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● ● ● CLINICAL OBSERVATIONS

Comment on Lenz et al, page 2667

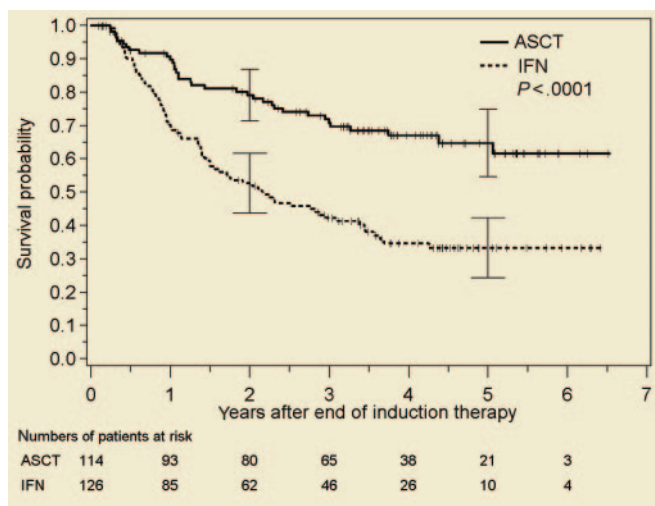
Autologous transplantation for newly diagnosed follicular lymphoma: cure at last or not yet?

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In this multicenter, randomized prospective study of patients with advanced follicular lymphoma, autologous stem cell transplantation resulted in a doubling of progression-free survival at 5 years. Further follow-up is needed to establish a survival advantage, if any.

The role of autologous stem cell transplantation (ASCT) in follicular lymphoma has long been controversial, because of the lack of carefully controlled prospective data. The study of the German Lymphoma Study Group (GLSG) reported by Lenz and colleagues in this issue of *Blood* provides important new information and a much better definition of the benefits of ASCT. This study

included patients younger than age 60 with advanced indolent lymphomas including follicular lymphoma, small lymphocytic lymphoma, and mantle cell lymphoma. The large majority of patients had follicular lymphoma and constitute the subject of the report. Standard treatment consisted of 8 cycles of cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) followed by interferon



PFS after high-dose radiochemotherapy followed by ASCT and IFN- α maintenance in follicular lymphoma. See the complete figure in the article beginning on page 2667.

maintenance. Those patients randomized to the investigational arm received 6 cycles of CHOP, 1 cycle of Dexamethasone 3 \times 8 mg by mouth, days 1-10; BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea] 60 mg/m² intravenously, day 2; melphalan 20 mg/m² intravenously, day 3; etoposide 75 mg/m² intravenously, days 4-7; cytarabine 2 \times 100 mg/m² intravenously, days 4-7; and granulocyte-colony-stimulating factor [G-CSF] initi-

ated on day 11) for stem cell mobilization, and ASCT with cyclophosphamide-total body irradiation (TBI) conditioning. Randomization occurred after the second course of induction therapy. (A second randomization, to an alternative induction regimen of mitoxantrone, chlorambucil, and prednisone [MCP], was stopped after preliminary analysis showed decreased stem cell mobilization with MCP).

Toxicities were as expected, with more myelosuppression, severe infections, gastrointestinal (GI) toxicity, and mucositis in the transplant arm and more muscle and bone pain and depression in the interferon arm. Treatment-related mortality was extremely low in both arms. The primary end point of the trial was progression-free survival (PFS), which was monitored continuously, so that the trial could be stopped as soon as significant superiority or, alternatively, futility of the transplant arm was documented. The results of the study in 240 evaluable patients and a median follow-up of longer than 4 years confirm superiority of ASCT over interferon maintenance. PFS is nearly doubled in the transplant arm (64.7% vs 33.3% at 5 years) and two thirds of patients randomized to transplant remain in remission at 5 years (Figure 1). The analysis focuses on those who completed induction therapy but an additional analysis of all randomized patients confirmed the results and ruled out any selection bias. The results are consistent with other recently reported randomized studies of ASCT in first or subsequent remission of follicular lymphoma.¹⁻³

This does not mean that ASCT should now be accepted as the standard of care for patients with follicular lymphoma. First, more prolonged follow-up is needed to establish whether the advantage in PFS will also translate into a survival benefit. The high incidence of secondary myelodysplastic syndrome (MDS) in this and other studies of ASCT is of concern and could affect overall survival rates. Whether the excess risk for MDS is due to the conditioning regimen, the stem cell mobilization regimen, or even to a protective effect of interferon in the standard treatment arm remains an open question. Second, in a preliminary analysis of a more recent study, the GLSG demonstrated that addition of rituximab to CHOP yields comparable benefits to ASCT and may therefore represent a suitable alternative.⁴ Randomized trials of radioimmunotherapy (CHOP-tositu-momab) and

of anti-idiotype vaccines are also under way. Their results may further alter therapeutic options. Thus, optimal treatment for follicular lymphoma remains to be defined.

Still, the availability of several new drugs and the completion of large studies with positive results are rapidly changing the paradigm of treatment for follicular lymphoma, long considered an incurable illness. If ASCT results in 5-year remission for two thirds of patients and CHOP-rituximab does the same, what about the combination? Only the future and more studies will tell. ■

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The results of this study provide very encouraging news for the hemophilia gene therapy community. However, ongoing concerns about the potential adverse outcomes from insertional mutagenesis and the extent to which studies in fetal mice can be extrapolated to humans will require further work to corroborate this study.

In the related work of Sabatino and colleagues, another important advance in developing mouse models for preclinical testing of hemophilia gene therapy is reported. To date, 3 mouse models of hemophilia B exist.¹⁻³ In each of these models, the resulting gene disruption has produced a null phenotype for murine FIX with the consequence that any FIX produced by these animals is likely to be immunogenic. These investigators have addressed this limitation of the murine hemophilia B model by introducing a wild-type and several different mutant human FIX transgenes into the gene-disrupted hemophilia B mouse. These FIX mutations represent a small sample of the several hundred genetic alterations now documented to produce this phenotype in humans. Mice transgenic for the various human FIX constructs (wild-type, 5' and 3' nonsense mutations, and 2 missense mutations) were generated by a standard microinjection technique and transgene-positive males were crossed with hemophilia B females to obtain animals transgenic for the human FIX sequences on a mouse FIX null background.

The biosynthetic characteristics and functional activity of the human FIX constructs were studied in cell culture and in the transgenic mice, and, most importantly, the host immune response to an adeno-associated virus (AAV)-mediated intramuscular delivery of a human FIX transgene was evaluated in the mice. These latter studies showed results that would be predicted from our knowledge of FIX immunogenicity in human hemophiliacs, with the appearance of anti-FIX antibodies only in the original FIX null mice and in the 2 transgenic strains with nonsense mutations.

As preclinical studies of hemophilia gene therapy continue, the development of animal models that best reflect the likely efficacy and safety of this therapeutic approach in humans is critical. This is particularly important for the assessment of the host immune response to the transgene product. The report of Sabatino and colleagues represents an important advance toward the attainment of such a model for hemophilia B. ■

● ● ● GENE THERAPY

Comment on Waddington et al, page 2714, and Sabatino et al, page 2767

Testing novel hemophilia therapies: of mice and men

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Two articles in this issue provide further hope for the future of novel hemophilia therapies. In one of these articles, long-term therapeutic expression of factor IX has followed lentiviral-mediated prenatal transgene delivery, while the second article describes studies of factor IX expression and immunogenicity in hemophilia B mice rendered transgenic for several human factor IX mutations.

While current hemophilia treatments with both plasma-derived and recombinant clotting factor concentrates are safe and effective, there continues to be progress toward the development of novel therapies that might ultimately result in long-term cure of this disease. In this issue, 2 articles describe important preclinical advances for the treatment of hemophilia B.

Waddington and colleagues report their results of using lentiviral-mediated delivery of a human factor IX (FIX) transgene to immunocompetent mice at 16 weeks gestation by injection into the yolk sac vessels, a route of delivery corresponding to umbilical vein injection in humans. This mode of administration targets the liver, and in this study, in which 50% of the fetal liver cells were found to be in a proliferative state, up to 5% of hepatocytes were transduced with the therapeutic lentivector.

In 3 hemophilic and 6 normal outbred mice, these single-transgene administrations

resulted in therapeutic plasma levels of human FIX out to more than 400 days after injection. In the hemophilic animals, the human FIX antigen levels ranged from 0.11 to 0.18 U/mL at around 300 days after treatment. Throughout the study, the levels of functional human FIX:C showed a significant correlation with the FIX:Ag levels but were consistently and inexplicably approximately 5-fold higher than the antigen levels. In contrast, mice treated prenatally with an adenoviral FIX construct showed only low-level and transient human FIX expression.

In addition to documenting the long-term therapeutic expression of FIX, this study has also shown a number of other promising details. There was no evidence of hepatotoxicity, no apparent germ line transmission of the lentivector, and none of the mice developed anti-human FIX antibodies, even after being challenged with human FIX coadministered with adjuvants.