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**Combination of nonmyeloablative stem cell transplantation and Imatinib in accelerated phase CML**Frédéric Baron,\* Pascale Frère,\* Christian Herens,<sup>o</sup> Georges Fillet,\* Yves Beguin\*\*Department of Medicine, Division of Hematology; <sup>o</sup>Department of Genetics;

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Imatinib (STI571) has been shown to induce sustained cytogenetic responses in some patients with accelerated phase CML.<sup>1,2</sup> The median time to achieve a cytogenetic response was less than 3 months and survival without progression was poor in patients who did not achieve a major cytogenetic response. The Seattle team has recently developed a low-intensity nonmyeloablative conditioning regimen combining low dose TBI and fludarabine. They observed a high response rate in chronic phase CML but results in accelerated phase were disappointing with high rate of graft rejection.<sup>3</sup> This report demonstrates the feasibility of combining nonmyeloablative stem cell transplantation and Imatinib in accelerated phase CML. A 59-yr-old man was diagnosed in August 2001 with accelerated phase CML (more than 20% basophils in his blood). After one month on hydroxyurea, Imatinib was started at 600 mg/day. Bone marrow analysis 3 months later evidenced a hematologic remission with a minor cytogenetic response (persistence of 74% of Ph<sup>+</sup> metaphases). The patient underwent an allogeneic peripheral blood stem cell (PBSC) transplantation from his HLA-identical sister after a nonmyeloablative conditioning regimen combining 2 Gy total body irradiation and 90 mg/m<sup>2</sup> fludarabine, as previously reported.<sup>3,4</sup> Imatinib was interrupted at the time of transplant to avoid its potential toxic effect on normal hematopoiesis.<sup>5</sup> Post-transplant immunosuppression was carried out orally with cyclosporine and mycophenolate mofetil and the patient was followed in the outpatient setting. On day 28, his blood count was 16.5 x 10<sup>9</sup>/L with 10% basophils and bone marrow analysis showed a hematologic relapse with 21/25 abnormal [46 XY, t(9;22)] and 4/25 normal (46 XX) metaphases. Bone marrow and peripheral blood CD3 and CD13 chimerism (measured with FISH as previously reported)<sup>4</sup> were 13%, 14% and 13%, respectively. Imatinib (600 mg/day) therapy was restored on day 28 and the patient achieved a normal blood count 14 days later. Bone marrow analysis on day 40 showed a minor response (60% PH-positive metaphases). The patient did not experience acute GVHD and received a first donor lymphocyte infusion (DLI) on day 60 because of poor T cell chimerism. We decided to maintain cyclosporin during DLI according to Zaucha *et al.* who demonstrated in the Seattle dog model that increasing the duration of posttransplantation immunosuppression with CSP from 35 to 100 days favorably influenced stable donor engraftment.<sup>6</sup> Imatinib was then reduced to 400 mg/day because of fluid retention. Bone marrow analysis on day 100 revealed a hematologic remission with a major cytogenetic response (3/31 XY metaphases with t(9;22) and 28/31 XX metaphases). A second DLI was given on day 150. The patient did not experience acute or chronic GVHD nor severe cytopenia. Bone marrow analysis on day 180 after the transplant showed a complete cytogenetic response (21/21 XX metaphases) that was confirmed on day 250 (26/26 XX metaphases) with no BCR-ABL rearrangement on FISH analysis (although rt-PCR remained positive). CD3 and CD13 chimerism evolutions are shown in the Figure 1.

Imatinib therapy for CML relapse after allogeneic HSCT has been shown to induce complete cytogenetic responses and complete restoration of donor-type hematopoiesis in some patients.<sup>7-9</sup> Our patient had a hematologic relapse and only

13% T cell chimerism on day 28, a value strongly associated with a high incidence of graft rejection, even with additional DLI.<sup>3,10</sup> Although it cannot be totally excluded that DLI alone could still have achieved it, this suggests that Imatinib therapy followed by DLI permitted to avoid graft rejection by rapidly suppressing Ph-derived hematopoiesis. Furthermore, whereas a similar course on 600 mg/day did not produce a significant cytogenetic response before the transplant, normal metaphases of recipient origin disappeared by day 180 and a complete cytogenetic response was achieved with a 3-mo course of 400 mg/day Imatinib therapy. This strongly suggests that some GVL effect also occurred under Imatinib therapy. Further studies are needed to confirm this preliminary result and to study the impact of Imatinib on the achievement of a full donor T cell chimerism as well as on the GVL effect.<sup>11</sup>

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