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Does Dasatinib Improve Outcomes and Tolerability in Patients with Chronic Myeloid Leukemia as Compared to Imatinib?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not dasatinib improves outcomes and tolerability in patients with chronic myeloid leukemia as compared to imatinib.

Study Design: Review of three English language, non-blinded randomized controlled trials from 2009, 2010, and 2010.

Data Sources: Randomized, controlled, non-blinded clinical trials comparing dasatinib to imatinib or comparing dasatinib once daily vs dasatinib twice daily, found using the PubMed database.

Outcomes measured: Overall survival and progression-free survival were measured at one and two years after initiation of therapy. Safety profiles and incidence of adverse effects were also measured. This is graded on a scale of 1 to 4, from lowest in severity to highest in severity. Additionally, adverse effects were noted as hematologic (neutropenia, anemia, thrombocytopenia) or nonhematologic (fluid retention, diarrhea, vomiting, fever).

Results: When comparing dasatinib to imatinib, both drugs provided similar figures for progression-free survival (96% vs 97% respectively) and overall survival (97% vs 99% respectively). However, patients taking dasatinib progressed to accelerated or blastic phases of CML 1.9% of the time, and those taking imatinib progressed 3.5% of the time. Dasatinib had higher rates of hematologic adverse events, and imatinib had higher rates of nonhematologic adverse events.

When comparing dasatinib 140 mg once daily to dasatinib 70 mg twice daily, the twice daily dose produced higher overall survival at 12 months (84% vs 78%) and at 24 months (72% vs 63%), as well as fewer deaths due to progressive disease (43% vs 52%). Rates of nonhematologic adverse events were similar between the two groups. However, the once daily dose lead to lower incidence of gastrointestinal bleeding (8% vs 13%) and pleural effusion (20% vs 39%).

Conclusions: Dasatinib improves outcomes and tolerability in patients with chronic myeloid leukemia as compared to imatinib. This is advantageous not only considering patient quality of life, but also morbidity and mortality from complications such as pleural effusions, congestive heart failure, and bleeding. Additionally, by improving tolerability, patients are less likely to discontinue treatment before completion of a full course of therapy.

Key Words: Chronic myeloid leukemia, dasatinib, imatinib

INTRODUCTION

Chronic myeloid leukemia (CML) is a form of cancer originating in the bone marrow that results in increased and unregulated growth of myeloid cells and their precursors.[2] It is associated with a characteristic translocation on the Philadelphia chromosome.[2] Survival has increased dramatically since the introduction of tyrosine kinase inhibitors (TKIs) such as imatinib (brand name Gleevec) and dasatinib (brand name Sprycel).[2]

Imatinib, a first generation TKI, is the standard first-line therapy for patients with CML.[3] Dasatinib, a second generation TKI, has been approved as second-line treatment for patients with CML if imatinib therapy fails.[3] In patients who fail or are unable to tolerate imatinib therapy, dasatinib induces a complete cytogenic response approximately 50% of the time.[3]

This paper evaluates three randomized controlled trials comparing the effectiveness and tolerability of imatinib and dasatinib.

Chronic myeloid leukemia has an incidence of 1-2 per 100,000 people, occurring most commonly in middle-aged and elderly adults. This represents 15-20% of all adult leukemia.[2] Ionizing radiation exposure, including radiation treatments used to treat other cancers, is the only well-described risk factor for developing CML.[2] In 2010, there were 4,870 newly diagnosed cases of CML

Tyrosine kinase inhibitors are the gold standard for treatment of CML. Imatinib averages $3170.40 for a 30 day supply, whereas Dasatinib averages $4676.40.[3] While the cost is significant, CML that is not treated with a TKI is associated with longer hospital stays and higher morbidity.[3]

CML is a bone marrow stem cell disorder that causes proliferation of mature granulocytes (neutrophils, eosinophils, and basophils) and their precursors.[2] Patients are often asymptomatic at diagnosis, presenting incidentally with elevated white blood cell count on routine complete blood count.[2] Symptomatic patients may present with splenomegaly, malaise, arthralgia, low-grade fever, immune compromise, anemia, and thrombocytopenia.[2] A characteristic genetic abnormality of CML is translocation on the Philadelphia chromosome (translocation between chromosomes 9 and 22), resulting in BCR-ABL protein abnormalities.[2] TKIs selectively inhibit the oncogene BCR-ABL, impeding the pathogenesis of CML.[2]

Imatinib is a first generation TKI that is proven to increase overall survival in CML.[3] Dasatinib is a second generation TKI that may have higher overall survival in CML compared to imatinib, as well as a more favorable safety profile.[3]

OBJECTIVE

The objective of this systematic review is to determine whether or not dasatinib improves outcomes and tolerability in patients with chronic myeloid leukemia as compared to imatinib.

METHODS

All three randomized controlled trials utilized for this review were selected because their population group included chronic myeloid leukemia patients greater than 18 years of age. Two of the studies utilized patients who had shown resistance or intolerance to imatinib. In these studies, one group of patients would receive dasatinib 140 mg once daily and the other group would receive dasatinib 70 mg twice daily. One study focused on newly diagnosed patients with CML. This study administered 100 mg of dasatinib once daily to one group of patients, with the other receiving 400 mg of imatinib once daily.

The comparisons made in these studies were between imatinib and dasatinib. In the case of the two studies utilizing different schedules of dasatinib, the comparison is between not only imatinib and dasatinib (as these patients had received imatinib in the past), but also between dasatinib 140 mg daily and dasatinib 70 mg twice daily. The outcomes measured in all three trials were overall survival, progression-free survival, and safety profiles (adverse reactions to therapy).

Information utilized in this review was found using the PubMed database. Inclusion criteria included randomized controlled trials limited to the English language and published in peer-reviewed journals. The key words used used in searches were: "chronic myeloid leukemia", "dasatinib", and "imatinib". Research was conducted by the author. Articles were selected based on relevance to the clinical question and on the importance of outcomes to the patient (POEMs). The inclusion criteria includes that the studies were randomized, controlled, prospective, and included patient oriented outcomes (POEMs). Exclusion criteria included trials with patients under the age of 18 and studies that focused exclusively on disease oriented outcomes (DOEs). Ultimately, three studies were found and analyzed. They included: 1) a randomized, open-label, multinational phase 3 trial comparing dasatinib 100 mg daily and imatinib 400 mg daily in patients with newly diagnosed CML, 2) a randomized, 2-arm, multicenter, open-label, phase 3 trial comparing dasatinib140 mg daily and dasatinib 70 mg twice daily in patients with CML who had proven to be imatinib resistant or imatinib intolerant, and 3) a randomized, multicenter, open-label, phase 3 trial comparing dasatinib 140 mg daily and dasatinib 70 mg twice daily in patients with CML who had proven to be imatinib resistant or imatinib intolerant. A summary of the statistics used include: p-values, RRR, ARR, NNT, NNH.

Table 1: Demographics of included studies

Study	Type	Number of patients	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Kantarjian 2009[1]	Randomized, 2-arm, Phase 3 trial	317	18+	Patients stopped treatment with imatinib due to resistance or intolerance, Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2, adequate hepatic/renal function	Treatment with imatinib, within 7 days of initiation, uncontrolled or significant cardiovascular disease, history of a significant bleeding disorder unrelated to CML, any other concurrent malignancy other than CML	206	Randomized to receive dasatanib 140 mg QD or dasatinib 70 mg BID
Kantarjian 2010[3]	Randomized, Phase 3 trial	519	18+	Chronic CML diagnosed by means of bone marrow biopsy within 3 months of study, no previous treatments for CML, ECOG performance status score of 0-2 and adequate hepatic and renal function	Women who were breast-feeding/pregnant/ could potentially become pregnant, serious comorbidities, active infections, serious cardiovascular disease, history of a significant bleeding disorder unrelated to CML, concurrent malignancy other than CML	90	Randomized to receive dasatinib 100mg QD or imatinib 400mg QD
Saglio 2010[4]	Randomized, Phase 3 trial	210	16 - 78	Resistance or intolerance to imatinib previously, no previous treatments for CML, ECOG score of 0-2, adequate hepatic/renal function	Serious comorbidities, active infections, serious cardiovascular disease, history of a significant bleeding disorder unrelated to CML, concurrent malignancy other than CML	198	Randomized to receive dasatanib 140 mg QD or dasatinib 70 mg BID

RESULTS

The results were presented in dichotomous form in all three studies analyzed. In the Kantarjian et al 2010 study, the rate of complete cytogenic response by 12 months was significantly greater among patients receiving dasatinib than those treated with imatinib (77% versus 66%, P=0.007). Progression to the accelerated or blastic phase of CML occurred in 1.9% of patients receiving dasatinib, compared to 3.5% of those receiving imatinib. At 12 months, the rates of progression-free survival were similar for patients receiving dasatinib versus imatinib (96% vs 97%). The rates of overall survival were also similar for patients receiving dasatinib versus imatinib (97% and 99%).

Table 2: Efficacy of Dasatinib versus Imatinib in patients with CML

	Progression to accelerated or blastic phase of CML	Progression-free survival (at 12 months)	Overall survival (at 12 months)
Dasatinib	1.9%	96%	97%
Imatinib	3.5%	97%	99%

The safety profiles revealed greater differences in patient responses to the two drugs. As noted in **Table 3**, dasatinib had higher rates of hematologic adverse events (neutropenia, thrombocytopenia, and anemia). However, imatinib had higher rates of nonhematologic adverse events (fluid retention, diarrhea, nausea, etc.). The overall rates of discontinuation of therapy because of toxic drug effects were 5% with dasatinib and 4% with imatinib. There was one death in each group that was attributed to study treatment, both the result of myocardial infarction.

Table 3: Adverse events associated with Dasatinib and Imatinib

	Neutropenia	Thrombocytopenia	Anemia	Fluid retention	Diarrhea	Vomiting
Dasatinib	65%	70%	90%	19%	17%	5%
Imatinib	58%	62%	84%	42%	17%	10%

In the Saglio et al study, dasatinib 140 mg daily is compared to dasatinib 70 mg twice daily in patients who have already failed imatinib therapy. The median progression-free survival is for the once daily arm and twice daily arm is 3.8 months and 3.7 months respectively. However, the 24 month progression-free survival rate was 11% for the once daily regimen and 18% for the twice daily regimen. The median overall survival was also similar, with 7.9 months in the one daily arm and 7.7 months in the twice daily arm. The 24 month overall survival rates were 24% in the once daily arm and 28% in the twice daily arm. The majority of deaths were considered to be from CML, with 54% in the once daily arm and 41% in the twice daily arm.

Table 4: Efficacy of Dasatinib 140 mg daily versus Dasatinib 70 mg twice daily in patients with imatinib-resistant or intolerant CML

	Median PFS	PFS Rate	Median OS	OS Rate
Dasatinib 140 mg daily	3.8 months	11%	7.9 months	24%
Dasatinib 70 mg twice daily	3.7 months	18%	7.7 months	28%

The more common adverse events were fluid retention, diarrhea, headache, bleeding, nausea, fatigue, and rash, and these were typically mild (Grade 1 or 2). The rates were similar in both arms. Cytopenias also had a similar incidence in both arms.

Table 5: Cytopenias associated with Dasatinib 140 mg QD compared to Dasatinib 70 mg BID

	Neutropenia	Thrombocytopenia	Anemia	Leukocytopenia
Dasatinib 140 mg QD	65/72 (90%)	67/72 (93%)	70/72 (97%)	60/72 (83%)
Dasatinib 70 mg BID	65/73 (89%)	67/73 (92%)	73/73 (100%)	61/71 (84%)

In the Katarjian et all 2009 study, dasatinib 140 daily was compared to dasatinib 70 mg twice daily in patients with accelerated phase resistant CML or patients intolerant to imatinib. The overall survival rates were 78% (95% CI, 71-84%) and 84% (95% CI, 65-79%) for the once daily and twice daily groups respectively at 12 months. At 24 months, the rates were 63% (95% CI, 56-71%) for once daily and 72% (95% CI, 65-79%) for twice daily (P=.140). Among patients who died during the study, a similar number died of progressive disease in each of the two treatment groups (52% for the once daily group, 43% for the twice daily group; P=.435).

Table 6: Overall survival rates with Dasatinib 140 mg QD compared to Dasatinib 70 mg BID

	OS at 12 months	OS at 24 months	Deaths due to progressive disease (among total deaths)
Dasatinib 140 mg QD	78%	63%	52%
Dasatinib 70 mg BID	84%	72%	43%

Both dasatinib schedules were relatively well tolerated during the study, with a majority of adverse events being mild or moderate (Grades 1 or 2). The rates of non-hematologic adverse events were similar between the two groups, though there was a lower incidence of gastrointestinal bleeding seen with the once daily group compared to the twice daily group (8% versus 13% respectively, P=.2036). Pleural effusion rates were also lower in the once daily group (20% once daily versus 39% twice daily, P <.001). The rates of congestive heart failure or other cardiac dysfunction were 0% in the once daily group and 3% in the twice daily group. The

most common non-hematologic adverse events included diarrhea, fluid retention, nausea, headache, and fatigue. Incidences of all-grade cytopenia were high and comparable in both groups.

DISCUSSION

The randomized controlled trial comparing dasatinib to imatinib in newly diagnosed patients with CML showed that with either drug, survival rates are extremely high. However, dasatinib proved to prevent progression to the more severe blastic phase of CML significantly better than imatinib. With dasatinib therapy, progression rates we reduced by about half. When comparing safety profiles, the two drugs had similarly high rates of cytopenias. Tyrosine kinase inhibitors (such as imatinib and dasatinib) prevent ATP binding to BCR-ABL gene expressing cells, leading to selective growth disadvantage or apoptotic death of those cells. Because of this, hematologic cell growth is expected to be diminished to some degree. However, dasatinib had a significantly lower rate of non-hematologic adverse events. The rates of fluid retention are more than halved when using dasatinib rather than imatinib, which not only increases quality of life but also decreases potentially deadly complications such as congestive heart failure and pleural effusion. There was also a significant decrease in constitutional symptoms such as myalgia, vomiting, and diarrhea.

The second two randomized controlled trials compared dasatinib 140 mg once daily to dasatinib 70 mg twice daily. This patient population was different than in the first study analyzed because they had already discontinued imatinib therapy due to failure of therapy or intolerability of adverse effects. These patients tended to have more progressive disease, and therefore, higher morbidity and mortality.

In both studies that compared the two dose schedules, efficacy was quite similar. This was noted in both progression-free survival and overall survival. However, the once daily regimen had improved tolerability. This is significant when considering both quality of life and potential complications in patients treated with dasatinib. Once daily scheduling showed decreased incidences of fluid retention (manifesting itself as superficial edema, pleural effusion, pericardial effusion, and congestive heart failure) as well as gastrointestinal bleeding. These are significant sources of morbidity and mortality amongst patients with CML.

There were a few limitations to these studies. The two studies involving dasatinib dosed daily or twice daily only focused on patients who had already failed imatinib therapy. It is not known which dose schedule would be more effective or tolerable in a newly diagnosed patient. These studies were also not blinded. Large numbers of patients withdrew from these studies for a multitude of reasons, including disease improvement, intolerability to therapy, disease progression, and death.

CONCLUSION

Overall, dasatinib does improve outcomes and tolerability in patients with chronic myeloid leukemia as compared to imatinib. While overall survival is similar between the two drugs, progression-free survival is significantly improved with dasatinib. There is also a substantial improvement in tolerability when using dasatinib. This is advantageous not only considering patient quality of life, but also morbidity and mortality from complications such as pleural effusion, congestive heart failure, and bleeding. Additionally, many patients discontinue imatinib before completing a full course of therapy. By improving tolerability, patients are more

likely to complete the prescribed treatment regimen and, therefore, will receive the maximum response.

Currently, treatment with dasatinib is only indicated after imatinib therapy has failed. The first generation ABL-BCR tyrosine kinase inhibitor is still considered first line therapy, with second generation TKIs such as dasatinib being second line therapy. In the future, it may be beneficial to study dasatinib as first line therapy in newly diagnosed CML. This would allow researchers to determine the response to dasatinib in patients who have less progressive disease and have not already been exposed to other cytotoxic therapies.

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