Navigating the road toward optimal initial therapy for chronic myeloid leukemia.

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Navigating the road towards optimal initial therapy for chronic myeloid leukemia

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Abstract

Purpose of review—Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML) and are now widely accepted as the initial therapy of choice in this disease, supplanting interferon and allogeneic stem cell transplantation. There are currently three drugs approved by the Food and Drug Administration (FDA) for front-line treatment of CML: imatinib, nilotinib, and dasatinib. A fourth drug, bosutinib, is expected to win FDA approval in 2011. The goal of this review is to summarize the most recent information on initial treatment of CML and to aid clinicians in managing newly diagnosed CML patients.

Recent findings—Phase III studies comparing imatinib with nilotinib or dasatinib in newly diagnosed CML were published in July 2010, leading to accelerated FDA approval for both of these “second-generation” TKIs for initial therapy of CML. There are significant differences between the agents in terms of frequency and rate of responses, progression-free survival, and side effects. However, the follow-up period on these trials is short, and there are as yet no significant differences in overall survival. Guidelines for monitoring CML patients on TKI therapy have been recently revised.

Summary—Management of newly diagnosed CML patients in the coming decade will begin to resemble antibiotic treatment of infection, with therapy individualized based on patient risk factors, co-morbidities, and tolerability. In addition, the cost of therapy will emerge as an important consideration as generic imatinib becomes available in 2015. In this context, clinical trials to guide decision-making in newly diagnosed CML patients are needed.

Keywords
Chronic myelogenous leukemia; bosutinib; dasatinib; imatinib; nilotinib; tyrosine kinase inhibitor

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm of the hematopoietic stem cell genetically defined by translocation of the ABL1 gene on chromosome 9q34 to the BCR gene on chromosome 22q11, an event manifested in most patients as the Philadelphia (Ph) chromosome. The product of the Ph chromosome, the constitutively active BCR-ABL1 fusion protein-tyrosine kinase, recapitulates CML-like leukemia when expressed in hematopoietic stem cells in mice, prompting the development of ABL1 tyrosine kinase inhibitors [1]. The initial clinical trials of the first ABL1 TKI, imatinib mesylate, quickly demonstrated that this agent gave vastly superior hematologic,
cytogenetic, and molecular responses in CML when compared to previous therapies, and had a favorable toxicity profile [2]. The IRIS (International Randomized study of Interferon and STI571) trial, a randomized crossover trial of imatinib (400 mg/d) versus interferon-alpha and cytarabine in newly diagnosed CML patients in chronic phase (CML-CP) demonstrated the superiority of imatinib for all endpoints studied [3] including complete hematologic responses (CHR), major and complete cytogenetic responses (MCyR/CCyR), and major molecular responses (MMR), leading to FDA approval for imatinib. Subsequently, the second-generation TKIs dasatinib and nilotinib, which are more potent inhibitors and retain activity against many imatinib-resistant mutants of ABL1, were developed and approved for treatment of CML patients whose disease has relapsed on or is refractory to imatinib [4, 5].

With the recent FDA approval of nilotinib and dasatinib for the up-front treatment of CML-CP and the expectation that bosutinib may soon follow suit, clinicians will have at least four choices for initial TKI therapy of these patients. In this review, we summarize the latest clinical information in this area and provide an overview of initial management of CML. The focus is on individualizing therapy, monitoring disease responses, optimization strategies including escalation of imatinib dose or switching to second generation TKIs, and possible combination therapies to improve response rates and the possibility of cure.

**TKIs are the preferred initial therapy in CML**

Allogeneic HSCT, which remains the only known curative treatment for CML (see “Can TKI therapy cure CML?” below), yields five-year survival rates of 60-80% in favorable risk patients [6] but is complicated by the potential for increased morbidity and mortality. A randomized study of alloHSCT vs. best available drug treatment as initial therapy in CML found a survival advantage for drug therapy [7]. Although about 20% of the patients in the drug therapy arm on this study received imatinib, the majority were treated with interferon, suggesting that the results may underestimate the relative advantage of current drug therapy. In the IRIS trial, it was not possible to demonstrate a survival advantage for imatinib, since over 90% of the patients randomized to interferon crossed over to imatinib after nine months [3] and subsequently enjoyed clinical responses similar to patients in the imatinib arm [8]. However, two retrospective comparison studies found superior three-year survival of patients treated with imatinib vs. interferon-containing regimens [9, 10]. Hence, the current expert consensus is that imatinib (or one of the second-generation TKIs newly approved for front-line use) represents the best initial therapy for CML [11, 12]. The only possible exception might be a very young (age <20 years) patient with an HLA-matched sibling donor (European Group for Blood and Marrow Transplantation Risk Assessment Score of 0; [6]), where the excellent outcomes with HSCT and chance for permanent cure might favor transplant.

**Imatinib as initial therapy in CML-CP**

As the first ABL1 TKI introduced into clinical practice, we have over a decade of experience with imatinib mesylate (Gleevec®, Novartis) and an excellent understanding of the clinical results and long-term safety of the drug. For this reason, imatinib remains the initial therapy of choice in CML-CP for many experts, but questions remain about choosing an initial dose and concerning dose escalation.

**Is 400 mg the optimal dose of imatinib?**

A maximum tolerated dose was never defined in the imatinib phase I/II trials, and the current “standard” dose of imatinib, 400 mg daily, was selected for the phase III IRIS trial based on clinical considerations. Eight-year follow-up of the IRIS trial has demonstrated an
event-free survival (EFS) rate of 81%, freedom from progression to accelerated phase (AC) or blast crisis (BC) of 92% (progression-free survival, PFS), and an estimated overall survival (OS) rate of 85%. Interestingly, the estimated annual rates of progression to AP or BC have declined with time on imatinib therapy, from 1.5% to 2% in the first three years to 0% to 0.9% in subsequent years. The complete cytogenetic response (CCyR) and major molecular response (MMR) rates at 8 years were 82% and 86%, respectively [13]. Side effects of imatinib are moderate, and include edema, nausea, diarrhea, muscle cramps, and rash, occurring in 10-30% of patients [14]. These results, confirmed in an independent prospective single-institution study [15], emphasize the tolerability and durability of clinical responses to imatinib. However, because the IRIS data, as reported, represent the best response obtained at any time, they tend to exaggerate the long-term outcomes observed with imatinib. Indeed, 18% of IRIS patients did not achieve a CCyR, 8% who achieved CCyR eventually lost their response, and 11% discontinued imatinib due to intolerance. For these reasons, approximately 37% of IRIS patients were no longer on imatinib after seven years.

Whether a higher initial dose of imatinib or increasing the dose in response to early clinical or laboratory data is beneficial in CML-CP has been explored in several trials (Table 1 [3, 15-21]). In the Tyrosine Kinase Inhibitor Optimization and Selectivity Study (TOPS), a recent phase III randomized trial comparing high-dose (800 mg/d) to standard dose (400 mg/d) imatinib, cytogenetic and molecular milestones were achieved at an initially faster rate in the high-dose group [16]. However, the MMR and CCyR rates at 12 and 24 months were not significantly different (Table 1), while the estimated PFS rates at 18 months were also comparable in the two treatment arms. Notably, the frequency of drug-related adverse events between the high and standard dose groups differed considerably, with 62% of the patients in the high-dose arm and 18% in the standard dose arm requiring dose reductions. Interestingly, after accounting for dose reductions, the average delivered daily dose of imatinib in the high-dose cohort was 662 mg/d, with over 75% of patients tolerating 600 mg/d. Furthermore, patients who received at least 600 mg/d had the greatest probability (62%) of achieving a MMR at 12 mo [16], while dose interruptions of >5d adversely affected outcome at either imatinib dose [22]. Similar results were obtained in the randomized phase III Italian GIMEMA study of 400 vs 800 mg imatinib in high Sokal risk CML-CP patients, where rates of CCyR and MMR at 12 months were not significantly different between the two cohorts (Table 1), but patients assigned to the 800 mg cohort who received at least 600 mg/d had a CCyR rate of 86% at 12 months [17].

Whether an initial imatinib dose of 600 mg might be superior to 400 mg has been addressed more directly in two trials. In the Therapeutic Intensification in DE-novo Leukemia (TIDEL) phase II trial, 103 newly diagnosed CML-CP patients initially received imatinib at 600 mg/d, with an option of dose escalation to 800 mg/d in patients not meeting specific response milestones. Cumulative CCyR rates at 12 and 24 months were 88% and 90%, while MMR rates were 47% and 73%, respectively (Table 1). In patients who maintained an average dose of imatinib of 600 mg/d for the first six months (n=60), MMR rates at 12 and 24 months were 55% and 77%, compared to 32% and 53% in those averaging less than 600 mg/d [18]. When compared to the IRIS trial data, the 12 and 24 mo CCyR rates in TIDEL were significantly higher. In the French SPIRIT trial, a randomized phase III trial that initially compared imatinib at doses of 400 or 600 mg to the combination of imatinib 400 mg plus either low dose cytarabine or pegylated interferon [19], the MMR rates at 12 and 24 months were 52% and 62% in the imatinib 600 mg arm, respectively, vs. 40% and 48% in the imatinib 400 mg arm (Table 1). Collectively, these studies suggest that the great majority of CML-CP patients can tolerate a dose of 600 mg/d, and this dose may result in superior cytogenetic and molecular responses at 12 and 24 months relative to the standard dose of 400 mg.
Should imatinib plasma levels or hOCT1 levels be measured in imatinib-treated CML-CP patients?

Imatinib has only modest (~μM) potency against CML cells in vitro, and two retrospective studies suggest that CML-CP patients who exhibited higher imatinib plasma trough levels achieved superior rates of CCyR and MMR [23, 24]. However, these findings were not confirmed in a third study [25], and the clinical value of monitoring imatinib plasma levels and changing therapy based on the results has not been defined [26]. An ongoing Australian study (TIDEL-II) where CML-CP patients are increased from 600 mg/d to 800 mg/d of imatinib for a day 22 imatinib plasma level of < 1000 ng/mL should help address this issue [27]. Patient compliance with imatinib therapy may be surprisingly low, and correlates with probability of achieving MMR [28]. Hence, obtaining an imatinib plasma trough level may be useful in patients who fail to achieve monitoring milestones (see “Monitoring the response to initial therapy in CML”, below). The transmembrane protein human organic cation transporter-1 (hOCT1) is a major determinant of transport of imatinib into leukemic cells, and analyses of the TOPS and TIDEL trials suggest that patients with low hOCT1 levels have suboptimal responses to imatinib doses < 600 mg [29, 30]. Because the cellular uptake of dasatinib and nilotinib is not dependent on hOCT1, it is plausible that such patients might also fare better on a second-generation TKI.

Second-generation TKIs as initial therapy in CML

The second-generation ABL1 TKIs, including nilotinib, dasatinib, and bosutinib, are generally 10-300 times more potent for inhibition of ABL1 than imatinib, and also inhibit a significant proportion of imatinib-resistant ABL1 mutants. Originally approved for the treatment of patients who were refractory to or intolerant of imatinib, nilotinib and dasatinib recently won FDA approval in the front-line setting. The fourth ABL1 TKI, bosutinib, is currently in a pivotal phase III trial. The availability of these agents will dramatically alter the landscape of initial treatment for CML patients.

Nilotinib

Nilotinib (Tasigna®, Novartis, formerly known as AMN107) is a derivative of imatinib that is highly selective for ABL1 and 10- to 50-fold more potent than imatinib [31, 32]. Data from two phase II studies of nilotinib 400 mg twice daily as initial therapy in newly diagnosed CML-CP patients demonstrated rapid induction of cytogenetic and molecular responses [33, 34], with 78-90% obtaining a CCyR by 3 months, and 96% by 6 months of therapy. Similarly, rapid MMR rates were achieved, with 40-52% at 3 months, 66-71% at 6 months, and 81-85% at 12 months. These promising results prompted the Evaluating Nilotinib Efficacy and Safety in clinical Trials-Newly Diagnosed patients (ENESTnd), a phase III, randomized, open label study that compared two doses of Nilotinib (300 and 400 mg bid) to imatinib (400 mg) with a primary endpoint of MMR at 12 months [20]. Rates of MMR at 12 months were 44%, 43%, and 22% for the nilotinib 300mg bid, nilotinib 400mg bid, and imatinib 400mg/d treatment arms, respectively, representing a significant increase for nilotinib (Table 2 [20-21]). CCyR rates at 12 months were also significantly higher in the nilotinib cohorts, 78-80% vs. 65% for the imatinib arm. The estimated PFS was 99% for nilotinib and 96% in the imatinib arm. Nilotinib, which must be taken on an empty stomach, was well tolerated, with grade 3 or 4 elevations in lipase and bilirubin, hypophosphatemia, and hyperglycemia observed in 4-8% of patients [20]. Prolongation of QTc and sudden cardiac death was observed in early trials of nilotinib and led to a “black box” warning for the drug, but QTc prolongation was not seen in the ENESTnd trial despite close electrocardiographic monitoring.
Dasatinib

Dasatinib (Sprycel®, Bristol-Myers Squibb, formerly known as BMS-354825) is a TKI with rather promiscuous inhibitory activity that includes SRC family kinases, which inhibits ABL1 approximately 300 times more potently than imatinib [35]. In a randomized phase II study, 50 patients with newly diagnosed CML-CP were assigned to receive dasatinib 100 mg/d or 50 mg bid as initial front-line therapy. Rapid CCyR and MMR rates were observed in both treatment arms, with 94% achieving CCyR and 63% obtaining MMR by 6 months. At 12 months, the CCyR and MMR rates were 98% and 71%, with 7% obtaining complete molecular remission (CMR), currently defined as >5-log reduction in BCR-ABL1 transcripts over baseline. The estimated 24 month EFS was 88% and there was no significant difference in response rates or toxicity profiles in the two treatment arms [36]. The DASatinib versus Imatinib Study In treatment Naïve CML patients (DASISION) was a phase III randomized trial that included 519 newly diagnosed CML-CP patients assigned to either dasatinib 100 mg/d or imatinib 400 mg/d, with CCyR at 12 months as the primary end point [21]. The rates of CCyR and MMR at 12 months were significantly higher for dasatinib compared to imatinib, 77% vs. 66% and 46% vs. 28%, respectively. Dasatinib was relatively well tolerated, with grade 3-4 cytopenias (10-21%) and effusions (10%) the most common side effects.

Bosutinib

Bosutinib (Wyeth/Pfizer, formerly known as SKI-606) is a dual ABL1/SRC TKI, that, like nilotinib and dasatinib, is more potent than imatinib and retains activity against several imatinib-resistant ABL1 mutants. Bosutinib has demonstrated activity in phase II studies of CML patients refractory to imatinib and other TKIs [37], and has recently completed accrual of a phase III randomized study involving 502 newly-diagnosed CML-CP patients assigned to bosutinib 500 mg or imatinib 400 mg daily [38], with a primary endpoint of CCyR at 12 months. The results, to be presented at the American Society of Hematology Meeting in December 2010, are anticipated to demonstrate superior responses for bosutinib and to serve as the basis for accelerated FDA approval of this agent, which would then become the fourth TKI approved for front-line therapy of CML.

Are second-generation TKIs now the initial therapy of choice in CML?

There is little doubt that both nilotinib and dasatinib provide faster cytogenetic and molecular responses in newly diagnosed CML patients, but does this mean that these TKIs should supplant imatinib as the new standard of front-line treatment in CML? Several points are relevant to a discussion of this issue. (i) The clinical importance of achieving CCyR and MMR in CML have been established from the IRIS data, where landmark analysis indicated that patients who achieved CCyR by 12 months or MMR by 18 months had PFS rates of 97% and 100% at 5 years, respectively [39]. Although it is biologically plausible that attaining a CCyR or MMR on a more potent ABL1 inhibitor will have the same clinical implications, this must be experimentally determined through long-term follow-up of the ENESTnd and DASISION trials, recognizing that the rates of CCyR and MMR will continue to increase with time in the imatinib cohorts. (ii) Perhaps the most striking finding from the phase III studies of nilotinib and dasatinib was the increased rate of progression to AP/BC experienced by imatinib-treated patients in the vulnerable first year on therapy. This difference was statistically significant for nilotinib, but not for dasatinib. Interestingly, the one-year progression rates on imatinib (3.5-4%) were higher in these trials than was observed in the IRIS or TOPS trials (1-1.5%), possibly reflecting the greater proportion of patients with high Sokal risk in the more recent studies. However, disease progression affected a very small absolute number of imatinib-treated patients in the two trials (a total of 20 out of 543), and because at least some patients with disease progression in CML can be salvaged by switching to other TKIs or by alloHSCT, the most important clinical parameter...
is overall survival (OS). (iii) OS did not differ significantly between the second-generation TKI and imatinib in either trial at one year (Table 2). In subsequent 18 mo follow-up analyses presented at the 2010 ASH meeting, the relative disease progression rates were essentially unchanged for both trials [40, 41]. The number of CML-related deaths was higher and OS rate lower in the imatinib arm of the ENESTnd trial (8/283 pts and 96.9%, respectively) than in either nilotinib arm, but the difference was not significant when compared to nilotinib at the FDA-approved dose of 300 mg bid (2/282 pts and 98.5%, respectively), whereas the number of patient deaths in the dasatinib arm of the DASISION trial exceeded that of the imatinib arm (4/260 pts vs. 1/259 pts, respectively). Hence, second-generation TKIs do not provide a survival advantage in CML vs. imatinib over the first 1.5-2 years of treatment. (iv) Both the ENESTnd and DASISION trials compared the efficacy of the second-generation TKI to imatinib at a dose of 400 mg, when considerable clinical evidence (cited above) suggests that imatinib 600 mg is a more effective and generally tolerated dose, and hence would represent a better comparator. (v) The cost of TKI therapy, the duration of which may be lifelong, will become an important health care issue as generic imatinib becomes available by 2015, at a price to the patient that may be 10- to 50-fold lower [42].

Collectively, these issues beg the question of whether the great majority of CML-CP patients can be initially treated with imatinib, with the second-generation TKIs reserved for treatment of patients who are at risk for disease progression or who fail to achieve certain disease responses early in the course of therapy. Because the responses for second-generation TKIs are superior to imatinib across all Sokal risk groups but are actually greater in the low-risk patients [20, 21], it is unlikely that selection of patients for initial therapy with a second-generation TKI based solely on high Sokal risk would be an effective strategy. An alternative approach is illustrated by the Australian TIDEL-II trial [27], where newly diagnosed CML-CP patients are initiated on imatinib 600 mg, but switched to nilotinib 400 mg bid if they fail to meet aggressive molecular milestones: BCR-ABL1 transcript levels (International Normalized Scale) of ≤0% at 3 mo, ≤1% at 6 mo, and ≤0.1% (equivalent to MMR) at 12 mo. Interim analysis of TIDEL-II showed that with a median follow-up of 18.9 months, 21/105 patients had been switched to nilotinib, with overall rates of CCyR and MMR at 12 mo of 92% and 66%, respectively [27], which compares favorably with the ENESTnd and DASISION data for upfront nilotinib and dasatinib. These results emphasize the emerging concept of actual or current event-free survival (CEFS) in CML in patients that are treated with sequential TKI therapies [43], as the conventional definition of EFS considers an event (such as disease progression) to have occurred irreversibly despite the fact that such a patient might be successfully treated with a subsequent TKI after failing the first inhibitor. Whether a strategy of initial imatinib therapy with switching to a second-generation TKI based on milestones would be equivalent or perhaps even superior to initiating therapy with the second-generation TKI will need to be tested in a prospective, randomized trial. Another issue that should be addressed in a clinical trial is a prospective, head-to-head comparison of nilotinib and dasatinib in the front-line setting.

In the meantime, what factors should guide the choice of initial therapy in CML for patients not participating in a clinical trial? Many experts feel that, in the absence of a documented survival advantage for any of the approved TKIs, it is difficult to categorically recommend one TKI over another for all patients. The choice of initial TKI in CML-CP should take into account the side effect profiles of the different drugs, and the health status, co-morbidities, and compliance potential of the individual patient.
Monitoring the response to initial therapy in CML

Five-year follow-up of the IRIS study suggested that there is a long-term PFS benefit when cytogenetic and molecular milestones are achieved within the first 12-18 months of therapy [39, 44]. Subsequently, the European LeukemiaNet (ELN) proposed response criteria for CML-CP patients treated with imatinib in the front-line setting that were recently updated in 2009 [45], which define responses as optimal, suboptimal, or failure (Table 3). These criteria have now been extended to front line treatment with second-generation TKIs. Retrospective studies of imatinib-treated patients demonstrate that those patients who meet criteria for treatment failure or suboptimal response have inferior long-term outcomes [46, 47]. As discussed above, more aggressive milestones might be considered appropriate within the context of a clinical trial.

A complete discussion of optimal management of patients whose response to initial TKI treatment falls into the “Suboptimal” or “Failure” categories is outside the scope of this review [48], but this should prompt an assessment of drug compliance, screening for ABL1 kinase domain mutations, and consideration of switching therapy to a different TKI based on the results.

Future directions

TKI therapy has made CML a truly chronic disease, and decreased the annual mortality for patients to below 2%. This, in turn, predicts that the population of CML patients in the U.S. will exceed 250,000 by 2040. The ultimate goal of oncologists is to cure cancer, and the focus of many clinical CML researchers has now turned to this area.

Can TKI therapy cure CML?

While imatinib has dramatically transformed the natural history of CML, fewer than 10% of patients achieve a long-term (>2 years) complete molecular response (CMR), defined as BCR-ABL1 transcript levels below the threshold of detection. Currently, the recommendation for patients who achieve a CMR is to remain on imatinib indefinitely to prevent disease recurrence. A recent multicenter STop IMatinib (STIM) trial evaluated the effect of discontinuing imatinib in 60 patients who achieved long-term CMR. Molecular relapse, defined as detectable levels of BCR-ABL1 transcripts on two successive occasions, occurred in 37 patients (62%) with a median follow-up of 17 months. The vast majority (96%) of these relapses occurred in the first 6 months following imatinib discontinuation, and all responded to re-initiation of imatinib therapy. Although not statistically significant, a trend towards sustained CMR was observed in those patients treated with interferon prior to imatinib therapy [49, 50]. Longer follow-up will be necessary to determine whether these remissions are durable and consistent with the possibility of clinical cure, but it should be recalled that similar long-term molecular remissions were observed in a minority of interferon-treated patients [51]. Whether CMRs induced by the more potent second-generation TKIs will be more frequent or robust remains to be determined.

Combination therapies to target CML stem cells: resurrecting interferon?

The ability of imatinib to induce and sustain clinically significant remissions in CML is counterbalanced by the observation that the most primitive leukemic “stem” cells in CML seem to be insensitive to TKIs [52, 53], which may account for the inability of TKI treatment to produce a functional cure in most patients as assessed by the rigorous criterion of long-term CMR upon discontinuation of the TKI [50]. Hence, there is current interest in testing combinations of TKIs with other agents in CML-CP patients to determine whether the CMR rate might be increased and perhaps more durable off therapy [54]. There are many novel agents that could be considered in this role, including histone deacetylase.
inhibitors [55], antagonists of the hedgehog signaling pathway [56], and inhibitors of autophagy [57]. However, considerable attention has been focused on a much older drug, interferon [58].

Prior to the advent of imatinib, interferon-based regimens were the treatment of choice in early CML-CP, providing a CCyR rate from 10% to 30%, and 78% of complete responders survived longer than 10 years [59]. Several strategies to incorporate interferon into TKI therapy for CML are feasible. The first is to add interferon to a TKI as initial up-front therapy. This was the approach of the French SPIRIT trial, a prospective randomized phase III study that compared standard dose imatinib (400 mg/d) with 3 experimental arms: imatinib 600 mg/d, imatinib 400 mg/d + cytarabine, and imatinib 400 mg/d + pegylated interferon α-2a (Peg-IFN2a) at a dose of 90 μg weekly. Interim analysis of this trial has demonstrated statistically significant improvements in MMR and CMR rates for the imatinib +Peg-IFN2a when compared to imatinib 400 mg/d at 24 months, 71% vs. 48% and 22% vs. 11%, respectively [20]. Notably, both hematologic (thrombocytopenia and neutropenia) and non-hematologic (rash, asthenia) grade 3/4 adverse events were higher in the imatinib+Peg-IFN2a group, resulting in discontinuation of Peg-IFN2a in 45% of patients. A subset analysis suggested that patients who tolerated at least 12 months of Peg-IFN2a had the best molecular responses, with an MMR of 82% at 18 months. While these results have been confirmed in an independent analysis of prospective interferon trials from Italy [60], the German CML IV study found no benefit of adding IFN to imatinib 400 mg [61]. The reason for the discrepancy in results is unknown, but might reflect the differing forms of interferon allowed in the German study, including interferon α-2b, which some evidence suggests may be less effective in the myeloproliferative neoplasms [58]. A second strategy is to add or continue interferon in TKI-treated patients with molecular evidence of persistent disease. An independent German study assigned 20 CML-CP patients to initial combination therapy with imatinib 400mg/d and either recombinant IFN (n=3) or peg-IFN2a (n=17). Following 2 years of combination therapy, imatinib was discontinued and molecular responses monitored while patients continued on interferon maintenance therapy. After a median of 2.4 years off imatinib, 10 of 15 evaluable patients had further decreases in BCR-ABL1 transcripts with the number achieving CMR increasing from 2 to 5 patients [62]. Collectively, these studies suggest that interferon can enhance molecular responses in CML, perhaps through targeting the quiescent CML stem cells [63]. Further randomized trials of this combination are warranted.

Conclusion

The future is indeed bright for the therapy and prognosis of newly diagnosed CML-CP patients. The current challenge for the clinician is how to most effectively utilize TKI treatment to obtain disease remissions, prolong survival, and possible cure the patient, with increasing attention to issues of quality of life, side effects, and health care costs. Additional clinical trials, preferably international in scope, are needed to address these issues and provide a map for navigating this road, which suddenly has many new forks in it.

Acknowledgments

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References and recommended reading


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50*. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010; 11:1029–1035. This paper describes the outcome of stopping imatinib therapy in CML patients who have achieved and maintained CMR for at least two years. [PubMed: 20965785]

Curr Opin Hematol. Author manuscript; available in PMC 2012 November 13.


Table 1

Summary of clinical trials of imatinib as initial therapy in CP-CML

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>No. of pts.</th>
<th>Dose (mg)</th>
<th>High risk&lt;sup&gt;d&lt;/sup&gt;</th>
<th>12 months</th>
<th>24 months</th>
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<tr>
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<td>MMR</td>
<td>CCyR</td>
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<td>12 months</td>
<td>24 months</td>
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</tr>
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<td>800</td>
<td></td>
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<tr>
<td>TIDEL-I</td>
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<td>600/800</td>
<td>27% (S)</td>
<td>88%</td>
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<td>27% (S)</td>
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<tr>
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<td>65%</td>
<td>22%</td>
</tr>
<tr>
<td>DASISION</td>
<td>[21]</td>
<td>259</td>
<td>400</td>
<td>19% (H)</td>
<td>72%</td>
<td>28%</td>
</tr>
</tbody>
</table>

<sup>a</sup>S=Sokal Risk Score, H=Hasford/Euro Risk Score

<sup>b</sup>N.S., not significant vs. imatinib 400 mg arm

<sup>c</sup>N.A., not available
Table 2

Phase 3 trials of second-generation TKIs vs. imatinib as initial therapy in CP-CML

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>No. of pts.</th>
<th>TKI/Dose (mg)</th>
<th>High risk[^d]</th>
<th>CCyR</th>
<th>MMR</th>
<th>Progression to AP/BC</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENESTnd</td>
<td>[20]</td>
<td>283</td>
<td>imatinib 400</td>
<td>28% (S)</td>
<td>65%</td>
<td>22%</td>
<td>4% (11/283)</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>281</td>
<td>nilotinib 400 bid</td>
<td>78%[^b]</td>
<td>78%[^b]</td>
<td>43%[^b]</td>
<td>&lt;1% (1/281)[^b]</td>
<td>99%^[^c]</td>
<td>100%^[^c]</td>
</tr>
<tr>
<td>DASISION</td>
<td>[21]</td>
<td>259</td>
<td>imatinib 400</td>
<td>19% (H)</td>
<td>72%</td>
<td>28%</td>
<td>3.5% (9/260)</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>260</td>
<td>dasatinib 100</td>
<td>83%[^b]</td>
<td>83%[^b]</td>
<td>46%[^b]</td>
<td>1.9% (5/259)[^c]</td>
<td>96%^[^c]</td>
<td>97%^[^c]</td>
</tr>
</tbody>
</table>

[^d]S=Sokal Risk Score, H=Hasford/Euro Risk Score
[^b]Statistically significant vs. imatinib 400 mg arm
[^c]Not significant vs. imatinib 400 mg arm
Table 3
Revised European LeukemiaNet criteria for responses in CML-CP patients initially treated with TKIs

<table>
<thead>
<tr>
<th>Evaluation time</th>
<th>Optimal</th>
<th>Suboptimal</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>CHR and at least minor CyR (Ph⁺ ≤ 65%)</td>
<td>No CyR (Ph⁺ &gt; 95%)</td>
<td>No CHR</td>
</tr>
<tr>
<td>6 months</td>
<td>At least PCyR (Ph⁺ ≤ 35%)</td>
<td>Less than PCyR (Ph⁺ &gt; 35%)</td>
<td>No CyR (Ph⁺ &gt; 95%)</td>
</tr>
<tr>
<td>12 months</td>
<td>CCyR</td>
<td>PCyR (Ph⁺ 1-35%)</td>
<td>Less than PCyR (Ph⁺ &gt; 35%)</td>
</tr>
<tr>
<td>18 months</td>
<td>MMR</td>
<td>Less than MMR</td>
<td>Less than CCyR</td>
</tr>
<tr>
<td>At any time during treatment</td>
<td>Stable or improving MMR</td>
<td>Loss of MMR; TKI-sensitive mutations</td>
<td>Loss of CHR; loss of CCyR; TKI-resistant mutations; CCA/Ph⁺</td>
</tr>
</tbody>
</table>

CCA, clonal cytogenetic abnormality; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response; CHR, complete hematologic response; MMR, major molecular response
Adapted from reference [45].