As pointed out, the CR rate was 34% by the modified IWG criteria and 40% in the best schedule (5-day intravenous). This compares favorably with prior experiences with decitabine and 5-azacitidine (CR rates, 6%-20%). Also, decitabine was less toxic than 5-azacitidine in relation to nausea/vomiting and local skin reactions (pain and induration in 5%-10% of patients on 5-azacitidine). The incidence of 65% of hospitalization is cumulative. As one delivers more courses of effective therapy, the probability of a 1-time hospitalization would be more likely after multiple courses than after 1 or 2 courses. In the summary briefing of the Food and Drug Administration (FDA) by Kaminskas et al., the incidence of serious adverse events (mostly febrile episodes and hospitalizations) was 60%, similar to our experience. Thus, short of directly comparative trials, the current studies suggest that at the current dose schedules, decitabine and 5-azacitidine are probably equally myelosuppressive.

The paper makes no comments on the relationship between p15 methylation and expression. In fact, analysis of the data shows that samples in which p15 methylation was greater than 15% had 6-fold lower expression of p15 than unmethylated samples, exactly as expected (deltaCT compared with GAPDH, −21.7 in the methylated group, and −19.2 in the unmethylated group; P < .001). No patients with a high degree of methylation had high levels of expression. However, a low degree of methylation was not necessarily predictive of high-level expression, suggesting that factors other than the methylation are also associated with p15 down-regulation in MDS. It is interesting to note that few patients in this study had high levels of p15 methylation. Thus, the p15 induction by decitabine observed came from both p15 hypomethylation-related and -unrelated epigenetic effects. It is also well known that DNA methylation inhibitors can affect gene expression independent of promoter methylation.

We agree that the results we observed may be confounded by the presence of lymphocytes. Unfortunately, no sorted samples are available from these patients to address this issue experimentally. Unpublished data from our laboratory (Y.O. and J.-P.I., 2006) showing a high degree of correlation between methylation in unsorted peripheral blood mononuclear cells and unsorted bone marrow mononuclear cells suggest that variable contamination with nonmalignant lymphocytes is unlikely to be significant. This issue clearly should be tested in future studies.

We hope this clarifies the points raised. Based on our experience, decitabine appears to be the most active anti-MDS single agent. Further experience with single-agent decitabine and with decitabine combinations may hopefully improve prognosis in MDS and CMM.

References


To the editor:

Recovery of spermatogenesis after total-body irradiation

We read with interest the paper by Rovo et al., who studied spermatogenesis in 39 long-term survivors after allogeneic stem cell transplantation (allo-SCT). Eleven patients had recovery of spermatogenesis. The authors found that a younger age (<25 years) and a non-total-body irradiation (TBI)-based conditioning regimen (CR) were independent factors predicting active sperm production after allo-SCT.

At our institution, male patients gave written consent to be enrolled in a long-term posttransplantation follow-up study, including annual semen analysis (SA). Of the 74 patients enrolled in the study, 40 were male, and 35 underwent SA. The indication for allo-SCT was chronic myelogenous leukemia (CML; 25 patients), myelodysplastic syndrome (MDS; 5 patients), acute myelogenous leukemia (AML; 3 patients), acute lymphoblastic leukemia (ALL; 1 patient), and chronic lymphocytic leukemia (CLL; 1 patient). Median follow-up after transplantation was 6 years (range, 3-13 years). Most (33) patients (median age, 38 years; range, 17-56 years) received a fractionated TBI (12-13.6 Gy)-based myeloablative stem cell transplantation (MST); 2 patients (aged 39 and 40 years) received a non-TBI nonmyeloablative stem cell transplantation (NST). Follicle-stimulating hormone (FSH) levels ranged from 6 to 46 U/L (median, 19 U/L; reference range, 2-15 U/L), and free testosterone levels ranged from 0.18738 to 0.82586 μM (5.4-23.8 ng/dL) (median, 0.449365 μM [12.95 ng/dL]; reference range, 0.3123-1.041 μM [9-30 ng/dL]) in all patients except for 1, who was treated with a testosterone patch. SA and morphology were assessed as described previously. Five (14.3%) patients showed evidence of sperm production (3 [9%] MST recipients and the 2 NST recipients; Table 1). Sperm production was associated with younger age at transplantation (< 30 years old; P = .04), and a follow-up of 7 years or more (3 of 5 vs 0 of 28; P = .002) in MST recipients. Both MST recipients had spermatogenesis and the highest sperm counts, despite their older age. We did not find a relationship with disease type (P = .874), acute graft-versus-host
Response:

Definition of prognostic factors: can the return of spermatogenesis after allogeneic HSCT now be predicted?

Gonadal dysfunction and infertility are of major concern in long-term survivors after allogeneic hematopoietic stem cell transplantation (HSCT); several publications have addressed this particular question by trying to identify prognostic factors.\(^1\)\(^-\)\(^4\) Despite differences in the patient cohorts, the data presented by the National Institutes of Health (NIH) group in this issue of Blood provide similar results to our recent publication.\(^5\) This confirms that return of spermatogenesis is associated with young age at transplantation and long follow-up, even in patients conditioned with myeloablative regimens that included TBI.

Savani et al reported sperm production in 5 of 35 male patients after HSCT. From 33 patients conditioned with TBI, 3 showed sperm in their seminal fluid after HSCT. Two patients conditioned with a reduced-intensity regimen had spermatogenesis recovery during their follow-up as well. The authors compared their experience with the results published by the Basel group. The median age of the NIH patients at time of transplantation was older (38 years; range, 17-56 years vs 25 years; range, 5-56 years for the Basel group), and follow-up time was shorter (6 years; range, 3-13 years vs 9 years, range, 2-20 years). Both publications demonstrated that a younger age at transplantation (Savani et al, \(\leq\) 30 years; Basel group, \(\approx\) 25 years) and longer follow-up (\(\geq\) 7 years and \(\geq\) 9 years, respectively) are prognostic factors for spermatogenesis recovery. The lower rate of recovery observed by Savani et al (14.3%) compared with the Basel group (28%) could be explained by the older age and a shorter follow-up.

Reduced-intensity conditioning should not be considered a synonym for fertility recovery, since the return of spermatogenesis also depends strongly on the treatment received before transplantation. For instance, most patients receiving allogeneic HSCT for multiple myeloma or lymphoma are often heavily pretreated with or without autologous HSCT, whereas patients with CML are not. So far, there are no data available on the long-term survivorship of patients conditioned with reduced-intensity modality; therefore, prospective studies should be conducted to address this particular issue.

The role of chronic graft-versus-host disease (cGVHD) as alloimmune-mediated damage of gonadal tissue remains an open question, since neither of the studies brought enough evidence for...
further conclusion. In our cohort, within all patients with some degree of spermatogenesis only 2 had mild cGVHD, and none had a severe presentation. There was statistically a trend in favor of the return of spermatogenesis in patients without chronic GVHD; thus, these data suggest that gonadal harm might be determined by extension and severity of cGVHD.

In conclusion, both studies remind us that spermatogenesis and fertility are seriously impaired after allogeneic HSCT. However, the current identification of prognostic factors allow for the prediction of the return of sperm production and gives some hope for prospective follow-up of male long-term survivors after allogeneic HSCT. Potential fertility and the related requirement of birth control counseling become an essential matter to be systematically discussed with the long-term survivors.

Alicia Rovo, André Tichelli, Alois Gratwohl, and Christian De Geyter

Correspondence: Alicia Rovo, Division of Hematology, University Hospital, Basel, Petersgraben 4, CH-4031 Basel, Switzerland; e-mail: rovoa@uhbs.ch.

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References


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Bipin N. Savani, Eleftheria Kozanas, Aarthi Shenoy and A. John Barrett