To the editor:

**Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis**

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) with a high propensity to develop acute myeloid leukemia, named at this stage blast phase (BP) of PMF. Oncogenic JAK2 signaling is an important event in MPN, but transformation process into BP, although not completely understood, often involves additional genomic lesions. Several models have been developed to predict survival in PMF. Concerning BP occurrence, leukocyte count more than 30 x 10^9/L, blast cell count more than 10%, platelet count below 50 x 10^9/L, red blood cell transfusion dependency, selected cytogenetic abnormalities, low JAK2(V617F) allele burden have been reported to shorten BP-free survival.

The International Working Group on Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) has recently developed a time-dependent prognostic model, named Dynamic International Prognostic Scoring System (DIPSS) to predict survival anytime in patients with PMF. This model includes age older than 65 years, hemoglobin level lower than 10 g/dL, white blood cell count more than 25 x 10^9/L, peripheral blood blasts equal to or higher than 1%, and constitutional symptoms.

In this study, we investigated whether DIPSS may also predict the occurrence of BP. The study was approved by the Institutional Review Board of each participating center, and the procedures followed were in accordance with the Declaration of Helsinki. On behalf of IWG-MRT, we surveyed the large-scale international database of 525 regularly followed patients with PMF, which allowed the definition of DIPSS. Blast phase was defined when a threshold of 20% peripheral blast cells was achieved during follow-up.

Among 525 patients, 70 (13%) developed BP after a median time of 2.8 years (range, 2-14.5). Median age was 68 years (range, 31-90 years), 58 (83%) patients were male, and 56 (80%) received cytotoxic agents during chronic phase. The incidence of BP was 0.3 (95% confidence interval [CI]: 0.04-1.2) x 100 patient/years in low-risk category, 0.7 (95% CI: 0.2-1.7) x 100 patient/years in intermediate-1, 2.6 (95% CI: 1.4-4.4) x 100 patient/years in intermediate-2, and 8.6 (95% CI: 6.4-11.4) x 100 patient/years in high risk.

We analyzed the categorical DIPSS score as a time-dependent covariate in a Cox survival regression model with BP as outcome (Figure 1). Overall, the Gehan Wilcoxon test showed that DIPSS stratified PMF patients for BP risk (P < .001). The increase in risk when changing risk category was further estimated as a hazard ratio (HR). The estimated HRs were: 2 (95% CI: 0.4-11.3; P = .4) if the risk category shifted from low to intermediate-1, 3.8 (95% CI: 1.2-11.4; P = .019) from intermediate-1 to intermediate-2, and 3.2 (95% CI: 1.8-5.8; P < .001) from intermediate-2 to high. Comparing higher risk categories to low-risk category, HR was 7.8 (95% CI: 1.8-34.2; P = .007) for intermediate-2 and 24.9 (95% CI: 6-102.3; P < .001) for high risk.

The study shows that modification of the DIPSS during follow-up of PMF patients may also predict different risks of BP. Patients belonging to the higher risk categories have a notable 7.8-fold and 24.9-fold higher risk of developing BP comparing to those who continue to fit in low-risk category. As BP evolution implies a dismal outcome, this observation recommends to approach patients with higher DIPSS categories for intensive or investigative treatments.

**Figure 1. Kaplan-Meier estimate of blast phase-free survival in primary myelofibrosis according to the DIPSS.** Risk categories were according to the score obtained anytime during follow-up. Values for score calculation are as follows: 1 for age > 65 years, 2 for hemoglobin level < 10 g/dL, 1 for white blood cell count > 25 x 10^9/L, 1 for peripheral blood blasts ≥ 1%, and 1 for constitutional symptoms. Risk categories are low (score: 0), intermediate-1 (score: 1 or 2), intermediate-2 (score: 3 or 4), and high (score: 5 or 6).
To the editor:

Toxic effects of sorafenib when given early after allogeneic hematopoietic stem cell transplantation

We read with interest the article by Metzelder et al showing sorafenib had antileukemic activity and could be given safely to patients with FLT-3 mutated AML relapsing after allogeneic stem cell transplantation (ASCT).1 Because sorafenib delays progression of renal cell carcinoma, we administered this drug to patients who had progression of metastatic kidney cancer after an ASCT. Besides the classic sorafenib hand-foot syndrome, we observed new-onset, biopsy-confirmed chronic graft-versus-host disease (cGVHD) of the skin (including one case of sclerodermoid cGVHD) and exacerbations of preexisting chronic skin GVHD in 4 of 7 patients treated with 400 mg of sorafenib given orally twice daily. Metzelder et al also noted cGVHD occurred in 2 of 4 patients receiving sorafenib after ASCT, although the temporal association of this drug with cGVHD is unclear from their study. Although the authors speculate sorafenib might be effective when given prophylactically after an ASCT to reduce FLT-3 mutated AML leukemia burden, it is important to note that the initiation of sorafenib in the 4 patients in their study was delayed months after the transplantation (87-322 days). In vitro and murine findings from our laboratory raise the concern that sorafenib may result in substantial toxicity and increase the risk of GVHD when this drug is administered early after a T cell–replete ASCT.

Using a major histocompatibility complex (MHC)–matched murine model of ASCT, we explored whether sorafenib would slow tumor progression potentially facilitating GVT effects in mice with established RENCA tumors. BALB/C mice conditioned with 950 cGy total body irradiation received either a T cell–depleted (bone marrow alone) or T cell–replete (bone marrow plus splenocytes) ASCT from MHC-matched, minor antigen–mismatched B10.d donors. Nontransplanted tumor-bearing BALB/C control mice that received sorafenib by oral gavage (60 mg/kg/day) had no evidence of drug toxicity and had slower tumor growth which improved survival compared with mice not receiving sorafenib (median survival 49 vs 34 days, respectively; P = .04). In recipients of a T cell–depleted ASCT, sorafenib by oral gavage was not associated with overt toxicities and also delayed tumor progression and
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