

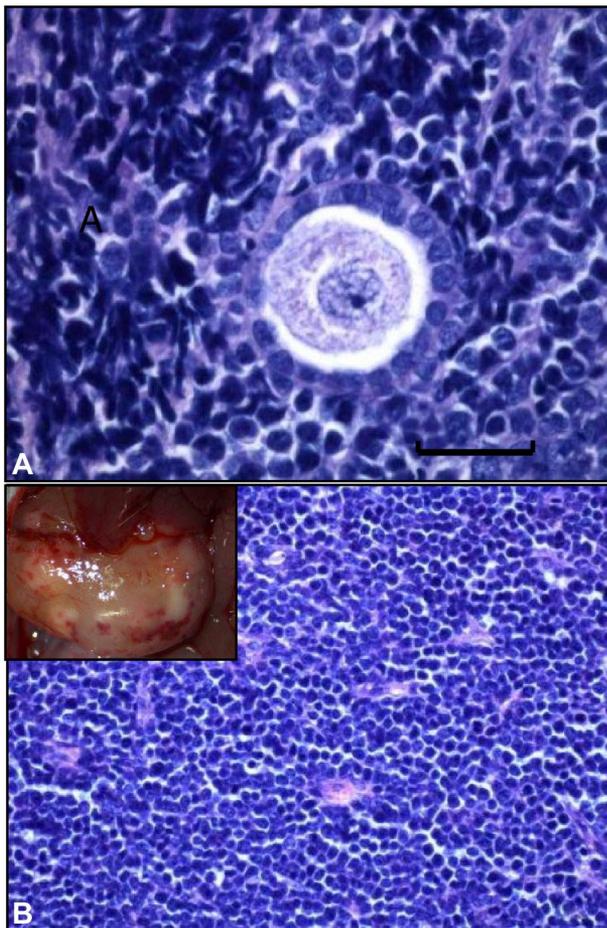
● ● ● CLINICAL TRIALS

Comment on Greve et al, page 4311

Safety of ovarian autotransplantation

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In this issue of *Blood*, Greve et al report that ovaries from leukemia patients in complete remission do not appear to contain viable malignant cells, in contrast to ovarian tissue retrieved before chemotherapy.¹



Grafted frozen-thawed ovarian tissue from a leukemia patient. (A) Histologic analysis of a frozen-thawed ovarian fragment from a leukemia patient recovered from a mouse after 6 months' xenografting. Normal ovarian stroma is no longer present, and a human follicle encircled by a large number of proliferating malignant lymphocytes can be seen (scale bar = 20 μ m). (B) Large, white, burgeoning mass that corresponded to massive peritoneal invasion by leukemic cells.

This paper raises a number of questions because 3 different teams (Meirow et al,² Rosendahl et al,³ and Dolmans et al⁴) have so far demonstrated by PCR that ovarian tissue from leukemia patients is positive for malignant cells in more than 50% of cases.

We have previously reported that xenografting of cryopreserved ovarian tissue from leukemia patients (chronic and acute leukemia) resulted in development of leukemic tumors (see figure).⁴ Differences between the results of these 2 studies may be explained, at least partially, by the fact that of the 25 women Greve et al studied, 17 had received chemotherapy and were in remission, 4 had received initial treatment but had not achieved remission, 3 had chronic-phase chronic myeloid leukemia, and 1 had an unknown remission status at the time of ovarian biopsy and cryopreservation.^{1,4}

In the study by Greve et al, of the 7 patients with a known marker and who had already received chemotherapy at the time of ovarian cryopreservation, 4 showed PCR-positive ovarian tissue (2 with chronic leukemia and 2 in remission with acute leukemia). Even if xenografts from these patients failed to induce tumoral development, it cannot be excluded that cancer cells may be present in other tissue pieces.

Nine of the initial 45 acute or chronic leukemia patients identified with cryopreserved ovaries had already died before initiation of this study. Unfortunately, the study of the preserved ovarian tissue from the dead women was not authorized by the local ethics committee.¹ It would have been extremely valuable to confirm the presence or absence of malignant cells in the ovarian tissue of these patients, as some were likely in complete remission at the time of the cryopreservation procedure. These patients probably presented with a more aggressive form of the disease and were thus most at risk of carrying malignant cells in their ovarian tissue.

Even if some of the results from Greve et al are reassuring and demonstrate that ovarian

tissue taken from leukemia patients in complete remission after chemotherapy does not induce tumors in a xenograft model, the presence of positive PCR should lead us to interpret these results with caution.

It is too early to be sure that frozen-thawed ovarian tissue from leukemia patients in complete remission contains nonviable malignant cells or too few cells to reintroduce cancer. From a hematologic point of view, blasts may be more fragile than ovarian tissue and not able to withstand the cryopreservation procedure. Moreover, if a few viable malignant cells remain in the tissue, time may be required before they become detectable. Late relapse can sometimes occur more than 2 years after remission is induced.

In conclusion, like Greve and colleagues, our team believes that the risk of cryopreserved ovarian tissue from leukemia patients in complete remission containing malignant cells is low. However, it cannot be completely excluded. This study should be confirmed by other teams before ovarian trans-

plantation is considered risk-free in these patients. We agree with Greve et al that alternative methods like in vitro maturation or isolated follicle transplantation should be evaluated for fertility preservation in leukemia patients.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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approximately 200 patients reported an 85% chance of cure with 7% TRM and 8% rejection risk.²⁻⁴ However, as demonstrated in a French study,⁴ the addition of rabbit antithymocyte globulin (ATG) allows for a large decrease in the risk of rejection, resulting in significant improvement in results over time with a 95% chance of cure. These results have now been confirmed by our experience with 120 more young patients who have received a transplant since 2000.⁵

To extend the possibility of cure to SCD adults with organ dysfunction, nonmyeloablative conditioning regimens were proposed, but initial trials failed to induce stable donor engraftment⁶ despite the HLA-identical context of the transplants. This underlines the singularity of transplantation for SCD where the recipient is fully immunocompetent and has a proliferative bone marrow, and GVHD has no utility. More recently a nonmyeloablative conditioning regimen based on alemtuzumab (Campath), low-dose total body irradiation (TBI), and transplantation with peripheral blood stem cells (PBSCs) from an HLA-identical donor followed by sirolimus was successfully applied to 10 adults.⁷ Remarkably, no TRM or GVHD occurred, and donor engraftment was observed in 9 of 10 recipients. Sirolimus (rapamycin), unlike cyclosporine, does not block T-cell activation and promotes T-cell tolerance.⁷ However, donor/recipient pairs with ABO incompatibility were excluded from this trial. Of note, despite frequent stable mixed chimerism in these studies,^{4,5,7} erythropoiesis was of donor origin, resulting in operational cure of the patient.

In countries with high standards of care the major obstacle to wide application of transplantation in SCD remains the paucity of HLA-identical related donors because less than 25% of children have a healthy familial-identical donor. However, as HSCT is not an urgent indication in SCD as is the case in malignant diseases, the chances of having an identical donor will increase during the infancy of the sick SCD child if the providers discuss HSCT early, and propose prenatal or preimplantatory diagnosis and sibling cord blood cryopreservation when parents are expecting another child. Nevertheless, HLA-identical unrelated donors from registries remain very difficult to find for minorities,⁸ and unrelated cord blood transplants (CBTs) gave disappointing results in SCD with high

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Haplo-BMT: cure or back to sickle cell?

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In this issue of *Blood*, Bolaños-Meade et al report promising results using a pioneering HLA-haploidentical bone marrow transplantation protocol in adults with sickle cell disease (SCD), including nonmyeloablative conditioning and post-transplantation high-dose cyclophosphamide.¹

Despite considerable progress made in the management of SCD such as the prevention of pneumococcal infections, the introduction of hydroxyurea therapy, and the early detection of cerebral vasculopathy with transcranial Doppler (TCD), SCD remains a disease with high risk of morbidity and early death. Hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment for SCD. Nevertheless, its use has been limited by the lack of available donors, and also by the risks of transplant-related mortality (TRM), graft-versus-host disease (GVHD), infertility, and its cost for a disease that principally affects patients living in countries with low gross domestic product.

For several years Luznik et al have been developing the interesting concept of tolerance induction by using early post-transplantation high doses of cyclophosphamide, which kill proliferative alloreactive T cells while preserving resting nonalloreactive T cells.² Bolaños-Meade et al report here their experience with 14 SCD patients who received a transplant using a haplo-identical donor. Their results will allow the expansion of the donor pool for most SCD patients in the future as almost every patient has a haploidentical-matched parent or sibling.

In the US and European countries, myeloablative HLA geno-identical transplantation is now a well-established treatment option in symptomatic children.^{3,4} Published results of