blood advances

COUNTERPOINT A second-generation TKI should always be used as initial therapy for CML

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This article has a companion Point by Hantel and Larson.

The development of imatinib in chronic myeloid leukemia (CML) represented a milestone in the treatment of cancer. Long-term results with frontline imatinib in chronic-phase CML demonstrate the continued success of imatinib.[1] Among patients evaluated 10 years from the start of therapy, 91.8% had a complete cytogenetic response (CCyR), 93.1% a major molecular response (MR), and 63.2% an MR4.5. This correlated with a low rate of transformation (6.9%) and excellent estimated 10-year event-free survival (EFS; 79.6%) and overall survival (OS; 83.3%).[1] However, in cancer, we aim to improve outcomes whenever possible. This is imperative when outcomes are not good, but also desirable when a good outcome can be made better. This has fortunately been the path in CML therapy over the past several years. Shortly after imatinib became standard therapy, second-generation tyrosine kinase inhibitors (2G-TKIs) emerged. These were first used after failure of imatinib and later as frontline therapy. Three 2G-TKIs (bosutinib, dasatinib, and nilotinib) have demonstrated in randomized clinical trials significant clinical benefit compared with imatinib.[2-4] All 3 are approved as initial therapy for CML in the United States.

It has sometimes been considered a disappointment that frontline therapy with 2G-TKIs has not improved survival compared with imatinib. It is perhaps unrealistic to expect a survival benefit, particularly with the short follow-up available for the randomized studies. Patients who achieve a CCyR already have a survival benefit and reach relative survival similar to that of the general population.[5] The cumulative CCyR rate with imatinib is 77% to 92%.[1,6,7] In the aforementioned IRIS trial, despite the vast difference in the CCyR rate between imatinib and interferon, it took 10 years of follow-up to demonstrate a small survival benefit (83.3% vs 78.8%, respectively). Part of this was due to the high rate of early crossover, but in a way, the same has happened with imatinib as many patients have crossed over to a 2G-TKI, obscuring a possible survival benefit with frontline 2G-TKIs. Nevertheless, some interesting trends are emerging. In ENESTnd, both the 5-year OS and freedom from death resulting from progression with 400 mg of nilotinib twice daily, and freedom from death resulting from progression with 300 mg of nilotinib twice daily, were significantly better compared with imatinib.[4] In BFORE, deaths in the bosutinib and imatinib cohorts occurred in 0.4% and 2.4% of patients, respectively.[2] However, it is entirely possible that the survival improvement has been maximized with imatinib, and therefore, a meaningful survival benefit for patients treated with 2G-TKIs may never be observed. Other traditional end points also favor 2G-TKIs. The 10-year EFS with imatinib in IRIS might be overestimated because of the many patients censored early. Other studies have reported 5-year EFS rates of 63% to 71%.[6,8] ENESTnd reports a trend for improved 5-year EFS with nilotinib vs imatinib (95% vs 92.6%; $P = .1874$), which is statistically significant with nilotinib 400 mg twice daily (96.9%, $P = .0188$). Although transformation to accelerated or blast phase is relatively uncommon with imatinib (~7% to 8%), all randomized trials report a lower rate of transformation with 2G-TKIs.[2-4,9]

Because survival has neared that of the general population, other end points have greater value and offer additional benefit. Early responses are important and constitute part of the definition of optimal response.[10] *BCR-ABL* transcript levels <10% at 3 months and <1% at 6 months correlate with improved EFS and OS. The difference in long-term outcome between those with and without such responses is relatively small but consistent across multiple reports. The outcome is similar whether the response is achieved with imatinib or a 2G-TKI. However, consistently, early responses are achieved significantly more frequently with 2G-TKIs (~85% to 90%) than with imatinib (~65%).[2,4,11,12]

As therapies and monitoring tools have improved, our end points and goals have also advanced. Deep MRs (DMRs) are today the most relevant end point for most patients. Despite initial doubts regarding their impact on survival end points, there is some suggestion that those who achieve a DMR may eventually have a survival benefit.[5,13] But the strongest and least controversial benefit of a DMR, which is becoming of greater relevance to patients, is the potential for treatment discontinuation. A sustained DMR is an essential prerequisite for considering an attempt at treatment discontinuation.[14] This is

Table 1. Summary of selected end points from pivotal randomized trials of 2G-TKIs vs imatinib

	DASISION, %		ENESTnd, %			BFORE, %	
			Nilotinib, mg†				
Outcome*	Dasatinib	Imatinib	300	400	Imatinib	Bosutinib	Imatinib
3-mo *BCR-ABL/ABL* <10%	84	64	90.6	89.2	69.2	75.2	57.3
12-mo MMR	46	28	44	43	22	47.2	36.9
5-y MMR	76	64	77	77	60	—	—
5-y MR4.5	42	33	53.5	52.3	31.4	—	—
5-y sustained MR4.5	NR	NR	41	44	26	—	—
Transformation to AP/BP	4.6	7.3	<1	<1	4	1.6	2.5
OS	91	90	93.7	96.2	91.7	99.6‡	97.9‡
CML-related deaths	3.5	6.6	2.1	1.4	5.6	NR	NR
PFS	85	86	92.2	95.8	91.0	3.7§	6.4§
Remain on therapy	61	63	59.9	61.9	49.8	78	73.2

AP, accelerated phase; BP, blast phase; MMR, major MR; NR, not reached; PFS, progression-free survival.
*5-y data presented for DASISION and ENESTnd and 1-y data for BFORE unless otherwise specified.
†Twice daily.
‡At 12 mo.
§EFS-defining events at 12 mo.

typically defined as MR4.5 sustained for at least 2 years, ideally longer. The 5-year cumulative rate of MR4.5 is significantly higher with nilotinib (52% to 54%)[4] or dasatinib (42%)[3] than with imatinib (31% to 33%).[3,4] The cumulative rate of MR4.5 with imatinib has been reported to reach nearly 60%,[1,7] but not until 10 years of therapy, which means much longer treatment is required to reach a level obtained in approximately half the time with 2G-TKIs. In addition, the rate of sustained MR4.5 is significantly higher with nilotinib (41% to 44%) than with imatinib (26%).[15] In a multivariate analysis of factors associated with achievement of sustained MR4.5, treatment with a 2G-TKI was an independent favorable predictive factor for the probability of achievement of sustained MR4.5.[16] Such responses were also achieved significantly earlier with 2G-TKIs.[6] This suggests that considerably more patients would be eligible for an attempt at treatment discontinuation and that criteria for treatment discontinuation would be reached earlier. Whether the relapse probability is different depending on which TKI is used as initial treatment remains to be determined, but one report suggests fewer relapses among those treated with 2G-TKIs,[17] perhaps suggesting deeper (or better) responses. This possible advantage remains to be confirmed.

The safety profile of all TKIs is favorable, but they all have unique toxicities that may be relevant for individual patients. A recent concern with 2G-TKIs is the risk of arterio-occlusive events. Both ENESTnd and DASISION have reported significantly more such events with nilotinib[4] and dasatinib[3]; the risk with bosutinib seems not to be significantly increased.[18] These events have mostly been seen among patients with additional risk factors (eg, hypertension, diabetes, hyperlipidemia), and it is possible that suboptimal management of such risk factors during TKI therapy augmented the risk. The incidence has also not been adjusted for exposure time, which is generally longer with 2G-TKIs. This could still be a reason to favor imatinib, at least in patients at greatest risk for such events. However, an overall assessment of adverse events in the randomized trials of 2G-TKIs vs imatinib generally favors 2G-TKIs for most events, with a few exceptions (eg, pleural effusion with dasatinib,[3] hyperglycemia with nilotinib,[4] and diarrhea with bosutinib[2]). There are also other risks with imatinib that have been underappreciated, such as the significant decrease in glomerular filtration rate.[19] Furthermore, the possibility of shortening the overall exposure to TKIs by obtaining more, faster, and deeper MRs that may lead to successful treatment discontinuation by using 2G-TKIs may end up decreasing overall risks, including those related to long exposure to any TKI, such as some second cancers.[20] Ultimately, with proper integral patient management and adequate management of comorbidities, in a great majority of patients, any TKI can be safely administered in seeking the best outcome possible. However, it should be underscored that the clinical trial data available to date represent a selected patient population with strict eligibility criteria, control of the use of concomitant medications, and other factors. Therefore, the safety profiles of all these agents as published from these trials may not be fully extrapolated to the totality of the CML population.

It is unfortunate that cost and access are frequent limitations to offering the best possible care to many patients around the world. Imatinib might be less costly because of the multiple generic options available. However, the cost of generics is not yet low enough everywhere to compensate for the benefits, and the quality of many generics available has not been properly assessed. In addition, available support programs for some drugs can help patients in need, and the cost of drugs is a fluid situation, including the fact that generics will emerge for 2G-TKIs over time. One would hope that delivering the best treatment option is not limited by considerations of cost or quality.

We are fortunate to have numerous safe and effective therapies for patients with CML. Patients with proper access to a TKI and who are managed well are likely to enjoy a normal life expectancy. Imatinib will likely remain the most frequently used TKI around the world for the foreseeable future for reasons of cost, access, and familiarity, among others, including in situations where the risk of arterio-occlusive events may be considered prohibitive. Patients treated with imatinib may have an excellent outcome with proper management and attention to achievement of the proper end points

at the proper times, offering change of therapy opportunely when indicated. However, when all options are available, 2G-TKIs offer many advantages that provide patients the best possibility of achieving optimal end points, from response to therapy to treatment discontinuation (Table 1). These include more, deeper, and faster responses, lower risk of transformation, and greater probability of becoming eligible for treatment discontinuation. A 2G-TKI is what I would use for myself if I had the disease, and it is what I offer my patients with newly diagnosed CML today.

Authorship

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