropenia, compromise the safety of this method. Delaying and implementing oocyte retrieval after achieving remission, when it might be possible to delay treatment and the coagulopathy and neutropenia have already been resolved, is discouraged, as the quantity of oocytes retrieved is low,⁵ and there is a theoretic risk of DNA damage and aneuploidy, at least in animal models.⁶ For pre-pubertal patients with leukemia, and for patients in whom the treatment cannot be delayed, the only realistic option is ovarian tissue cryopreservation (OTC) after achieving remission followed by ovarian tissue auto-transplantation (OTT) when ovarian failure is documented and a pregnancy is desired. Prior studies suggest that chemotherapy exposure prior to OTC does not reduce the probability of conceiving.⁷ Moreover, the OTT leads to

high rates of restoration of ovarian endocrine function. However, a concern was previously raised regarding the re-introduction of leukemic cells upon transplanting the ovarian tissue.⁸ The modalities available for fertility preservation in females with acute leukemia are illustrated in Figure 1.

In this issue, Chevillon and colleagues report the largest cohort of 13 female survivors of alloSCT who successfully underwent OTT in order to be able to conceive, all without other contraindications for pregnancy and all in long-term remission after transplantation.⁹ This cohort represents the tip of the iceberg of candidates for alloSCT who are referred to OTC, and yet the results are very disappointing, with only 3 women who became pregnant and only one live birth at the risk of a presumed OTT-originated relapse. The work by Chevillon *et al.* raises the issue of the true overall effectiveness of OTC in patients for whom alloSCT for acute leukemia is planned. The 5-year survival post alloSCT is only 40–70%, and as many as 30–40% of survivors will experience chronic extensive graft-versus-host disease (GvHD) which precludes pregnancy. Even allowing for recent advances in GvHD prevention and management (e.g., post-transplant cyclophosphamide, roxutinib, belomusudil), the rates of chronic extensive GvHD is 15–20%.¹⁰ Many of the survivors will suffer from sexual dysfunction or be left unemployed and thus be unable to support a child. Indeed, 3 of the women in this paper had planned for a pregnancy and therefore had agreed to OTT but later declined this for non-medical issues. This emphasizes the socio-economic burden of alloSCT in survivors. Moreover, the concept of requiring the eradication of measurable minimal residual disease (MRD) prior to transplant¹¹ has only been prospectively established in B-ALL with blinatumomab. Thus, many patients with AML at higher risk are likely to have MRD at the time of alloSCT and, as a consequence, presumably also in the ovarian tissue.¹² In such patients, OTT would be contraindicated.

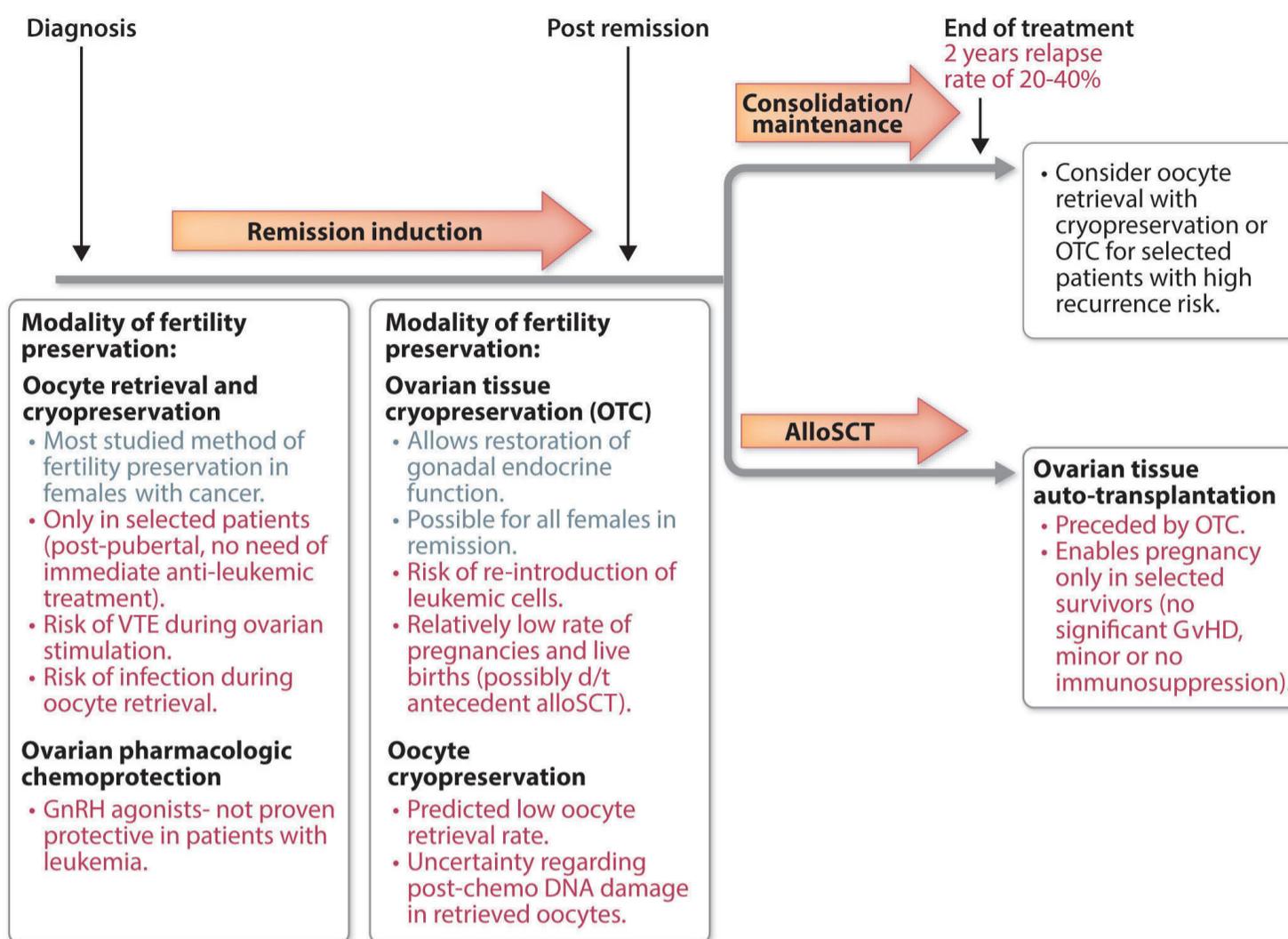


Figure 1. Timeline of various fertility preservation methods in female patients with acute leukemia. Advantage of modality in gray. Disadvantage of modality in red. Note that after completion of post-remission chemotherapy, spontaneous pregnancy is often possible as the risk of ovarian failure is <20%. alloSCT: allogeneic bone marrow transplantation; d/t: due to; GvHD: graft-versus-host disease; VTE: venous thromboembolism.

In addition to the cost-effectiveness, the safety of OTT is a matter of debate, as the ability to truly rule out the presence of leukemic cells in ovarian tissue is limited. The best MRD standard testing methods are at a sensitivity of 10^{-5} , which might not be sufficient. Indeed, the patient who relapsed in the current paper had unmeasurable MRD in the ovarian tissue, and yet experienced relapse, although it remains unproven whether the relapse occurred from occult leukemic cells in the ovarian tissue. Furthermore, many of the patients with genetically defined high-risk AML and some of the ALL patients have no molecular marker for qPCR monitoring. These patients are often monitored with flow cytometry at a lower sensitivity of 10^{-3} - 10^{-4} . In summary, Chevillon *et al.* are challenging the practice of fertility preservation by OTC followed by OTT in alloSCT candidates both by the questionable safety and the low efficacy of the procedure. Given the lack of alternatives for

fertility preservation in these patients, future improvement in GvHD treatment, potential post-alloSCT maintenance therapies (e.g., menin inhibitors in AML) as well as more precise methods for MRD detection, such as NGS-based patient-specific IGH/TCR testing and customized qPCR for AML with unique translocations might enable an enhanced risk-benefit assessment. For centuries, the desire of women to attain motherhood has gone far beyond the simple rationale. As physicians, we must be sensitive to this and not automatically discourage all women who are determined to conceive. Given the current knowledge, it is likely that OTT will continue to be offered to selected women who are determined to have a child, after full consideration of all the risks.

Disclosures

No conflicts of interest to disclose.

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