clonal cells in the CD19 compartment in a cohort of patients with myeloma, including all patients in the reported study, by combining single-cell ASO IgH RT-PCR with flow sorting and Poisson statistics. These data were obtained to verify a rationale for CD19 depletion of stem cell products from patients with myeloma. But the data were not included in the paper since they did not contain novel information concerning the controversial aspects addressed in the paper.

We determined the proportion of clonal CD19+ cells after peripheral blood stem cell transplantation in 10 patients and found variable levels of clonal cells in the CD19 compartment after transplantation, ranging from 0.101% to 6.103% (mean, 1.60%) of CD19+ cells. This is comparable to the clonal cell levels reported by Chen and Epstein, who found levels from 0.04% to 5.00% (mean, 1.60%). Rottenburger et al9 reported PCR negativity in CD19+ -enriched fractions in approximately 50% of patients with multiple myeloma (MM) in remission. In contrast, we found clonal cells in the CD19+ compartment in all 10 patients with MM observed in continuous remission for at least 3 months. Pilarski’s group reported that cells originating from the lymphocyte gate contained a polyclonal B-lymphocyte population with a minor fraction of clonotypic CD19+ cells.1 In general, nearly all CD19+ cells that we have identified in patients with myeloma originate from the lymphocyte gate. The frequency of clonotypic cells that we identified within this CD19+ lymphocyte gate was comparable to that found both by Pilarski’s group3 and Chen and Epstein2; thus, on this point, there is no controversy.

Pilarski’s group reported the controversial finding that most cells originating from the monocyte gate were clonotypic, expressing CD34 and CD19 but with an altered CD19 epitope. We have addressed these issues previously using ASO IgH RT-PCR on cells originating from both the lymphocyte and monocyte gate.6,7 In a single case, we identified a high frequency of clonotypic cells that we identified in patients with multiple myeloma (MM) in remission. The frequency of clonotypic cells that we identified within this CD19+ lymphocyte gate was comparable to that found both by Pilarski’s group1-3 and Chen and Epstein2; thus, on this point, there is no controversy.

The high numbers of circulating clonal cells found by Pilarski’s group were also reported to be insensitive to chemotherapy.9,10 In the published study, we showed that in general, there is a low frequency of circulating clonal cells in patients with myeloma, and most importantly, we showed that circulating clonal cells respond well to induction therapy, even in situations where high numbers of clonal cells were present. Although most circulating clonal cells responded to chemotherapy, we have (like Cremer et al) also found a small proportion of CD19+ cells that are resistant to high-dose chemotherapy. But whether there is a rationale for consolidation therapy using anti-CD20 antibodies is questionable, since there is no proof that the clonotypic B lymphocytes are involved in the pathogenesis of the disease. Additionally, our ongoing studies on the nature of the circulating CD19+ clonotypic B lymphocytes have resulted in identification of a CD19+/CD20− subset (Figure 1).

To the editor:

Dalteparin-induced alopecia in hemodialysis patients: reversal by regional citrate anticoagulation

Chronically intermittent hemodialysis for end-stage renal failure requires anticoagulation to prevent clotting in the extracorporeal circuit. Anticoagulation usually is performed by continuous infusion of unfractionated heparin or by bolus administration of low-molecular-weight heparin.1 At our hemodialysis unit, we use an intravenous bolus injection of an average of 80 IU dalteparin (Fragmin; Pharmacia, Stockholm, Sweden) per kilogram of body weight. In 1998, regional citrate anticoagulation was introduced for patients at high risk for hemorrhage, for patients suffering from heparin-induced thrombocytopenia type II, or for patients in which the extracorporeal circuit clotted despite an extremely high dalteparin dose.2,3 During the last 3 years, 5 of our female patients on long-term anticoagulation with dalteparin complained about excessive hair
loss (Table 1). In patient 1, poor growth of hair, but no pathologic hair loss or even alopecia, was noticed. In the other 4 patients, hair was coming out in handfuls, leaving large areas of mutilating patchy alopecia. Those 4 patients reported that hair loss had begun approximately 6 weeks to 3 months after initiation of hemodialysis. We suspected that repeated anticoagulation with dalteparin, which shares many side effects with heparin,2 was responsible for the unexplained hair loss in our patients. To test this hypothesis, regional citrate anticoagulation23 was initiated, thus avoiding further exposure to dalteparin. Six weeks to 3 months after the anticoagulation regimen had been changed, all 5 patients reported cessation of the excessive hair loss. In patients 2 to 5, normal hair growth allowing fashionable hairstyling was observed. Citrate anticoagulation was stopped in patient 2, and excessive effluvium reoccurred some weeks after readministration of dalteparin. In patient 1, objective changes in hair growth were not observed.

In summary, in 4 of 5 chronic hemodialysis patients, a clear temporal association of excessive hair loss with the start of dalteparin anticoagulation was observed. The resolution of the excessive effluvium in these 4 patients and the restoration of normal hair growth after the anticoagulation had been switched to citrate suggest that dalteparin was responsible for the mutilating alopecia. The recurrence of the hair loss in patient 2 soon after reexposure to dalteparin is a further hint in favor of this hypothesis. Our case series supports the observation of Barnes et al, who reported a potential association of alopecia with the administration of dalteparin in a child treated for sinus venous thrombosis.5 We conclude that long-term anticoagulation with dalteparin causes alopecia in some chronic hemodialysis patients. Regular hair growth can be restored by replacing low-molecular-weight heparin by regional citrate anticoagulation.

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References

Table 1. Demographic data of 5 female hemodialysis patients with dalteparin-induced alopecia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Cause of chronic renal failure</th>
<th>Time on hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Wilms tumor</td>
<td>6 y*</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>Hypertension</td>
<td>6 mo</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>Hypertension</td>
<td>2 mo</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>PKD</td>
<td>3 mo*</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>Hypertension</td>
<td>5 mo</td>
</tr>
</tbody>
</table>

PKD indicates polycystic kidney disease.
*Previous renal graft.

To the editor:

Transient mixed hematopoietic chimerism in dogs given thymic irradiation before and pharmacologic immunosuppression after marrow transplantation

We used postgrafting immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP) to control both graft-versus-host and host-versus-graft reactions in a canine model of dog leukocyte antigen (DLA)-identical littermate marrow transplants. This way, the single pretransplantation dose of total body irradiation (TBI) otherwise needed for sustained allografts could be lowered from 920 cGy to the sublethal level of 200 cGy.1 We next substituted 450 cGy irradiation targeted to the cervical, thoracic, and upper abdominal lymph node chain for 200 cGy TBI in this model.2 Prompt and sustained engraftment was seen in unirradiated marrow and lymph nodes as early as week 6. This indicated that creation of marrow space by cytotoxic agents was not required for homing of transplanted stem cells. Rather, some degree of host immunosuppression was sufficient to set the stage for successful allografts. The concept was validated in a 30-year-old patient with common variable immunodeficiency disease who received no conditioning therapy and in whom durable allogeneic marrow engraftment was achieved solely with postgrafting MMF/CSP.3

The field of lymph node chain irradiation in these studies included the thymus. Reports by others on nonmyeloablative regimens for major histocompatibility complex (MHC)–matched and mismatched murine and porcine transplantations have emphasized the pivotal importance of thymus irradiation in the success of grafts.4,5 It is not clear whether the engraftment of the transplanted cells was facilitated through creation of thymic space or elimination of thymic alloreactivity by thymic irradiation. Here, we evaluated in the canine model whether the success of central lymph node chain radiation could largely be attributed to inclusion of the thymus in the radiation field. We asked whether sustained grafts of DLA-identical littermate marrow could be achieved using 450 cGy thymic irradiation before and MMF/CSP after transplantation.

Litters of beagles weighing from 7.5 to 11.4 kg (median, 9.0 kg) and 6 to 9 months old (median, 7 months) were used. Research was conducted per the principles outlined in the Guide for Laboratory Animal Facilities and Care (National Academy of Sciences, National Research Council). The Institutional Animal Care and Use Committee of the Fred Hutchinson Cancer Research Center approved the research protocol. Kennels are certified with the American Association for Accreditation of Laboratory Animal Care. A high-energy linear accelerator (Varian CLINAC 6, Palo Alto, CA) delivered 450 cGy thymic irradiation at 200 cGy/min in a single setting with a tightly collimated 6 million electron volt beam using 2 isocentric parallel-opposed anterior and posterior ports, 2.5 cm wide and 3.5 cm long, to include the thymus with margins. A radiograph verified the portal...
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