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Efficacy and Feasibility of Sorafenib as a Maintenance Agent after Allogeneic Hematopoietic Stem Cell Transplantation for Fms-like Tyrosine Kinase 3 Mutated Acute Myeloid Leukemia: an update

Running title: Efficacy and feasibility of sorafenib after HSCT for FLT3 mutated AML

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Dear Editor,

Patients diagnosed with acute myeloid leukemia (AML) with Fms-like tyrosine kinase 3 (FLT3) mutations have a very poor prognosis[1]. Use of allogeneic hematopoietic stem cell transplantation is now a standard practice in this setting of patients, but disease relapse may occur, with difficulties to obtain a complete remission despite salvage treatments[2]. More recently, the incorporation of FLT3-inhibitors in the treatment of these patients has shown promising results[3][4].

We previously reported the safety and efficacy of sorafenib, a FLT3-inhibitor, as a maintenance agent after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients diagnosed with acute myeloid leukemia (AML) with FLT3 mutations[5]. Since our report, other retrospective series confirmed our results showing significant overall (OS) and progression-free survival (PFS) gain in patients receiving sorafenib before and/or after allo-HSCT[6]. More recently, preliminary conclusions of a prospective trial randomizing use of maintenance treatment with sorafenib versus placebo introduced during the first 60-100 days after allo-HSCT, further supported the use of this drug in this high-risk setting[7].

Therefore, we would like to update the follow-up of the 27 patients with FLT3 mutated AML who received sorafenib as a single maintenance agent. In our cohort, FLT3-ITD AML was detected in 25

patients, whereas FLT3-TKD was found in the remaining 2 patients. Median age at time of transplant was 46 (range 16-58) years. Disease status at time of transplant was complete remission (CR) in 26 patients (including 3 CR2 and 1 CR3) and active disease in the remaining one. Of note, minimal residual disease remained detectable at time of allo-HSCT in 12 patients. Conditioning was myeloablative in 20 patients, reduced-intensity in 5 patients and sequential in the two remaining patients. Sorafenib was introduced at a median time after transplant of 70 (range 29-337) days with different starting doses, subsequently adjusted to the best tolerated dose according to side effects. Toxicities occurred in 11 out of 27 patients, mainly being grade 1 or 2 and reversible in all cases. These events were mostly hematologic (2 patients), gastrointestinal (6 patients, including 1 patient with hematologic toxicity), cardiac (1 patient), cutaneous (3 patients, including 1 patient with gastrointestinal toxicity), and biochemical (amylase and lipase elevation [1 patient]). Drug withdrawal or dose reductions due to toxicity were made in 5 and 3 patients, respectively. Thirteen patients developed graft-versus host disease (GVHD) with a median time to onset after sorafenib introduction of 14 (range 5-56) days, prompting to either drug withdrawal or dose reduction in 3 and 4 patients, respectively. Among patients starting with a dose of 400 mg BID and needing a dose reduction, in most of them the final dose was 200 mg BID. A possible synergistic effect of sorafenib and alloreactive donor T cells in facilitating long-term disease control has also been proposed in murine models in which sorafenib apparently exacerbated GVHD[8][9].

After an initial median follow-up of 18 months, we previously reported a 1-year-PFS rate of 92%±5% and 1-year OS of 92±6%, with 2 patients dying of GVHD or infection. At that time point, 18 patients out of 27 were still on sorafenib with a median treatment duration of 14 (range 3-46) months.

We are now at a median follow-up from allo-HSCT of 40 (range 15-68) months and 12 patients are still receiving sorafenib out of 18 patients in the initial report. Interestingly, the main reason for treatment withdrawal in the six patients was physician choice in 3 while in one patient, after intermittent use of sorafenib, the drug was definitively stopped when chronic GVHD occurred two years after allo-HSCT.

In the two remaining patients, withdrawal was related to disease recurrence. One of those patients achieved a second CR with salvage chemotherapy followed by a second allo-HSCT. In the second patient salvage chemotherapy also allowed second CR. Of note, in the previous report we also described a case of sorafenib withdrawal followed by the use of prophylactic and then curative 5-azacitidine in relation to molecular relapse, allowing CR at 20 months after allo-HSCT. A second relapse occurred in this patient at 27 months from allo-HSCT and, despite 2 further salvage regimens, death occurred due to disease progression. Interestingly, at time of relapse this patient presented different size of FLT3-ITD mutation as compared to those found at time of diagnosis.

Finally, at the last follow up, 22 patients are still alive. The 2-years PFS is 73%±9% while the 2-year OS is 80%±8% (Figure 1). These results are similar to those previously reported by Brunner et al. who reported 2-year PFS and OS of 82% and 81%, respectively, in FLT3-mutated AML receiving sorafenib after allo-HSCT[10]. Importantly, in the current study, stratification of patients according to their FLT3 mutant-to-wild-type allelic ratio at the time of diagnosis was not possible because it was not systematically performed in the 3 centers.

In conclusion, our results with longer follow-up further support the use of sorafenib as a maintenance agent after allo-HSCT, allowing persistence of impressive long-term disease control.

Figure 1. Two-year progression-free (a) and overall (b) survival in patients receiving sorafenib after allogeneic hematopoietic stem cell transplantation.

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