HTLV-I–infected MT2 cells undergo senescence after long-term AZT treatment, as determined by senescence β gal assay. See the complete figure in the article beginning on page 1021.

Because HTLV-I–transformed cells are resistant to nearly all apoptosis-inducing agents, the treatment of ATLL patients using conventional chemotherapy has very limited advantage. Zidovudine (AZT), which was initially synthesized as part of an anticancer drug discovery program, has been shown to inhibit HTLV-I transmission in vitro. More recently, antiretroviral therapy using the combination of AZT and interferon alpha (IFN-α) has also been shown to induce a high rate of complete remission and to prolong the survival of some ATLL patients.1,2

But until the report by Datta and colleagues in this issue of Blood, the mechanism of action of AZT and IFN-α was controversial. Some studies argued in favor of an antiviral effect through the inhibition of HTLV-I replication, while others proposed a direct antiproliferative effect of the drugs on the leukemic cells.3,4 For these reasons, the predictive markers for choosing AZT rather than another drug for treating ATLL patients were unknown.

Here, instead of treating the HTLV-I–infected cells for a short period of time, as is usually the case in vitro, Datta and colleagues performed a long-term treatment with AZT. AZT can act as an inhibitor of the telomerase functions, and indeed, under these circumstances all HTLV-I–infected cell lines tested entered senescence rather than apoptosis. This was concomitant with a reduction of the telomerase activity and a decrease in telomere length.

Of interest, the levels of the p53 tumor suppressor were much higher in cells that were exposed to AZT for several weeks, but no effect was seen after 24 hours of treatment. Because p53 protein is inactive but wild type in sequence in most HTLV-I–infected cells,6 Datta and colleagues determined whether AZT prolonged treatment–reactivated p53 functions. Following ionization-radiation of AZT–treated cells, the mRNA levels of p21waf and Bax (2 p53–dependent genes) increased and confirm the working model. The required duration of AZT treatment in vitro is consistent with the slow kinetic that is observed in vivo in ATLL–treated patients. Datta and colleagues also demonstrate that AZT treatment induces telomere shortening of fresh ATLL cells. The percentage of ATLL patients who are refractory to AZT is very similar to that of the patients whose p53 gene is mutated. For this reason, the authors investigate whether there was a correlation between these 2 observations. In a retrospective analysis, they demonstrate that there was a perfect parallel between the p53 status and the response to AZT treatment: all patients carrying a wt-p53 gene responded to AZT and went into partial or complete remission. By contrast, AZT had no effect in ATLL patients carrying a mutated p53 sequence.

It is estimated that several thousand ATLL patients pass away each year. Until this work, it was unclear why some AZT–treated patients enter remission while others die. This very nice study provides for the first time a rationale for treating or not treating HTLV-I ATLL patients with AZT. Patients with a mutated p53 gene might therefore be treated with alternative drugs, such as arsenic trioxide, which target both the Tax protein and the NF-κB pathway.7

REFERENCES

Never say never again!

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Irreversible gonadal failure has previously been considered an inevitable consequence of allogeneic stem cell transplantation and an unfortunate but acceptable price to pay for cure of the underlying disease.

In this issue of Blood, Rovó and colleagues present convincing evidence that our earlier gloomy predictions may have been exaggerated. Thirty-nine male survivors of allografting participated in a snapshot survey of spermatogenesis and 11 (28%) had some degree of recovery. Restoration of spermatogenesis was associated with younger age at transplantation, longer intervals since transplantation, and the absence of chronic graft-versus-host disease (GvHD). Gonadal recovery in men has been reported previously,1,3 but this study is sufficiently large to identify prognostic factors. Younger age at transplantation, a well-recognized prognostic feature for women, has not been considered so important for males. In fact, in this study only one male older than 25 years recovered.

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sperm production, and more than half of those younger than 25 years at transplantation and more than 9 years from grafting recovered. Perhaps the most interesting result is the association of return of spermatogenesis with an absence of chronic GvHD, introducing the possibility of alloimmune-mediated damage of gonadal tissue.

The study, although most encouraging, still leaves us with some unanswered questions. First, is gonadal recovery impossible in older men? From the figure, it would appear that older men do not generally survive more than 2 years from transplantation. In fact, older patients were less likely to participate in the study, and this is academically regrettable. Older men were more likely to have a family prior to transplantation and perhaps less interested in their personal results. One can speculate about other reasons, including perhaps that their partners were beyond the normal biologic age of conception. Second, how likely is recovery in the prepubertal or peripubertal boy? From this study, it seems that this group has a high chance of recovery with time, but further information regarding their optimal management is required. Third, is the chance of recovery affected by the preparative regimen, particularly pertinent in this time of reduced-intensity conditioning (RIC)? All 3 patients who received transplants using cyclophosphamide as the single agent for severe aplastic anemia (SAA) recovered. However, the 3 recipients of RICT were less than 3 years from transplantation and none showed evidence of recovery. Time will tell. Fourth, what was the effect of prior chemotherapy? Unfortunately, there were no data regarding spermatogenesis immediately prior to transplantation, and so any available information was uninterpretable. Finally, does recovery of spermatogenesis always indicate return of fertility? None of the participants had completely normal spermatogenesis as defined by WHO guidelines and only 3—those who underwent transplantation for SAA, had fathered children since their transplantation.

The demonstration that return of spermatogenesis is possible will give hope to prospective male recipients of a transplant, particularly for their future quality of life. In practice, however, this study also shows 70% of individuals had not recovered and confirms the need for knowledgeable counseling and semen cryopreservation prior to treatment. Paradoxically, it also alerts us that counseling regarding birth control will become a more regular feature of post-transplantation follow-up! ■

REFERENCES

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Glucocorticoid resistance: a persistent riddle

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Resistance of ALL blasts to glucocorticoid therapy does not appear to be due to decreased up-regulation of receptor promoter or receptor transcripts.

We know a great deal about how glucocorticoid hormones act in normal tissues. Upon entry into cells, they bind to receptors that are then translocated to the nucleus. In the nucleus, the receptor-steroid complex binds to response elements on DNA, thereby affecting transcription of specific genes.

Glucocorticoids have been an important component of the treatment of acute lymphoblastic leukemia (ALL) for more than 50 years. Nevertheless, we are still in the dark regarding mechanisms affecting sensitivity and resistance to these drugs. Hypotheses have included differences in the following: receptor numbers, receptor polymorphisms, splice variants, receptor phosphorylation, glutathione levels, multidrug resistance, transcription factor complex components, apoptosis pathways, and induction of endonuclease activity. Although each of these may affect corticosteroid activity, none adequately explains sensitivity and resistance.

In this issue of Blood, Tissing and colleagues investigated the in vitro expression of mRNA for glucocorticoid receptor promoters and glucocorticoid receptors in leukemic blasts at baseline and after exposure of these...
Never say never again!

Jane F. Apperley