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Minimal Residual Disease Detected by the PCR in Chronic Myeloid Leukemia

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Comparison of Cyclophosphamide-Total Body Irradiation and Busulphan-Cyclophosphamide Bone Marrow Transplantation Conditioning

Allogeneic bone marrow transplantation (BMT) is the only proven curative treatment for chronic myeloid leukemia (CML). It is however associated with significant early and late toxicity. In an attempt to minimize these side effects, a number of alternatives to the classical cyclophosphamide-total body irradiation (Cy-TBI) conditioning regimen have been developed. Low rates of leukemia recurrence have been seen using high-dose busulphan (Bu, 16 mg/kg) and cyclophosphamide (120 mg/kg) [1], however no randomised prospective trials have compared Bu-Cy with Cy-TBI BMT conditioning. The follow-up of patients transplanted using Bu-Cy conditioning is also insufficient to adequately assess the incidence of leukemic relapse in slowly progressive diseases such as CML. In view of these uncertainties, GEG-MO (Group Française d'Etude de la Greffe de Moelle Osseuse) commenced a randomised prospective trial comparing Cy-TBI and Bu-Cy BMT conditioning in Philadelphia-positive chronic-phase CML in 1988. The trial was stopped in early 1991 when preliminary analysis revealed an excess of non-engraftment or late

rejection in the Bu-Cy arm (6/66) compared to the Cy-TBI arm (0/56, $p = 0.06$) [2]. No differences were observed between the two groups in terms of early toxicity, infection, acute or chronic graft-versus-host disease. There has been one relapse in each group.

The polymerase chain reaction (PCR) is a sensitive method of detecting residual disease in CML. The incidence of persistent bcr/abl message after BMT has been variable [3]; however, PCR-positive cases appear to be uncommon more than 6 months after unmanipulated BMT for chronic-phase CML [4], consistent with the low incidence of relapse seen clinically in this setting. Persistent bcr/abl expression has also been shown to precede relapse in some patients [4,5].

We have used a previously described two-step nested PCR method [6] in an attempt to predict leukemic relapse in all surviving patients entered into this GEGMO trial from a single study centre (Hôpital Saint Louis). Table 1 shows the clinical details of these patients with the PCR findings and the interval between BMT and the PCR studies. All pa-

tients were in remission and more than 6 months after BMT. Nine patients entered into the trial from this centre had died of transplant-related complications at the time of writing; there was no evidence of leukemic relapse in these patients at the time of death. One patient from the Bu-Cy group had persistent expression of the bcr/abl message, detected at 328 and 431 days after BMT. None of the patients in the Cy-TBI group were PCR positive. These findings suggest that the expression of the bcr/abl gene is uncommon more than 6 months after unmanipulated BMT for chronic-phase CML, using either of these conditioning regimens. Long-term follow-up of patients randomised into this clinical trial will be required to compare the antileukemic efficacy of these regimens. The value of PCR as a predictor of leukemic relapse will be further assessed by clinical observation of the patients studied here. PCR may be useful in the assessment of new treatments for CML although the study of large groups of patients may be necessary to demonstrate differences between protocols.

Condition

Table 1. Clinical details of the patients,
PCR findings and interval between BMT
and the PCR studies regimen
Patient Age Sex Acute GVHD Chronic PCR Days after
No. (grade)GVHD results transplant

Bu-Cy
Cy-TBI

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