Improving Frontline Treatment for Chronic Myeloid Leukemia: Emerging Evidence for Use of Nilotinib and Dasatinib

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Abstract: The approval of imatinib in 2001 changed the landscape of chronic myeloid leukemia (CML) management, becoming the standard of care and improving the survival rates of patients. With the prevalent use of imatinib worldwide, it was observed that up to one-third of patients are resistant to or intolerant of imatinib therapy, fueling the search for safer and more effective agents. The newer and more potent tyrosine kinase inhibitors nilotinib and dasatinib were first indicated for the treatment of imatinib-resistant/-intolerant patients, for whom these agents are both safe and efficacious. More recent clinical studies have examined nilotinib and dasatinib in the frontline setting in newly diagnosed patients. Data reported from the phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) study and the DASISION (Dasatinib versus Imatinib in Patients with Newly Diagnosed Chronic-phase CML) trial support the use of nilotinib and dasatinib as potential new standards for frontline care of newly diagnosed patients with CML in chronic phase. Furthermore, both agents have received regulatory approval for use as frontline agents. These agents have demonstrated significantly superior efficacy compared with imatinib, as measured by complete cytogenetic response and major molecular response rates. In addition, progression to advanced disease was significantly lower for nilotinib, and a trend toward lower progression was observed with dasatinib. Although both nilotinib and dasatinib are generally well tolerated in the frontline setting, they have different safety profiles that may affect their selection as treatment. Understanding the efficacy, safety profiles, and patterns of resistance to various BCR-ABL1 mutations of these newer agents, as well as implementing management strategies to treat adverse events, will help physicians to provide the best therapy options for their patients with CML.

Keywords
Imatinib, nilotinib, dasatinib, cytogenetic response, molecular response, tyrosine kinase inhibitors

Introduction

Chronic myeloid leukemia (CML) treatment has evolved significantly. With improved understanding of the pathogenesis of CML, tyrosine kinase inhibitors (TKIs) that inhibit BCR-ABL1—a constitutively active oncogenic tyrosine kinase—have been developed. Three TKIs

are approved by the US Food and Drug Administration (FDA) for the treatment of CML: imatinib mesylate (Gleevec, Novartis), nilotinib (Tasigna, Novartis), and dasatinib (Sprycel, Bristol-Myers Squibb). Imatinib, the first TKI approved for CML, has dramatically improved outcomes, increasing rates of freedom from progression (FFP) to advanced disease, compared with interferon alfa (INF-α) and chemotherapy. However, a notable proportion of patients are resistant to, or intolerant of, imatinib, and the regulatory approval of nilotinib and dasatinib provide new treatment options.

CML Therapy Prior to Imatinib

As understanding of CML pathophysiology, biology, and response evolves, it is useful to revisit the clinical lessons of the past. Hydroxyurea and busulfan resulted in hematologic responses in patients with CML but did not halt disease progression.[1] INF-α was the first agent to decrease disease progression[2]; it was approved by the FDA for early CML chronic phase (CML-CP) on the basis of 4 prospective, randomized, controlled trials showing improved median survival of approximately 20 months versus hydroxyurea or busulfan.[2-5] Overall survival (OS) was greater in patients achieving complete and partial cytogenetic remission with INF-α. However, limitations of INF-α treatment include significant adverse events, especially flu-like symptoms, low rates of cytogenetic remission, and the lack of durable responses.[2]

Imatinib

Imatinib selectively inhibits BCR-ABL1 protein tyrosine kinase. Imatinib was initially approved by the FDA on the basis of 3 open-label, single-arm, phase II studies in previously treated patients with CML-CP, CML accelerated phase (CML-AP), and CML blast crisis (CML-BC).[6] Expedited regulatory approval of imatinib was granted based on the high rates of complete hematologic response (CHR), major cytogenetic response (MCyR), and progression-free survival (PFS) associated with this agent.[7] Substantially more patients achieved CHR and MCyR with imatinib than with INF-α plus cytarabine; in addition, lower toxicity was demonstrated with imatinib.[8]

Results from the landmark, randomized, phase III IRIS (International Randomized Study of Interferon versus STI571) study established imatinib as a treatment for newly diagnosed CML-CP.[8] With a median follow-up of 19 months, response rates were significantly higher for imatinib than for INF-α plus cytarabine (MCyR rates, 85% vs 22%, respectively; $P<.001$).[8] Disease progression at 18 months was significantly less likely for imatinib versus INF-α plus cytarabine (estimated FFP, 96.7% vs 91.5%, respectively; $P<.001$). Regulatory bodies, health care practitioners, and patients embraced imatinib as the new standard of care in CML management.

Data at 5 years of follow-up demonstrated that the efficacy of imatinib was maintained, with an estimated event-free survival (EFS) of 83%; 93% of patients had not progressed to AP or BC.[9] At the 8-year follow-up evaluation, the estimated OS rate was 85%; however, if only CML-related deaths and deaths prior to stem cell transplant (SCT) were considered, the estimated OS rate was 93%.[10] Thirty-one percent (171/553) of patients discontinued imatinib for various reasons, including resistance to, or intolerance of, therapy.[10] Although the incidence of grade 3/4 adverse events was relatively low and decreased over time,[10-11] grade 1/2 adverse events in practice are relatively common and may become troublesome over time in affected patients. Ideally, low-grade adverse events are managed with supportive care.

The recommended dose of imatinib is 400 mg/day for patients with CML-CP and 600 mg/day for patients with CML-AP or CML-BC.[12] Studies have evaluated escalated doses of imatinib in an attempt to optimize outcomes (Table 1). These studies were based on the hypothesis that higher doses may induce earlier and deeper responses to avoid imatinib resistance and improve long-term outcomes.[13-21] Both high-dose and combined-therapy (cytarabine, pegylated [PEG]-INF-α, or INF) imatinib cohorts achieved earlier major molecular responses (MMR), and higher complete cytogenetic response (CCyR) and MMR rates, than standard-therapy cohorts. However, these findings did not translate into improved long-term outcomes; greater toxicity was also observed with higher imatinib doses and combination arms.

Nilotinib

Nilotinib binds to the inactive conformation of the ABL tyrosine kinase, blocks the substrate-binding site, and inhibits the catalytic activity of the enzyme.[22] Nilotinib is more selective than imatinib, inhibiting the tyrosine kinase activity of platelet-derived growth factor and c-KIT receptors but showing relatively little activity for other protein kinases including c-SRC.[22] The increased potency of nilotinib confers activity against the most common imatinib-resistant BCR-ABL1 mutations except T315I.[23,24] Nilotinib 300 mg twice daily is approved by the FDA for newly diagnosed patients; nilotinib 400 mg twice daily is approved for imatinib-resistant or imatinib-intolerant CML-CP and CML-AP patients.[25]

An open-label, phase II study examined the efficacy of nilotinib 400 mg twice daily in patients with imatinib-resistant or imatinib-intolerant CML-CP.[26]

Table 1. High-Dose Imatinib Trials in Newly Diagnosed Patients With CML

				Hematologic and Cytogenetic Responses (%)			Survival Rates (%)
Imatinib High-Dose Trials	**N**	**Median Follow-up (mo)**	**Imatinib Dose (Initial)**	**CHR**	**CCyR**	**MCyR**	**PFS, EFS, or OS**
Single-arm							
MDACC[13]	114	15	400 mg bid	98	90	96	2 yr OS: 94
RIGHT[14]	115	18	400 mg bid	93	83	96	NA*
GIMEMA[15]	78	24	400 mg bid	97	91	94	NA*
TIDEL[18]	103	24	600 mg qd	98	90	90	2 yr OS: 94 2 yr PFS: 93
Multi-arm							
TOPS[17]	476	24	400 mg qd vs bid	NA	76, both arms	NA	2 yr OS: 97 vs 98 2 yr PFS: 97 vs 98 EFS: 95 vs 95
ISTAHIT[21]	227	12	400 mg qd vs bid	82 vs 90	37 vs 48	59 vs 57	Data not evaluable for all patients at interim analysis
ELN[16]	216	12	400 mg qd vs bid	NA	58 vs 64	74 vs 68	3 yr OS: 84 vs 91 3 yr PFS: 86 vs 88 3 yr EFS: 66 vs 62
German CML-Study IV[64]	1,014	28 vs 43 vs 48	800 mg qd vs 400 mg qd vs 400 mg qd + IFN-α	NA	63 vs 49 vs 50	NA	3 yr OS: 95 (all 3 arms) 3 year PFS: 94 (all 3 arms)

*Not a study endpoint.

bid=twice daily; CCyR=complete cytogenetic response; CHR=complete hematologic response; EFS=event-free survival; ELN=European LeukemiaNet; GIMEMA=Gruppo Italiano Malattie e Matologiche dell'Adulto; IFN-α=interferon alpha; ISTAHIT=Imatinib Standard Dose Versus High Dose Induction; MCyR=major cytogenetic response; MDACC=MD Anderson Cancer Center; NA=not applicable; OS=overall survival; PFS=progression-free survival; qd=once daily; RIGHT=Rationale and Insight for Gleevec High-Dose Therapy; TIDEL=Trial of Imatinib with Dose Escalation in chronic myeloid Leukemia; TOPS=Tyrosine Kinase Inhibitor Optimization and Selectivity.

Durable CHR, MCyR, and CCyR rates were observed, as well as high FFP rates up to 24 months.[27] In an open-label, multicenter, phase II study of CML-CP patients (N=39) who were intolerant or resistant to both imatinib and dasatinib, 43% of patients achieved an MCyR with nilotinib.[28]

Three single-arm, phase II studies (Table 2) evaluated the efficacy and safety of nilotinib in newly diagnosed CML-CP patients.[29-31] The MD Anderson Cancer Center (MDACC) and Gruppo Italiano Malattie e Matologiche dell'Adulto (GIMEMA)[29,32] studies reported high response rates. CCyR and MMR were rapidly achieved and durable. In the GIMEMA study, 96% of patients achieved a CCyR at both 6 and 12 months, and 66% and 85% of patients achieved an MMR at 6 and 12 months, respectively. The MDACC study reported that 96%, 97%, and 93% of patients achieved a CCyR at 6, 12, and 24 months, respectively. MMR was achieved by 71%, 81%, and 79% of patients at 6, 12, and 24 months, respectively. Survival rates were also high (Table 2). Grade 3/4 hematologic toxicities were similar to those observed with imatinib.[8,9] Grade 3/4 nonhematologic adverse events (eg, elevations of liver function tests [LFTs]) were managed with treatment interruption,[31] and 1 patient discontinued therapy.[29]

On the basis of 12-month efficacy and safety findings of the phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) trial,[33] nilotinib received FDA approval for the treatment of newly diagnosed adults with CML-CP.[25] ENESTnd is an ongoing, randomized (1:1:1), multicenter trial (N=846) comparing the efficacy and safety of nilotinib (300 mg and 400 mg twice daily) with imatinib (400 mg once daily).[33] Nilotinib could not be dose escalated, but imatinib could be dose escalated for suboptimal response or treatment failure.

Table 2. Efficacy Data Reported in Nilotinib Trials in Newly Diagnosed Patients With CML

				Cytogenetic and Molecular Responses (%)		Survival Rates (%)
Nilotinib Trial	**N**	**Median Follow-up (mo)**	**Nilotinib Dose (Initial)**	**CCyR**	**MMR**	**PFS, EFS, or OS**
Phase II						
MDACC[31]	51	24	400 mg bid	98	76	EFS: 90
ICORG[30]	15	3*	300 mg bid	80	60	PFS: 100
GIMEMA[29]	73	12	400 mg bid	96	85	NA
Phase III						
ENESTnd[33,36-38] (overall population)	282 281 283	12	300 mg bid 400 mg bid Imatinib qd	80 78 65	44 43 22	NA
	282 281 283	18	300 mg bid 400 mg bid Imatinib qd	85 82 74	66 62 40	OS: 98.5 OS: 99.3 OS: 96.9
	282 281 283	24	300 mg bid 400 mg bid Imatinib qd	87 85 77	71 67 44	OS: 98.0 OS: 97.7 OS: 95.2
ENESTnd by Sokal Risk Score at 12 mo and 18 mo						
High	78 78 78	12	300 mg bid 400 mg bid Imatinib qd	74 63 49	41 32 17	NA
High	78 78 78	18	300 mg bid 400 mg bid Imatinib qd	85 82 74	59 51 28	NA
Intermediate	101 100 101	18	300 mg bid 400 mg bid Imatinib qd	85 82 74	67 63 39	NA
Low	103 103 104	18	300 mg bid 400 mg bid Imatinib qd	85 82 74	70 69 51	NA

*Preliminary results.

bid=twice daily; CCyR=complete cytogenetic response; EFS=event-free survival; ENESTnd=Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients; GIMEMA=Gruppo Italiano Malattie e Matologiche dell'Adulto; ICORG=All Ireland Cooperative Oncology Research Group; MDACC=MD Anderson Cancer Center; MMR=major molecular response; NA=not applicable; OS=overall survival; PFS=progression-free survival; qd=once daily.

The primary endpoint of the ENESTnd trial, MMR (ie, BCR-ABL1 transcript level ≤0.1% in peripheral blood according to the International Scale [IS]) at 12 months, has been previously evaluated,[34] and has been shown to have long-term prognostic significance in imatinib-responding patients.[35] Only patients with a quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assessment who were in MMR at 12 months were considered to be responders. Of the nilotinib-treated patients, 44% and 43% (300-mg and 400-mg dose groups, respectively) achieved MMR at 12 months, versus 22% of imatinib-treated patients (P<.001, both comparisons; intent-to-treat [ITT] population).[33] The CCyR rates (ie, no Philadelphia chromosome-positive metaphase cells of 20 evaluable metaphases by conventional karyotyping) by 12 months, the secondary endpoint, were significantly higher for nilotinib (300 mg, 80%; 400 mg, 78%) versus imatinib (65%; P<.001, both comparisons; ITT population). The 18- and 24-month results demonstrated continued significant increases in CCyR and MMR rates for nilotinib versus imatinib (Table 2).[36,37] With 24 months

of follow-up, 25% of patients in the nilotinib 300-mg dose group and 19% in the nilotinib 400-mg dose group achieved complete molecular response (CMR [ie, BCR-ABL1 transcript levels ≤0.0032%, IS]) versus 9% in the imatinib group (P<.0001 and P=.0004, respectively).[37]

Patients were stratified by Sokal score, a measure of risk of disease progression. Among nilotinib-treated patients with a high Sokal risk score (>1.2), 12-month and 18-month MMR and CCyR rates were substantially higher than the corresponding rates for imatinib-treated patients (Table 2). Patients receiving nilotinib 300 mg and 400 mg twice daily had a significant improvement in the time to disease progression while on study treatment versus patients receiving imatinib (P=.01 and P=.004, respectively). Fifteen patients progressed to AP or BC (4% imatinib; <1% nilotinib, either dose). No patient who achieved MMR progressed to AP or BC. Results reported at 18 and 24 months reflected similar positive outcomes for nilotinib-treated patients.[36,37] Nilotinib-treated patients had a trend to a higher OS rate when considering CML-related deaths versus imatinib.[36]

The most frequent reasons for treatment discontinuation were adverse events (nilotinib 300 mg, 5%; nilotinib 400 mg, 9%; imatinib, 7%), suboptimal response or treatment failure (4%, 2%, 6%, respectively), and disease progression (<1%, <1%, 4%, respectively). Most grade 3/4 biochemical abnormalities were manageable through dose modification. The incidence of grade 3/4 events of thrombocytopenia and anemia was comparable among all groups; however, the incidence of neutropenia was higher in the imatinib-treated patients (Table 3). Common nonhematologic adverse events (≥15% of patients) are summarized in Table 3. No QTcF greater than 500 ms was observed in any treatment arm. All 4 deaths in the imatinib arm were due to disease progression. Of the 5 deaths in the nilotinib arms, 1 patient (400 mg) discontinued treatment due to disease progression, with subsequent death, and another died of gastric cancer; 1 patient each (300 mg) died from a small intestine obstruction, suicide, and during follow-up after bone marrow transplantation.[33] Nilotinib continues to be well tolerated through 24 months of follow-up.[37]

Dasatinib

Dasatinib is a small-molecule inhibitor of multiple tyrosine kinases (eg, BCR-ABL, SRC family kinases, c-KIT).[39-41] The 100-mg daily dose is approved by the FDA for newly diagnosed CML-CP and imatinib-resistant or imatinib-intolerant CML-CP, CML-AP, and CML-BC.[42]

The open-label, phase II START (SRC-ABL Tyrosine kinase inhibition Activity Research Trials) trial examined the efficacy and tolerability of dasatinib in imatinib-intolerant or imatinib-resistant patients.[43-46] In the 2-year follow-up of the comparative, randomized START-R trial of patients (N=150), dasatinib 70 mg twice daily demonstrated durable and significantly greater CHR, MCyR, and CCyR rates (P<.05) and PFS rates (P<.001) versus imatinib 400 mg twice daily.[46]

Two studies evaluated the efficacy and safety of dasatinib in a frontline setting in newly diagnosed patients with CML-CP[47,48] (Tables 4 and 5). The phase II randomized MDACC study evaluated the efficacy and safety of dasatinib 100 mg once daily or 50 mg twice daily (N=62).[48] Dose escalation was allowed for patients who did not meet defined response criteria. There were no significant differences in response rates (Table 4) between the 2 doses. The responses were durable; 94% of patients who had achieved a CCyR at any time and 87% of patients who had achieved an MMR at any time maintained their responses over a median follow-up period of 24 months. The EFS rate at 24 months was 88%, with no patient progressing to AP or BP. Both doses were well tolerated (Table 5), and nonhematologic toxicities were manageable.

The ongoing phase III DASISION (Dasatinib versus Imatinib in Patients with Newly Diagnosed Chronic-phase CML) study is a randomized, multicenter trial comparing the efficacy and safety of dasatinib 100 mg once daily versus imatinib 400 mg once daily (N=519).[47] Patients were stratified by Hasford risk score.[49] The study design allows for dose escalation of both treatments. CCyR and MMR rates were calculated using a "by" analysis; patients with a response at—or any time prior to—12 months were considered to be responders, even if they had discontinued treatment early, subsequently lost the response, or had a missing sample by 12 months. Confirmed CCyR rates (primary endpoint, CCyR at 2 consecutive assessments ≥28 days apart) by 12 months were significantly higher for dasatinib than imatinib (77% vs 66%, respectively; P=.007; ITT population). Cytogenetic responses were achieved more rapidly with dasatinib; patients in the dasatinib arm were 1.5 times more likely to achieve CCyR versus imatinib (hazard ratio [HR], 1.5; P<.0001). Best cumulative MMR rates by 12 months (secondary endpoint) were significantly higher for dasatinib versus imatinib (46% vs 28%, respectively; P<.0001; ITT population), and responses were achieved more rapidly; dasatinib-treated patients were twice as likely to achieve MMR compared with imatinib at any time (HR, 2; P<.0001). At 18 months of follow-up, 13% of dasatinib-treated patients and 7% of imatinib-treated patients achieved CMR (ie, BCR-ABL1 transcript level of ≤0.0032%).[50]

Table 3. Safety Data Reported in Nilotinib Trials in Newly Diagnosed Patients With CML

		Clinical Trials/Drug Dosages			
	MDACC[31]	GIMEMA (12-mo data)[29]	ENESTnd (12-mo data)[36]		
Adverse Events	Nilotinib 400 mg bid	Nilotinib 400 mg bid	Nilotinib 300 mg bid	Nilotinib 400 mg bid	Imatinib 400 mg qd
Grade 3/4 Hematologic Events (%)					
Neutropenia	12	4	12	10	20
Thrombocytopenia	11	2	10	12	9
Anemia	5	0	3	3	5
All Grades of Nonhematologic Events in ≥15% of Patients in Any Treatment Group (%)					
Fatigue	67	22	11	9	8
Rash	49	42	31	36	11
Headache	39	30	14	21	8
GI distress					
Nausea	38	NR	11	19	31
Abdominal pain	30	8	NR	NR	NR
Diarrhea	21	7	8	6	21
Gastric pain	NR	19	NR	NR	NR
Dyspnea	28	NR	NR	NR	NR
Nonneutropenic fever	26	11	NR	NR	NR
Anorexia	15	NR	NR	NR	NR
Bone/muscle/joint pain	NR	41	NR	NR	NR
Muscle spasm	NR	NR	7	6	24
Dry eye/conjunctivitis	NR	23	NR	NR	NR
Pruritus	NR	21	15	13	5

bid=twice daily; GI=gastrointestinal; ENESTnd=Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients; GIMEMA=Gruppo Italiano Malattie e Matologiche dell'Adulto; MDACC=MD Anderson Cancer Center; NR=not reported; qd=once daily.

CCyR and MMR rates by 12 months were higher for dasatinib versus imatinib across all Hasford risk categories (Table 4). There was no statistical difference between dasatinib and imatinib with regard to progression to BC (1.9% vs 3.5%, respectively) or 12-month estimated OS rates (97% vs 99%, respectively). No patient who achieved MMR progressed to AP or BC. At 18 months of follow-up, dasatinib continues to demonstrate superior efficacy versus imatinib.[50]

Most grade 3/4 biochemical abnormalities in the DASISION trial were manageable by dose modification.[47] Treatment discontinuation occurred in 5% and 4% of dasatinib- and imatinib-treated patients, respectively. Imatinib had significantly higher rates of low-grade edema and fluid retention events than dasatinib (Table 5). Grade 3/4 hematologic toxicity events were similar between treatment groups for anemia and neutropenia, but a higher incidence of thrombocytopenia was observed with dasatinib. The protocol mandated chest radiographs at baseline and at 6 months to monitor for pleural effusion. Pleural effusions were reported in 10% of patients receiving dasatinib 100 mg daily; all were grade 2 or lower. One patient in each group (0.4%) had a QTc interval greater than 500 ms. Deaths were reported in 3.9% of dasatinib-treated patients and 2.3% of imatinib-treated patients[51]; in both treatment groups, deaths occurred from disease progression (1.6%) and drug-related causes (0.4%).[47] Other causes of death in the dasatinib group were related to infection (1.6%) and myocardial infarction (MI) [0.8%]; deaths in the imatinib group were related to MI (0.4%) and clinical deterioration (0.4%).[47] The 18-month DASISION follow-up data demonstrated no new safety signals for dasatinib, and the drug continues to be well tolerated.[50]

Table 4. Efficacy Data Reported in Dasatinib Trials in Newly Diagnosed Patients With CML

				Cytogenetic and Molecular Responses (%)		Survival Rates (%)
Dasatinib Trial	**N**	**Follow-up (mo)**	**Dasatinib Dose (Initial)**	**CCyR**	**MMR**	**PFS, EFS, or OS**
Phase II						
MDACC[48]	50	12	50 mg bid 100 mg qd	96 100	71 71	2 yr EFS: 88
Phase III						
DASISION[47,49*†]	259 260	12	100 mg qd Imatinib qd	77 66	46 28	OS: 97; PFS: 96 OS: 99; PFS: 97
	259 260	18	100 mg qd Imatinib qd	78 70	57 41	OS: 96; PFS: 95 OS: 98; PFS: 94
DASISION by Hasford Risk Score at 12 mo and 18 mo						
High	19 19	12	100 mg qd Imatinib qd	78 64	31 16	NA
Intermediate	48 47		100 mg qd Imatinib qd	78 72	45 28	NA
Low	33 33		100 mg qd Imatinib qd	94 76	56 36	NA
High	19 19	18	100 mg qd Imatinib qd	73 64	51 30	NA
Intermediate	48 47		100 mg qd Imatinib qd	71 71	56 40	NA
Low	33 33		100 mg qd Imatinib qd	92 72	63 48	NA

*Confirmed CCyR for DASISION data.

†Best cumulative MMR rates for DASISION data.

bid=twice daily; CCyR=complete cytogenetic response; DASISION=Dasatinib versus Imatinib in Patients with Newly Diagnosed Chronic-phase CML; EFS=event-free survival; MDACC=MD Anderson Cancer Center; MMR=major molecular response; NA=not applicable; OS=overall survival; PFS=progression-free survival; qd=once daily.

The Next Horizon for CML Therapy

A major goal of CML therapy is prolonged duration of the CP and reduced incidence of progression to AP or BC; however, ultimately the attainment of disease remission or disease eradication is desired. It is unclear how to measure disease eradication; however, a CMR is the limit of detection of current technology used in routine diagnostic laboratories. Both the DASISION and ENESTnd trials are measuring CMR rates standardized to the IS. The higher CMR and MMR rates observed in newly diagnosed patients receiving nilotinib and dasatinib may provide the appropriate setting in which to investigate addition of novel therapies, such as vaccines. The foundation for the use of immunotherapy rests on the finding that graft-versus-leukemia reactions following allogeneic SCT effectively eliminate malignant cells. Two leukemia-associated antigens, Wilms tumor antigen-1 (WT1) and preferentially expressed antigen of melanoma, are currently being tested to determine their viability as vaccines that will trigger an effective immune response against these tumor antigens.[52-54] Another approach is to use small-molecule inhibitors to target signaling pathways that are important in the survival of leukemic stem cells, including those of the Hedgehog pathway and the Janus kinase 2 pathway.[55,56]

It is unknown whether sustained CMR reflects disease eradication, and whether treatment discontinuation after prolonged CMR is possible. Unfortunately, the majority of patients who discontinue imatinib while in sustained CMR relapse within 6 months of discontinuation.[57-59] The ongoing prospective STIM

Table 5. Safety Data Reported in Dasatinib Trials in Newly Diagnosed Patients With CML

Adverse Events	Clinical Trials/Drug Dosages			
	MDACC[48]		DASISION[47]	
	Dasatinib 50 mg bid	Dasatinib 100 mg qd	Dasatinib 100 mg qd	Imatinib 400 mg qd
Grade 3/4 Hematologic Events (%)				
Neutropenia	8	13	21	20
Thrombocytopenia	6	3	19	10
Anemia	5	2	10	7
All Grades of Nonhematologic Events in ≥15% of Patients in Any Treatment Group (%)				
Fatigue	37	35	8	10
Joint and muscle pain/ musculoskeletal pain	35	39	11	14
Diarrhea	29	24	17	17
Dyspnea	26	19	NR	NR
Headache	26	31	12	10
Nausea	26	19	8	20
Skin toxicity	26	32	NR	NR
GI	21	16	NR	NR
Mood alteration	18	18	NR	NR
Dizziness	18	18	NR	NR
Cardiac	16	5	NR	NR
Fluid retention/edema	15	18	19	42
Superficial edema	NR	NR	9	36
Pleural effusion	3	10	10	0
Other	NR	NR	5	8
Neuropathy	15	16	NR	NR
Ocular/vision	11	21	NR	NR
Insomnia	6	15	NR	NR
Memory impairment	5	15	NR	NR
Muscle inflammation	NR	NR	4	17
Rash	NR	NR	11	17

bid=twice daily; DASISION=Dasatinib versus Imatinib in Patients with Newly Diagnosed Chronic-phase CML; GI=gastrointestinal; MDACC=MD Anderson Cancer Center; NR=not reported; qd=once daily.

(Stop Imatinib) study follows patients (N=100) in CMR (ie, >5-log reduction in BCR-ABL1 transcript levels) who discontinue imatinib for at least 2 years. In an interim report of patients with at least 12 months of follow-up (n=69), 42 (61%) patients relapsed; patients demonstrated a 41% probability of persistent CMR. Low Sokal score, male gender, and imatinib treatment duration were factors predictive of CMR maintenance.[58] The STIM authors caution, however, that although imatinib may be safely discontinued in some patients, discontinuation should occur only within the context of a clinical trial.

Discussion

Imatinib has changed the paradigm of cancer care, dramatically improving OS in patients with CML. Despite the high response rates, up to one-third of imatinib-treated patients become resistant or intolerant to imatinib treatment. Studies demonstrated that nilotinib and dasatinib are effective in treating these patients.

Given their increased potency over imatinib, nilotinib and dasatinib have been evaluated in newly diagnosed patients to determine whether outcomes can be further improved. On the basis of phase III studies of nilotinib[36]

and dasatinib[47] versus imatinib, the superior efficacy of these TKIs in newly diagnosed patients has been verified. Due to differences in study design, results from the studies cannot be directly compared. In the ENESTnd study, patients are stratified by Sokal risk criteria, dose escalation of imatinib only is allowed, and statistical analyses are performed for patients achieving response on the milestone date. In the DASISION trial, patients are stratified by Hasford risk criteria, dose escalation of both dasatinib and imatinib are allowed, and statistical analyses assess patients achieving response at any time up to the milestone date. Nevertheless, trial results indicate that nilotinib and dasatinib may become the new standards of care for newly diagnosed CML patients.

ENESTnd and DASISION have reached 24- and 18-month follow-up periods, respectively.[34,50] The rates of molecular and cytogenetic responses in imatinib-treated patients are not increasing to meet the response rates in the respective comparator arms but are increasing at parallel rates. Longer-term nilotinib and dasatinib data are awaited; however, it should be recalled that imatinib was approved for previously untreated patients based on 18-month follow-up data from the IRIS trial.[8] Physicians and patients rapidly embraced imatinib based on the absolute magnitude of the differences in cytogenetic response rate, PFS, and toxicity between imatinib and INF-α plus cytarabine at an early time point. Long-term follow-up of the IRIS trial has confirmed the wisdom of this change in practice based on an early trial result. The PFS curves derived from the 2 arms of the IRIS trial data have been remarkably parallel following the first 18 months of the study, likely due to the crossover design of the study and the fact that the majority of patients switched therapy to imatinib from INF-α plus cytarabine. Furthermore, there was no difference in OS of patients randomized to imatinib versus INF-α plus cytarabine.

The 12-month milestone data demonstrated statistically significant differences in CCyR and MMR for nilotinib and dasatinib compared with imatinib. However, some have argued that these differences may decrease with longer follow-up. In fact, there was a statistically higher MMR rate with imatinib 800 mg daily compared with 400 mg daily at early time points (3 and 6 months) in the TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) trial[60]; however, the difference was not statistically significant at 1 and 2 years of follow-up.[17,60] There are several potential explanations for this observation, including the inability of patients to tolerate the higher dose of imatinib, resulting in dose reduction. In contrast, the longer-term data for nilotinib (12 and 24 months)[34,36] and dasatinib (12 and 18 months)[47,50] demonstrate statistically significant differences in improvements in MMR versus imatinib.

The selection of MMR rate as the primary or secondary endpoint in ENESTnd and DASISION, respectively, and as a surrogate marker for improved outcome may be questioned. FDA authorities reviewed and approved these study designs. MMR was used in the IRIS trial, and subsequent long-term analyses support the validity of MMR as a surrogate marker for positive outcomes. IRIS demonstrated the value of MMR at 12 months; no patients who had an MMR at 12 months progressed to advanced-phase disease by 60 months. Longer follow-up of IRIS confirmed the association of MMR by 12 months with favorable outcomes (as measured by EFS and disease progression to AP/BC).[38] Although some earlier studies failed to demonstrate a survival benefit associated with early MMR in patients initially treated with imatinib,[61-63] the results of the CML Study IV indicated patients with an MMR at 12 months, versus those without an MMR at 12 months, showed better PFS (99% vs 95%, respectively; P=.0143) and OS (99% vs 95%, respectively; P=.0156) at 3 years.[64]

Attempts to standardize the qRT-PCR assay for BCR-ABL1 fusion transcript are ongoing. Standardization involves defining the cell source for analysis (blood or marrow), use of an appropriate and consistent control gene standard, and harmonization of reporting results (ie, log reduction vs ratio).[65] Efforts are in progress to establish assays that deliver precise results that can be compared easily between laboratories[18] and that will allow easier comparisons and direct application of clinical trials to a broader patient population. Due to the difficulties with standardization of the assay and harmonization of the report, lack of achievement of MMR is not recognized as treatment failure by the National Comprehensive Cancer Network (NCCN) or European LeukemiaNet (ELN). Nonetheless, both the ENESTnd and DASISION trials confirm that MMR rates (as defined by the studies and performed in a single reference laboratory) are higher with nilotinib and dasatinib versus imatinib, and that MMR is associated with a reduced frequency of progression events in the first year.[36,47]

TKIs alone are not known to be curative of CML. Mortality is predominantly due to progression to advanced disease phases or treatment-related deaths following intensive therapy, including allogeneic hematopoietic SCT. Fortunately, the rate of progression is low with imatinib, and few oncologists have seen this type of failure of imatinib therapy in their practice. Results of a recent study revealed that the OS of CML patients who achieved CCyR after 2 years of imatinib therapy was not statistically significantly different compared with survival of the general population.[66] Nonetheless, prevention of progression to advanced-phase disease is likely the most important endpoint with TKI therapy in terms of current patient outcomes. Nilo-

tinib showed a statistically significant decrease in the rate of progression to advanced phase disease by 12 and 18 months[35,36] versus imatinib. Dasatinib was associated with a trend toward lower rates of progression to advanced-phase disease versus imatinib.[50] With most progression events in the IRIS trial occurring within 3 years of imatinib initiation, it is likely that the reduced number of progression events with nilotinib or dasatinib compared with imatinib will only be apparent during the first few years of treatment. It has not been possible to absolutely identify patients at risk for early progression.

An oral medication taken long-term will be of benefit provided that the agent is tolerable and patient adherence is high. TKIs are generally well tolerated, with few grade 3 and 4 adverse events. In ENESTnd and DASISION, the rate of study drug discontinuation due to adverse events was similar with imatinib, nilotinib, and dasatinib. The TKIs do have different safety profiles, however. Hematologic events vary among the 3 drugs. Although the frequency of grade 3/4 anemia was similar in comparisons of nilotinib and dasatinib versus imatinib, nilotinib had a lower frequency of grade 3/4 neutropenia than imatinib, and dasatinib demonstrated a higher frequency of grade 3/4 thrombocytopenia than imatinib. The low-grade edema, fluid retention, diarrhea, and muscle cramps occurring in imatinib-treated patients are less frequent in patients receiving either nilotinib or dasatinib as initial therapy. These toxicities have been demonstrated to directly affect patient adherence[67] and, ultimately, to affect response.[68]

Patient medical history may help when making a treatment choice between nilotinib and dasatinib. Dasatinib and imatinib would not be appropriate for patients at risk for pleural effusion, and dasatinib is not suitable for patients with bleeding disorders or for those undergoing antiplatelet therapy; nilotinib would be preferred for patients who have or are at risk for any of these conditions. Nilotinib should not be considered for patients with pancreatitis or hepatic disorders; dasatinib would be preferred for patients with a history of pancreatitis or with potential difficulty taking a twice-daily medication. Caution must be exercised when using nilotinib or dasatinib in newly diagnosed patients with cardiac disease, as this patient population was excluded from the ENESTnd and DASISION studies.[36,47] Differential sensitivity of the ABL tyrosine kinase domain mutations to nilotinib or dasatinib may impact therapeutic selection in the second-line setting[69,70]; however, the emergence of mutations in newly diagnosed patients receiving nilotinib or dasatinib remains an active area of study. Imatinib may be more appropriate for patients with preexisting cardiac disease, including QTc prolongation, conduction abnormalities, bundle branch block, unstable angina, and recent MI.

Conclusions

Clinicians and patients now have more therapeutic choices for the management of CML. The causes of resistance to TKI therapy are incompletely understood and remain an active area of research. We await data regarding the potential causes of resistance in patients who have received frontline nilotinib or dasatinib. In addition, researchers continue to study agents with activity against treatment-resistant mutations such as the T315I mutation, which is currently resistant to all commercially available therapies. Promising candidates include the multikinase inhibitor AT9283 (ponatinib).[71] As we await these data and the results of longer-term follow-up of ongoing clinical trials, physicians and patients can benefit from using the most active and well-tolerated agents as initial therapy in the management of CML.

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