To the editor:

**Acidic and neutral sialidase in the erythrocytes of patients with type 2 diabetes: an answer to comments by Richard et al**

In a recent letter to the editor by Richard et al,1 the authors made some comments about our work published early this year.2 In our study we observed a sharp decrease of neutral sialidase activity on the surface of erythrocytes of diabetic patients, which accounts at the same time for the significant increase (40%) of sialic acid content. At the end of our discussion, we hypothesized that the higher negative charge at the erythrocyte surface due to this increase results in a premature sequestration of diabetic red cells by macrophages, in accordance with the data reported by Mazzanti et al3 and Jain et al.4 Our hypothesis has been criticized by Richard and coworkers because it conflicts with the notion that a reduction of total sialic acid content is responsible for phagocytosis of senescent red cells.

Our thoughts on this matter are as follows: (1) The hypothesis reported by Richard et al has been extensively debated over the years,5 and contrary to what the authors hint, it is not the only one known nor the most accepted, nonetheless it was not in our intentions to discredit it. (2) We believe in the importance of sialic acid in the process of recognition of senescent red cells, but as part of a more complex process; where other molecules are involved, as suggested in other hypotheses.6 Indeed, according to Beppu et al7 and Kannan et al,8 the molecular consequences of the oxidative damage occurring in senescent erythrocytes are likely responsible for their clearance. We think that the reduction of sialic acid content in specific domains of the surface, and not its overall decrease, may trigger the macrophage recognition.9,10 (3) The theory reported by Richard et al is eventually unsuitable to explain our experimental results. In fact, if the overall sialic acid decrease was responsible for senescent erythrocytes recognition, we should have observed an increase in life span of erythrocytes in diabetes mellitus, yet we observed the opposite phenomenon.

In conclusion we would like to emphasize once again that it was not in our intentions to invalidate the role of sialic acid decrease in erythrocyte removal, even though we do believe in a different hypothesis on erythrocytes senescence, at least in diabetic patients.

**References**


To the editor:

**Increased CMV infection following nonmyeloablative allogeneic stem cell transplantation: a search for the guilty**

I read with interest the brief report by Bainton et al on cytomegalovirus (CMV) reactivation following the use of Campath-based nonmyeloablative conditioning regimens.1 The authors found a high incidence of CMV infection, similar to that reported by us.2 However, they suggest that fludarabine rather than Campath was responsible for this, but the existing literature on nonmyeloablative transplants does not seem to support the idea. A recent study reported CMV reactivation in 87% with and only 25% without the addition of alemtuzumab (Campath-1H) (P < .001) to fludarabine-melphalan regimen.3 The Seattle group did not find a difference in the incidence of CMV infection or disease with the addition of fludarabine to the low-dose radiation regimen.4 Similar low

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incidences of CMV reactivation were reported by other groups using fludarabine in combination with busulphan, melphalan, or low-dose total body irradiation (TBI) (21%-42%). The median time of onset of CMV infection was also beyond 45 days in all these studies. The only other regimen associated with a higher and earlier incidence of CMV infection has been a combination of fludarabine and antilymphocyte globulin. Thus, fludarabine used alone, without other antilymphocyte antibodies, does not seem to in-crease the predisposition to earlier or higher CMV infections. Whether Campath used alone rather than in combination with fludarabine would be associated with a lower incidence of CMV infection remains speculative and is not supported by the existent literature.

I would also like to make a few comments regarding the data presented by Bainton et al. Firstly, the patients receiving BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)-Campath (those not receiving fludarabine) received transplants only for lymphoma/chronic lymphocytic leukemia (CLL) and mostly received matched related grafts (14 of 18). On the other hand, those receiving fludarabine, either as a part of the protocol described by us or in addition to BEAM-Campath, were mostly recipients of unrelated donor grafts (11 of 18) and received transplants mostly for diseases other than lymphoma/CLL (11 of 18). Although the authors mention that there was no difference between related and unrelated donors (UDs), this comparison would be restricted entirely to the fludarabine group, as there were no transplants from unrelated donors in the other group. Thus, to attribute the increased CMV reactivation to fludarabine alone might not be entirely acceptable given the above differences. Given the small sample size and the heterogeneity, the power of a multivariate analysis taking the donor type or underlying diagnosis into account might not be satisfactory either.

Secondly, Bainton et al stated that there was no difference in the incidence of CMV reactivation between patients receiving Campath-1H (alemtuzumab) (15 of 16) and Campath-1G (13 of 20). In fact, the P value by Fisher exact test (2-tailed) turns out to be .05. Although the conventional cut-off for significance is .05, it might not be entirely acceptable to ignore a P value of .05 and formulate the inferences on a P value of .04 (the Fisher exact P value for CMV reactivation with and without fludarabine), given the small number of patients. Hence, the statistical interpretation indicates a suggestive trend toward significantly more CMV reactivation in the alemtuzumab group. The effect of alemtuzumab, as we had mentioned, was not only on the incidence of reactivation, but also on the recurrence both before and after 100 days. Late recurrences were correlated with slow recovery of CD4+ T cell counts. And without analyzing these factors and given the above data, it cannot be claimed with certainty that both of these antibodies have a similar effect on CMV reactivation. Finally, Bainton et al suggested that halving the dose of alemtuzumab might not result in reduction in reactivation of CMV. Indeed, that might be the case and further dose reduction could be necessary, but Bainton et al have used alemtuzumab to day 1 in the protocols other than the one similar to ours. The existing data suggests that the use of alemtuzumab closer to the time of transplant results in longer persistence of the antibody. Thus, only reduction in the dose of alemtuzumab might not suffice, and consideration must be given to its timing in relation to stem cell infusion. Ultimately, how and when to use Campath antibodies in nonmyeloablative conditioning are yet to be perfected, and clinical studies to explore that are ongoing.

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References


To the editor:

Cancer in Fanconi anemia

Three separate and complementary reports recently described the leukemia and solid tumor experience in cohorts of patients with Fanconi anemia (FA). Here we examine the similarities and differences of these reports (Table 1) in order to synthesize the most current evidence for physicians and patients.

The literature review (LIT) encompasses 1300 cases reported worldwide from 1927 to 2001. The International Fanconi Anemia Registry (IFAR) includes 754 North American patients ascertained between 1982 and 2001. Our North American Survey (NAS) collected cross-sectional data from 145 patients during 2000. These cohorts are not mutually exclusive, and each study has potential biases. LIT cases are susceptible to publication bias, due to preferential reporting of patients with interesting outcomes. IFAR and NAS cases are subject to selection bias, since they studied volunteers. Some of the data were obtained by unverified self-report, although in the latter 2 studies, neoplasm diagnoses were confirmed objectively.

A strength of the IFAR report is the large number of subjects; a limitation of NAS is its small numbers. All of the cohorts have missing data, hindering some comparisons. Also, IFAR does not distinguish myelodysplastic syndromes (MDS) from leukemia patients, nor solid tumor patients vis-à-vis prior transplantation.