Response:

Reinvestigation of colloid administration’s role in rituximab-induced tumor cell agglutination recommended

In a recent report of the fatal course of a rituximab-treated patient, we have demonstrated that tumor cell agglutination (TCA) might be a key mechanism of rituximab-induced adverse reactions. The pattern of intravascular leukostasis shown by histopathologic examinations was clearly different from findings in other patients with high leukocyte counts.1

Dr Muttuswamy Sivakumaran reports an interesting ex vivo finding regarding rituximab-induced tumor cell agglutination (RITCA). He suggests that various colloid preparations may induce or aggravate TCA in patients with a high number of circulating tumor cells, based on ex vivo observations in blood samples collected from 2 patients 6 hours after their first rituximab infusion.

In the course of his severe infusion-related syndrome, our reported patient also experienced hypotension, which was treated with hydroxyethyl starch (250 mL, 10% HES), after the administration of intravenous crystalloids (normal saline) did not increase blood pressure. Since HES was among the colloid preparations which induced TCA in Dr Sivakumaran’s ex vivo experiments, we cannot exclude the possibility that the administration of this colloid preparation aggravated infusion-related toxicities in our patient and finally contributed to the fatal course.

The induction of blood cell agglutination after administration of HES has not been described before, even in patients with abnormally high blood cell numbers. However, it has been shown that HES can preserve rather than induce platelet agglutination during and after cardiopulmonary bypass surgery.2 The in vivo effect of colloid preparations after infusion of therapeutic monoclonal antibodies such as rituximab are not known. Therefore, we recommend a reinvestigation concerning the administration of colloids in all rituximab-related fatalities that have been reported to date to further evaluate their role in RITCA.

The ex vivo observations by Dr Sivakumaran confirm our results suggesting that TCA may play a role in the pathogenesis of rituximab-related toxicities, especially in patients with a high number of circulating tumor cells. Until the exact function of colloids in this syndrome has been elucidated, we support Dr Sivakumaran’s suggestion that colloids should be avoided in the management of peripheral circulatory failure after rituximab infusion.

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References

To the editor:

Prognostic factors for acute graft-versus-host disease after donor lymphocyte infusions

Acute graft-versus-host disease (AGVHD) complicates donor lymphocyte infusion (DLI) treatment in 40% to 60% of cases.1,2 Although factors predictive of GVHD after allogeneic stem cell transplantation (SCT) could also be valid after DLI, patients receiving DLI are a select group, having survived the GVHD after transplantation and relapsed. We therefore investigated the role of possible factors in the development of AGVHD after DLI.

Sixty-three consecutive patients with BCR-ABL-positive chronic myeloid leukemia (CML) who relapsed after allogeneic SCT (31 from their respective HLA-identical siblings and 32 from volunteer-matched unrelated donors) were started on treatment with DLI between August 1990 and April 1999. At the time of DLI, 7 patients were in molecular relapse, 15 were in cytogenetic relapse, and 26 were in hematologic relapse (19 in chronic phase, 7 in accelerated phase). Twenty-seven patients received a single infusion of donor lymphocytes (bulk-dose regimen [BDR]), and 36 patients received lymphocytes according to our escalating-dose regimen (EDR).3 Molecular remission was defined as the absence of detectable BCR-ABL transcripts by reverse transcriptase–polymerase chain reaction (RT-PCR) analysis of peripheral blood on 2 consecutive occasions.4 AGVHD was graded according to the Glucksberg criteria.5 Grades II to IV were deemed of clinical significance.

Forty-five patients (71%) treated with DLI achieved molecular remission. Fifteen patients (24%) developed grade II to IV AGVHD, 48 patients (76%) showed no or minimal AGVHD. Results of the univariate analyses are presented in Table 1. No association was found between AGVHD after DLI and AGVHD after transplantation. The vast majority of patients who developed AGVHD following DLI treatment did not have a history of AGVHD after their original transplantation. Recipient-donor sex mismatch, patient-donor CMV seropositivity, and increasing patient age (> 35 years) were found to be significantly associated with AGVHD in the DLI setting. In accord with previous observations,1,2 patients who received T-cell–replete allografts suffered less AGVHD after DLI compared to those who received a T-cell–depleted stem cell preparation. We did not observe any association between achievement of complete remission and development of AGVHD. This finding contrasts with the results reported by other groups, whereby 89% of the responders suffered AGVHD.6 Such a difference may be attributed to the high proportion of patients receiving DLI according to an EDR in our study. In fact, the influence of method of administration was highly significant. In a multivariate logistic analysis, any positive patient-donor CMV
To the editor:

Chimerism induction and delayed onset of cytomegalovirus (CMV) infection after allogeneic reduced-intensity stem cell transplantation (RIST)

Although cytomegalovirus (CMV) infection has been identified as one of the primary causes of morbidity and mortality after allogeneic stem cell transplantation (SCT), very little is known about the characteristics of this disease after reduced-intensity stem cell transplantation (RIST). Junghanss et al recently reported that the onset of CMV disease was significantly delayed after nonmyeloablative transplantation (NST) compared with myeloablative NST-conditioning regimen consisted of low-dose (2 Gy) total body irradiation with or without fludarabine (Flu), which may allow most host cells to survive to provide overlapping immunity against CMV infection along with engrafted donor-derived cells. In our RIST study framework using Flu (180 mg/m²) or cladribine (0.66 mg/kg) plus busulfan (8 mg/kg), with or without antithymocyte globulin (ATG), achievement of T-cell chimerism was delayed when ATG was omitted. In this situation, we evaluated the correlation between the induction of T-cell chimerism

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Table 1. Incidence of AGVHD in 63 patients receiving DLI for relapse after allogeneic SCT for CML: univariate analysis of potential factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>AGVHD Grade</th>
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<tbody>
<tr>
<td></td>
<td>0 to I</td>
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<tr>
<td>AGVHD after SCT</td>
<td>28</td>
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<tr>
<td>Patient-donor sex</td>
<td>32</td>
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<tr>
<td>Patient-donor CMV serostatus†</td>
<td>20</td>
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<tr>
<td>GVHD prophylaxis at SCT‡</td>
<td>28</td>
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<tr>
<td>Patient age at time of DLI</td>
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<tr>
<td>Type of DLI regimen</td>
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<tr>
<td>Molecular remission after DLI</td>
<td>32</td>
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<tr>
<td>Donor type</td>
<td>35</td>
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<tr>
<td>Type of relapse at time of DLI</td>
<td>24</td>
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<tr>
<td>Interval SCT to relapse</td>
<td>24</td>
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<tr>
<td>Interval relapse to DLI</td>
<td>23</td>
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<tr>
<td>Interval SCT to DLI</td>
<td>22</td>
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</tbody>
</table>

TCD indicates in vitro or in vivo T-cell depletion with Campath monoclonal antibodies; EDR, escalating-dose regimen; BDR, bulk-dose regimen; Hem, hematologic; CP, chronic phase; AP, accelerated phase.
†Chi-squared or Fisher exact test.
‡CMV serostatus negative: when both donor and recipient were negative; CMV serostatus positive if only donor or only recipient or both were positive.

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References


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