Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials

Imatinib, a targeted inhibitor of the tyrosine kinase activity of the BCR-ABL oncoprotein, has demonstrated considerable efficacy in all phases of chronic myeloid leukemia (CML).[1] Recently, Palandri and colleagues reported on the long-term outcomes of patients with CML in accelerated phase[2] (CML-AP) and blast crisis[3] (CML-BC) treated with imatinib 600 mg/day. We have previously reported the results of phase II studies of imatinib for the treatment of CML-AP and CML-BC.[4-6] This letter complements the reports by Palandri *et al.* by providing long-term follow-up results for these studies of advanced-stage CML patients treated with imatinib.

Initially, patients with CML-AP who enrolled in the STI571 0109 trial (phase II study of imatinib in patients with CML in accelerated phase) were treated with imatinib 400 mg daily (n=62). Following phase I data, which confirmed that higher doses were safe, the starting dosage was increased to 600 mg daily (n=119). Dose escalation (initially to 600 mg once daily and subsequently to 400 mg twice daily) was permitted for patients who relapsed. A total of 181 patients with a confirmed diagnosis of CML-AP were enrolled in the study.[4] Analysis at 48 months indicated that 32 patients (18%) remained on imatinib therapy while 149 patients (82%) discontinued imatinib. Primary reasons for discontinuation included progression or lack of efficacy for 100 patients (67.1%), protocol violations or administrative reasons for 17 patients (11.4%), adverse events or toxicity for 13 patients (8.7%), bone marrow transplant for 5 patients (3.3%), and death for 14 patients (9.3%). Best observed responses included complete hematologic response (CHR) in 40%, partial cytogenetic response (PCyR) in 7%, and complete cytogenetic response (CCyR) in 20% of patients. The median overall survival (OS) was 43 months for CML-AP patients treated with imatinib 600 mg/day. At 48 months, the estimated median time to progression (TTP) was 22.7 months and the estimated OS rate was 45% for patients treated with imatinib 600 mg/day. Seventy-four percent of patients with a major cytogenetic response (MCyR) at three months were alive at 48 months, compared with 41% without an MCyR (p=0.009) at three months. Safety data were unchanged since the prior report in 2002. As of November 2008, 42 patients (23%) remained on study follow-up with 16 patients (9%) continuing to receive the study drug.

A total of 229 patients with a confirmed diagnosis of CML-BC were enrolled in the STI571 0102 trial (phase II study of imatinib in patients with Ph+ CML in myeloid blast crisis) and treated with imatinib 400 or 600 mg/day.[5] At 48 months, 3% of patients remained on imatinib therapy while 223 (97%) had discontinued imatinib therapy. The primary reasons for discontinuation included progression or lack of efficacy for 154 patients (69.0%), protocol violations or administrative reasons for 14 patients (6.3%), adverse events or toxicity for 19 patients (8.5%), bone marrow transplant for 10 patients (4.5%), and death for 26 patients (11.7%). Best observed hematologic response (HR) was achieved in 34% of patients, with 9% achieving a CHR. MCyR was achieved in 16% of patients and CCyR in 7% of patients. The estimated median TTP was 4.4 months and the estimated OS rate was seven months for patients treated with imatinib 600 mg/day. As of November 2008, 13 patients (6%) remained on study follow-up with 3 patients (1%) continuing to receive the study drug.

These results are consistent with the responses observed by Palandri *et al.* and the GIMEMA Working Party. Extended follow-up of these large, phase II trials demonstrate sustained imatinib efficacy among responding patients with either CML-AP or -BC as well as a favorable long-term safety profile supporting the use of imatinib in patients with advanced phases of CML. While these trials demonstrate significant survival improvements for patients with advanced CML receiving imatinib therapy compared with previous treatment options, the small number of patients remaining on therapy after four years illustrates the need for improved treatment options for patients with advanced phases of the disease.

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R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: influence of prior autologous stem-cell transplantation on outcome

We have read with interest the excellent editorial by Sud and Friedberg about salvage therapy for relapsed or refractory diffuse large B-cell lymphoma (DLBCL).[1] The authors cite and comment upon our recently published GEL/TAMO study which evaluates the influence of prior rituximab use on response rates and survival in patients with DLBCL treated with R-ESHAP as salvage therapy.[2] As the editorial authors mention, our study is the first comprehensive analysis of the efficacy of rituximab in salvage therapy in patients with prior exposure which is relevant to the current standard of care.

We agree with the authors that our study may have important shortcomings, as do many other retrospective multicenter studies. However, we disagree that patients with previous autologous stem-cell transplantation (ASCT) should have been excluded from the analysis (taking into account that these patients have historically been poorly responsive and potentially incurable with further therapy). In our study, 16 patients were treated with ASCT in first complete remission prior to R-ESHAP due to high-risk disease at diagnosis. These patients received the R-ESHAP regimen with a curative purpose. Thirteen out of 16 patients had not previously been exposed to rituximab. The median age of these patients was 54 years (range 23-62). The overall response rate to R-ESHAP was 100%, with 11 patients achieving complete remission and 2 partial remission. Three patients were treated with a second ASCT, and one patient with an allogeneic transplantation. In this group of 13 patients who had not been exposed to rituximab prior to R-ESHAP, progression-free survival and overall survival (both estimated at five years) were 74% and 83%, respectively. These excellent results are all the more remarkable considering the poor prognosis of patients relapsing after an ASCT. The remaining 3 patients had previously been exposed to rituximab. These patients were 34, 48 and 49 years of age, and they had a very good performance status. Although these patients had little hope of being cured, a second ASCT or an allogeneic transplant could be a possibility if they reached a good response after the salvage therapy. Two of the 3 patients achieved partial remission to R-ESHAP, and one patient was treated with allogeneic transplantation after the salvage therapy. All 3 patients died within the first year after R-ESHAP administration. This data strongly supports the main conclusion of the study that the survival outcome after R-ESHAP is significantly better in rituximab-naïve patients. For these reasons, these 16 patients were not excluded from the analysis.

The influence of prior ASCT on survival is explained in the survival analysis section of our paper and is also mentioned in the discussion section.[2]

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