Is it safe to have a transplant yet?

Should I go for a transplant or not? This is often a difficult question for patients with CLL. Until recently the answer was, “Not if you can avoid it,” but since the introduction of reduced intensity conditioning regimens, toxicity has been reduced and the age range for which allografting is contemplated has increased. The question has to be asked anew, and to help us with that a series of 62 patients with CLL has recently been published by a consortium of doctors from Britain and Spain.

This is not a clinical trial. Although there were two cohorts of patients, there was no randomization. It was a retrospective look-back at experience between 1999 and 2007. Four institutions were involved, and patients who were eligible were generally young, with disease refractory to chemotherapy or in early relapse, and/or had poor risk cytogenetics. All the patients had reduced intensity conditioning with fludarabine and melphalan. The results were analyzed according to whether the patient had had alemtuzumab (Campath) for prevention of graft-versus-host disease (GVHD). Unfortunately, the categories were not clean cut, which probably explains why the paper has been published in a relatively obscure journal (Biol Blood Bone Marrow Transplant 2008; 14:1288-97). In the first cohort, 40 patients received ciclosporin and alemtuzumab to prevent GVHD. The dose of alemtuzumab was 100mg given over 5 days from day -8 to -4; but 8 patients received only 60mg, 3 received 40mg, 2 got 30mg and 5 had 20mg. In the second cohort, patients with a sibling donor with a complete tissue match were given methotrexate as well as ciclosporin while those with matched unrelated donors received mycofenolate mofetil (MMF) with their ciclosporin. In addition, two patients with 1 locus mismatched unrelated donors also received anti-thymocyte globulin.

The characteristics of the two cohorts were not significantly different, though with numbers this small that statement may be meaningless. The median age at transplant was 53 (range 34-64) and 73% were male. Transplantation took place at a median of 55 months after diagnosis (range 5-132 months).

Since this was not a randomized trial, differences in outcome between the two cohorts, or indeed similarities could be due to a whole host of different causes other than the treatment protocol. The comparisons therefore cannot be used for anything other than hypothesis generating. Bearing that in mind, how did the two cohorts compare? There was no significant difference between them in terms of overall survival. For both cohorts there seems to be a plateau at 60% alive extending out from 3 years to nine years when nobody died. But the numbers are so small that this cannot be said to be predictive of what would happen to you.

In terms of progression-free survival there is again no significant difference between the cohorts, but whereas the non-Campath cohort seems to have a plateau at 50% non-progressive after 3 years, the Campath group continues to relapse. Again, because the numbers are so small this is not a statistically significant difference, but it is what you might expect – if you wipe out more of the T cells, you are more likely to relapse.

Another consequence of wiping out all the T cells might be failure to engraft. The incidence of mixed donor chimerism (this means that you have a mixture of the donor cells and the patient's own cells) at 6 months was significantly greater in the Campath cohort (43% v 11%; p=0.03), however, most of these attained full engraftment following donor lymphocyte infusion (DLI) and the incidence of secondary graft failure was the same in both cohorts (12% v 9%).

Acute graft versus host disease was not significantly different in either cohort (37% v 57%; p=0.18) though this could be a type II error where you don't have enough patients to detect a difference. Similarly with severe acute GVHD, 20% is not significantly different from 38% with such low numbers (p=0.14), though GVHD that didn't respond to treatment with steroids was significantly more common in the non-Campath cohort (10% v 33%; p=0.03). Chronic GVHD was greater in the non-Campath cohort 68% v 29%; p=0.016) and extensive chronic GVHD needing systemic rather than local therapy was also greater (48% v 10%; p=0.03). Mortality from GVHD was also greater in the non-Campath cohort (33% v 10%; p=0.034)

Severe infections were common in both cohorts (73% v 67%; not significant) and 18% died of infection which was often related to GVHD. There was no difference between the two cohorts. As might be suspected there were a lot of viral infections in patients who received Campath – herpes simplex in 7, EBV in 6, adenovirus in 5, RSV in 4, influenza in 3, zoster in 2, and metapneumovirus and parainfluenza each in one. CMV reactivation occurred in 66%, neither for viral infection nor CMV reactivation did the excess in the first cohort reach statistical significance. Again, this is probably because the numbers were so small. Fungal and bacterial infections were equally distributed between the cohorts.

To summarize, reduced intensity conditioning has extended allografting into the CLL community by raising the age of eligible patients. It becomes an immunologic treatment where the graft attacks both the CLL and the patient. Reducing the number of T cells in the graft diminishes both attacks. GVHD is a dangerous thing to have: it can kill you directly, it can make infection more likely and it can make life not worth living. Getting rid of T cells (which is what Campath does) reduces the amount of GVHD but also reduces the attack on the CLL. So if you use Campath you have less GVHD but also you are more likely to have residual leukemia. Less T cells also means less able to fight virus infections, and although some of these can be withstood by other means (ganciclovir for CMV, rituximab for EBV) others can't be resisted.

So it's swings and roundabouts; you gain on one and lose on the other. This study identifies the problems, but because it is not a randomized prospective trial it can't weigh up the relative risks.