fibrinogen, elevated D-dimer) were initially made more than 4 hours after the snake bite, when there has been ample time to exhaust endogenous clotting factors. Furthermore, the rate of recovery (based on INR) after antivenom treatment is expected to correlate with resynthesis of the consumed clotting factors. Notably, no reference was made to prothrombin levels after envenomation. We speculate that this information could provide greater insight into the robustness of the brown snake versus tiger snake venom, as indicated by Masci et al.

While the final extent of the coagulopathy may indeed be independent of venom FV, we would argue that the rate of development will not be the same. This is an important point since pt-FV-FXa (pseutarin C) is expected to act very quickly, as pt-FV is constitutively active, functions in the absence of anionic membranes, and is resistant to activated protein C. These factors are expected to have a measureable effect on the rate and intensity of the initial development of the coagulopathy in humans and, more importantly, for effective envenomation of their natural prey. In fact, this is consistent with further human clinical research referred by Isbister and colleagues. In this study, presented in abstract form, they observe a discernible delay in the development of coagulopathy after tiger snake envenomation compared with that of brown snake in 112 patients. An immediate fall in the concentration of fibrinogen, FV, and FVIII was observed after the brown snake bite, whereas there was a delay of 1 to 2 hours for that upon tiger snake envenomation. The presence of constitutively active pt-FV in the brown snake venom allows for rapid activation of prothrombin after envenomation, causing immediate clotting. In contrast, tiger snake venom does not have an active FV component; therefore, the observed delay in coagulopathy is likely due to the activation of several clotting factors, including human FV. Interestingly, members of our team have shown that pt-FV on its own is a potent procoagulant in mice and is an effective anti-bleeding agent in a mouse tail excision model (Patent Collaboration Treaty patent: P.P.M. and J.d.J., “Hemostasis-Modulating Compositions and Uses Therefor”; Publication number: PCT/AU/2008/001866 and WO/2009/079690; World Intellectual Property Office; Filing date December 18, 2008), further supporting the effectiveness of pt-FV.

Finally, although we accept that studies carried out in vitro must be viewed with caution when extrapolating to what happens in vivo, we nevertheless believe that our work is entirely consistent with the outcome of envenomation by the brown snake. Rather than looking at toxin research in an isolated system as a “pifall,” we submit that both in vitro biochemical work and clinical studies, done carefully, can complement each other.

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To the editor:

Reduced-intensity conditioning allogeneic stem cell transplantation in HIV patients with hematologic malignancies: yes, we can

The early enthusiasm for allogeneic stem cell transplantation (ASCT) in patients with HIV infection was tempered by the high transplantation-related mortality and rapid progression of HIV infection after allografting, casting serious doubts about the feasibility of this curative modality in HIV+ patients with hematologic malignancies. While the development of reduced-intensity conditioning (RIC) regimens has improved the outcomes of ASCT in general, its role in the HIV+ patient population remains to be defined.

We used a uniform strategy of RIC consisting of fludarabine (30 mg/m²/day, days −7 to −3), busulfan (0.8 mg/kg/dose intravenously × 8 doses) with (n = 2) or without (n = 1) thymoglobulin in 3 HIV+ patients with advanced hematologic malignancies

References


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Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus (0.03 mg/kg/day intravenously, commencing on day 0) and mini-dose methotrexate (5 mg/m² on days 1, 3, 6, and 11). To assess donor-cell chimerism, pretransplantation peripheral blood samples were used to identify polymerase chain reaction (PCR)–short tandem repeat informative fragments for each donor/recipient pair. After transplantation, lineage-specific chimerism analysis was performed as previously described. Patients’ HIV-RNA PCR (COBAS Ampliprep/COBAS TaqMan HIV-1 real time PCR test), CD4, and CD8 counts were determined at baseline and on days +90, +180, and +360. All investigations were approved by The Ohio State University Institutional Review Board and Clinical Scientific Review Committee, and complied with the recommendations of the Declaration of Helsinki.

Median patient age was 51 years (range, 39-55 years). One patient each had AML (UPN 1), Burkitt lymphoma (UPN 2) and plasmablastic lymphoma (CD138⁺, CD20⁺, HHV8⁺, EBER1⁺, EBER2⁺; UPN 3). All patients were in second complete remission (CR) at the time of transplantation. Median pre-ASCT CD4 count was 339 cells/µL (range, 189-457 cells/µL). HIV RNA viral load at baseline was undetectable in 2 patients and 814 copies/mL in UPN 1. Donors included sibling (n = 1) or unrelated donor (n = 2). Conditioning regimens included fluorouracil (flu)/busulfan (Bu) or flu/Bu/ATG. GVHD prophylaxis was MTX/tacrolimus. HAART during transplantation was atazanavir, lamivudine, tenofovir (UPN 1), efavirenz, emtricitabine, tenofovir (UPN 2), and efavirenz, emtricitabine, tenofovir (UPN 3). Patients’ HIV-RNA PCR (COBAS Ampliprep/COBAS TaqMan HIV-1 real time PCR test), CD4, and CD8 counts were determined at baseline and on days +90, +180, and +360. All investigations were approved by The Ohio State University Institutional Review Board and Clinical Scientific Review Committee, and complied with the recommendations of the Declaration of Helsinki.

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unrelated volunteers (n = 2). Highly active antiretroviral therapy (HAART) was not interrupted during RIC-ASCT. All patients successfully engrafted. Only UPN3 developed transient grade II acute GVHD. Posttransplantation HIV RNA viral loads remain undetectable in 2 patients. UPN1, with a 20-year history of heavily pretreated HIV/AIDS, developed elevated HIV RNA viral loads (15 000 copies/mL) 18 months after ASCT, which responded to switching HAART to tipranavir and lamivudine. No AIDS-related opportunistic infections were seen. The details of other infectious complications are summarized in Table 1. Donor-cell chimerism and immune reconstitution after ASCT were prompt (Table 1).

Initial experience with RIC-ASCT in HIV+ patients (n = 2), showed development of acute retroviral syndrome after transplantation, likely secondary to interruption of HAART. Uninterrupted HAART was attempted in another study using nonmyeloablative conditioning ASCT (n = 2), but disease relapse and GVHD appeared problematic, probably due to nominal intensity of the conditioning regimen and less aggressive GVHD prophylactic strategy used. Our study provides critical preliminary evidence that in the modern era, RIC-ASCT with uninterrupted HAART is safe and feasible in HIV+ patients. Moreover, our data suggest that for HIV+ patients lacking sibling donors, unrelated donors are acceptable, and that in this patient population, administration of thymoglobulin (for GVHD prophylaxis) and donor lymphocyte infusion (after relapse) does not cause any unexpected toxicities.

In conclusion, our encouraging experience strongly argues that HIV+ patients with advanced hematologic malignancies should no longer be routinely denied the potentially curative modality of RIC-ASCT.

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