Frontline therapy with high-dose imatinib *versus* second generation tyrosine kinase inhibitor in patients with chronic-phase chronic myeloid leukemia – a propensity score analysis

Tyrosine kinase inhibitors (TKI) improve survival in patients with chronic myeloid leukemia in chronic phase (CML-CP), with the survival of patients treated with such agents approaching that of the general population.[1,2] High-dose imatinib has also been reported to induce higher rates of deep and earlier molecular responses compared to the standard dose of imatinib.[3,4] However, the efficacy of high-dose imatinib has never been compared to that of nilotinib and dasatinib. The aim of this study is to compare cytogenetic and molecular response rates and survival outcomes obtained with high-dose imatinib or second generation TKIs.

Patients with newly diagnosed CML-CP who enrolled in four consecutive or parallel prospective single-institution clinical trials of imatinib (single-arm 800 mg daily; randomized 800 mg daily ± pegylated interferon),[5] nilotinib (400 mg twice daily),[6] and dasatinib (50 mg twice daily, or 100 mg daily)[7] were analyzed. Patients who received imatinib 800 mg daily + pegylated interferon were excluded from this analysis. These trials were registered at *clinicaltrials.gov identifier: 00038649, 00050531, 00254423, 00129740*. The inclusion criteria were similar for all the trials, including age ≥15 years, adequate organ function, and performance status 0-2. Standard definitions for cytogenetic and molecular response were used.[8] The definition of overall survival (OS), event-free survival (EFS), transformation-free survival (TFS), and failure-free survival (FFS) were as previously published.[2,3]

Logistic regression was used for propensity score calculation from baseline patient characteristics, including age at diagnosis, sex, race, Sokal, Hasford and European Treatment and Outcome Study scores, white blood cell, hemoglobin, platelets, blasts, eosinophils and basophils in peripheral blood and bone marrow, albumin, urea nitrogen, creatinine, lactate dehydrogenase, total bilirubin, alanine aminotransferase, the proportion of Philadelphia chromosome by conventional karyotype and fluorescence in situ hybridization, the presence of clonal evolution, the type of BCR-ABL transcript, and time from diagnosis to therapy. Propensity score analysis with 1:1 matching was performed with the caliper matching method using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score.[9] Cox proportional hazards for survival were performed for unbalanced variables after propensity score matching.

Table 1. Main patient characteristic after propensity score matching and clinical outcome.

	No. (%) or Median (range)		*P*	No. (%) or Median (range)		*P*
	IM800 [n=87]	Dasatinib [n=87]		IM800 [n=97]	Nilotinib [n=97]	
Age at diagnosis, (y)	46.5 (17.2-81.6)	45.8 (18.5-82.5)	0.576	48.2 (17.2-79.6)	49.1 (17.0-86.4)	0.790
Sokal risk, No. (%)						
Low	55 (63)	63 (72)	0.356	65 (67)	64 (66)	0.922
Intermediate	25 (29)	17 (20)		25 (26)	27 (28)	
High	7 (8)	7 (8)		7 (7)	6 (6)	
BCR-ABL <10% at 3M	96	92	0.260	91	95	0.296
Full dose at 3 months, (%)	62 (67)	80 (87)	0.002	49 (67)	63 (86)	0.006
Reason for dose reduction within 3 months, (%)						
Hematologic toxicity	11 (12)	1 (1)	0.003	12 (16)	2 (3)	0.005
Non-hematologic toxicity	19 (21)	11 (12)	0.110	12 (16)	8 (11)	0.336
Cumulative response within 1 year, (%)						
MR4.5	43	37	0.438	37	50	0.082
MR4	49	40	0.223	45	54	0.196
MMR	81	72	0.211	78	81	0.591
CCyR	91	90	0.818	90	92	0.621
Full dose at 1 year, (%)	56	68	0.177	57	54	0.767
Toxicity-related discontinuation at 1 year, (%)	6	3	0.404	7	4	0.515
Cumulative response within 3 years, (%)						
MR4.5	67	63	0.634	64	67	0.651
MR4	74	66	0.249	71	71	1.000
MMR	87	83	0.395	88	90	0.651
CCyR	91	91	0.981	91	92	0.800
Full dose at 3 years, (%)	41	43	0.841	45	39	0.455
Toxicity-related discontinuation at 3 year, (%)	10	8	0.771	10	4	0.150
5-year outcome, (%)						
FFS	71	70	0.780	75	72	0.298
TFS	92	91	0.929	96	88	0.011
EFS	83	89	0.483	87	85	0.381
OS	92	96	0.465	94	94	0.681

IM800: imatinib at a dose of 800 mg/day; M: month; CCyR: complete cytogenetic response; MMR: major molecular response; MR4: more than or equal to 4 log reduction of BCR-ABL on the international scale; MR4.5: more than or equal to 4.5 log reduction of BCR-ABL on the international scale; FFS: failure-free survival; TFS: transformation-free survival; EFS: event-free survival; OS: overall survival.

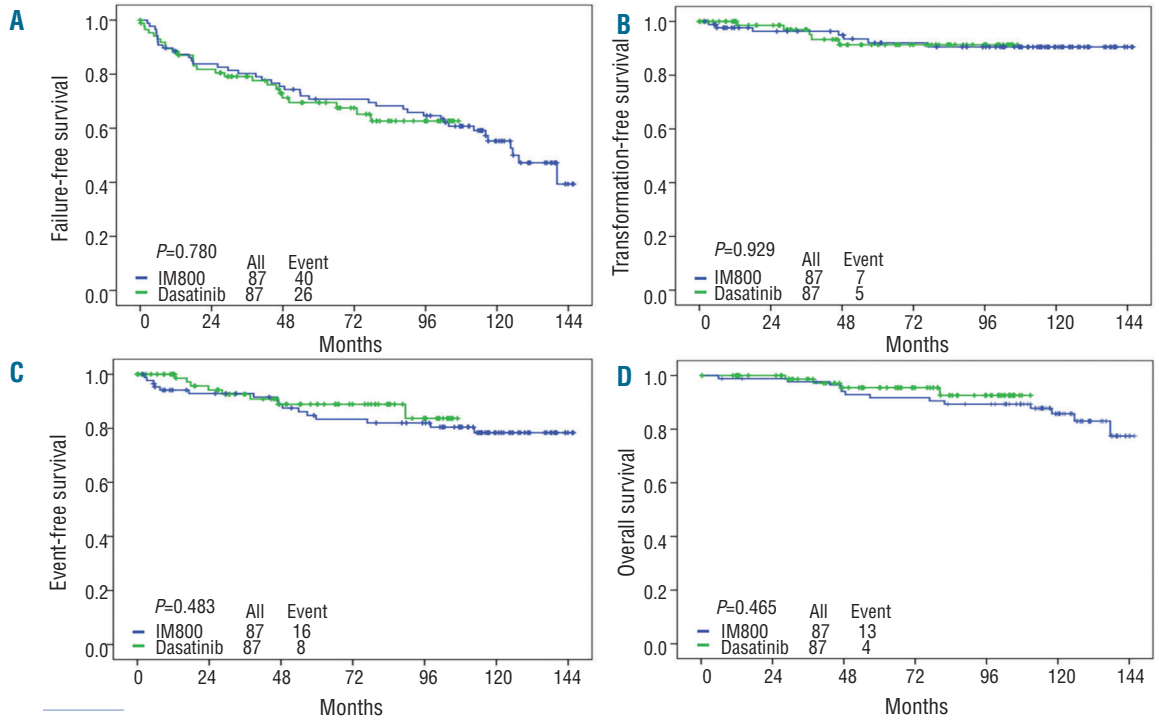

Figure 1. High-dose imatinib and dasatinib outcome after matching: 1A) failure-free survival, 1B) transformation-free survival, 1C) event-free survival, 1D) overall survival. IM800, imatinib at a dose of 800 mg/day,

From June 2001 to November 2014, 456 patients with CML-CP were enrolled in these clinical trials (imatinib 800 mg/day [IM800], n=158; nilotinib, n=148; dasatinib, n=150). One patient in nilotinib was excluded from the analysis due to incomplete baseline data for propensity score matching. After propensity score matching, 87 patients each for the IM800 *vs.* dasatinib analysis, and 97 patients each for the IM800 *vs.* nilotinib analysis were identified (table 1). The median follow-up was 120.5 and 67.3 months in the IM800 and dasatinib cohorts, respectively ($P<0.001$), and 124.4 and 60.7 months in the IM800 and nilotinib cohorts, respectively ($P<0.001$). Baseline differences identified between IM800 and dasatinib, and between IM800 and nilotinib, did not affect FFS, TFS, EFS, or OS by univariate analysis with Cox proportional hazards models except univariate analysis for OS between IM800 and nilotinib showing shorter days from diagnosis to therapy as an adverse prognostic factor (HR, 0.948; 95% CI, 0.913-0.984; $P=0.005$). In the IM800 and nilotinib cohorts, the median of days from diagnosis to therapy was 26 days (range, 1-196; 25%-75% IQR, 9-35.5), and 14 days (range, 0-168; 25%-75% IQR, 5-33.5) ($P<0.001$), respectively. The IM800 cohort required dose reduction within 3 months due to hematologic toxicity more frequently than the nilotinib and dasatinib cohorts ($P=0.003$; $P=0.005$). Cumulative incidence of toxicities is described in *Online Supplementary Table S1*. Median 3-year actual dose was 600 mg/day in IM800, 80 mg/day in dasatinib, and 800 mg/day in nilotinib.

For the propensity-matched cohorts there were no significant differences in the rates of CCyR or molecular response (MMR, MR4 or MR4.5) between IM800 and either dasatinib or nilotinib (Table 1). There were no differences in FFS, TFS, EFS, or OS between IM800 and dasatinib, or between IM800 and nilotinib, except for TFS between the IM800 and nilotinib matched cohorts ($P=0.011$) (Figure 1; Figure 2).

Among the IM800 and dasatinib matched cohorts, 17 died (IM800, 13 deaths; dasatinib, 4 deaths). Of the 13 deaths on IM800, 2 died of complications of stem cell transplant performed after progressive disease; 5 of cardiovascular diseases; 2 each of dementia, and unknown causes; and 1 each of suicide, and surgical complications after bowel obstruction. Of the 4 deaths on dasatinib, 1 each died of of disease progression, car accident, complications after heart surgery, and unknown cause, respectively. One of the 2 patients on imatinib who died after disease progression did not receive 2nd generation TKIs (unavailable at the time). In the IM800 and nilotinib matched cohorts, 19 deaths were recorded (IM800, 13; nilotinib, 6). Of the 13 deaths on IM800, 3 died of cardiovascular events, 2 each of car accidents, and unknown causes, and 1 each of progressive disease, stem cell transplant complications after progressive disease (to blast phase), progression of concomitant chronic lymphocytic leukemia, metastatic breast cancer, dementia, and end stage live failure due to hepatitis C. Of the 6 deaths on nilotinib, 2 patients died of sepsis (in MMR and MR4.5, respectively), 1 each of accidental fall, cardiovascular event, surgical complications after femur fracture, and unknown cause at the age of 92 years. Among the IM800 and nilotinib matched cohorts, 14 had progression to advanced phase (IM800, 4; nilotinib, 10). Of the 4 patients on imatinib, 1 had disease progression on study, and 3 died while on study (car accident, cardiovascular event, and metastatic breast cancer, respectively). Of the 10 patients on nilotinib, 4 had disease progression while on study, and 6 died as described in preceding paragraph.

To our knowledge, this is the first report of a comparative analysis of patients with CML-CP treated frontline

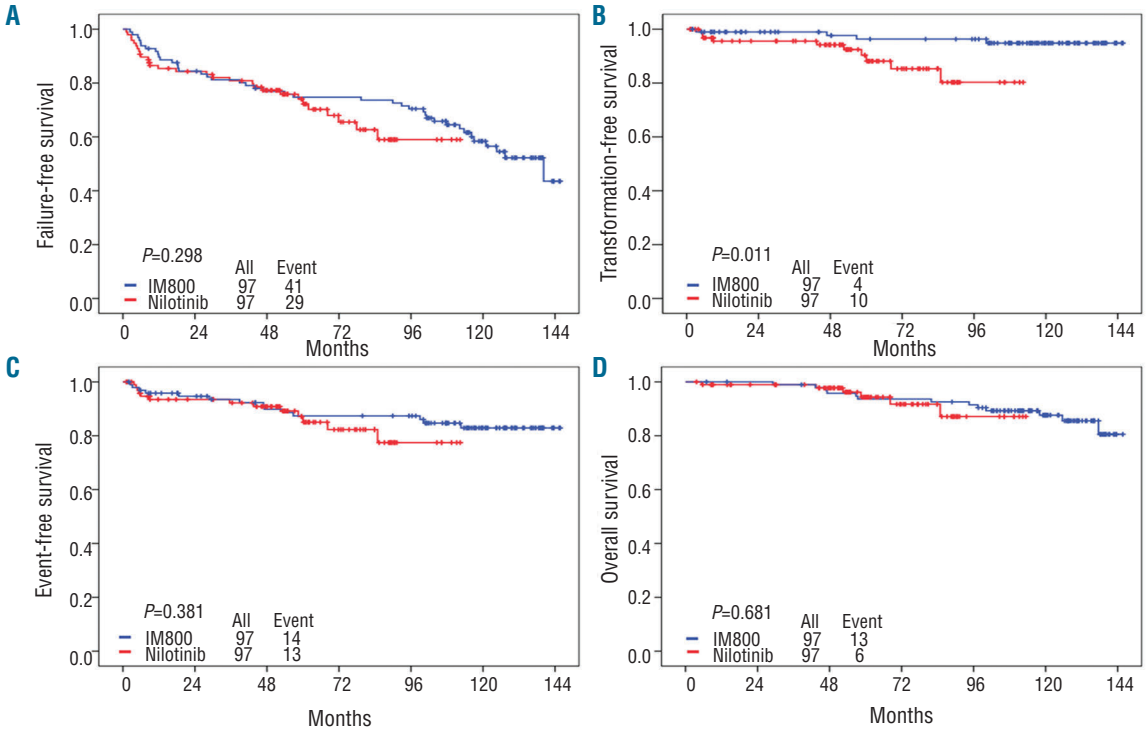

Figure 2. High-dose imatinib and nilotinib outcome after matching: 2A) failure-free survival, 2B) transformation-free survival, 2C) event-free survival, 2D) overall survival. IM800: imatinib at a dose of 800 mg/day.

with IM800 or second generation TKIs. IM800 and second generation TKIs induce faster and deeper responses than those seen with imatinib 400 mg/day.[3,4,10,11] However, no randomized trial has compared the outcome of treatment with 2nd generation TKI to IM800 and, to our knowledge, none is ongoing. Therefore, we performed this analysis to investigate the possible differences or similarities in outcome of these two strategies. The cumulative response rates and 5-year survival endpoints for the IM800 cohort were nearly identical to those of their matched dasatinib or nilotinib counterparts except 5-year TFS between the IM800 and nilotinib cohorts. This difference appears to be due to deaths on the nilotinib arm from unrelated causes (which were counted within the definition of TFS that includes deaths from any cause while on study). This, together with the fact that multiple comparisons may yield a false positive statistically significant difference, suggests that there is likely no difference in outcome between IM800 and either nilotinib or dasatinib.

As the patent for imatinib expires and generic versions become available, the medical cost related to TKIs will decrease. Estimated annual costs in the U.S. in 2013 were $92000 for imatinib 400 mg/day, $115500 for nilotinib, and $123500 for dasatinib.[12] In this setting, doubling the dose of imatinib would result in increased costs. We recently reported that OS in patients with CML-CP who have access to TKI is similar to that of the general population.[2] However, the Surveillance, Epidemiology, and End Results (SEER) reported that the 5-year relative survival from 2005 to 2011 was 63.2% in all ages, ranging from 87.3% in age <45 to 26.5% in age ≥75.[13] The decrement of relative survival, particularly in young ages, might be influenced, at least partially, by the lack of access to TKI. As generic imatinib becomes less expensive and more widely available, these barriers will be lowered. The use of high-dose imatinib could then potentially become a valid alternative to second generation TKIs.

There are several limitations in our study. Firstly, the median follow-up in the IM800 cohort was significantly longer than that of the nilotinib or dasatinib cohorts. We thus selected time points for evaluation of cumulative response rate that are shorter than the median follow-up in the nilotinib or dasatinib cohorts. It is possible that longer follow-up could alter these comparisons. Nonetheless, the current data with dasatinib and nilotinib suggest that the incremental improvement of the deepest responses seems to slow down or plateau after approximately 5 years. Secondly, several baseline patient characteristics were still significantly different after propensity score matching. Univariate analysis for FFS, TFS, EFS, and OS with the Cox proportional hazards model, however, did not show any correlation of these variables with outcome, except for days from diagnosis to therapy with univariate analysis for OS between IM800 and nilotinib. The difference in median days from diagnosis to therapy between the cohorts was only 12 days. There is still, however, the possibility of latent variables not accounted for by this matching.

In conclusion, patients treated with high-dose imatinib may have similar response and long-term survival endpoints compared to those treated with 2nd generation TKIs. In the absence of a randomized trial to confirm this observation, these results suggest that such an approach might be valid initial therapy for patients with CML-CP. A prospective, randomized trial is warranted to confirm these observations.

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