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Is bosutinib effective and safe enough to be used as a first line treatment option for patients who suffer from chronic myeloid leukemia?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not bosutinib is effective and safe enough to be used as a first line treatment option for patients who suffer from chronic myeloid leukemia.

STUDY DESIGN: This review consists of two randomized control trials and one cohort study.

DATA SOURCES: All articles were written in English and selected from peer reviewed articles published in PubMed or OVID. All articles were published between 2016 and 2018. Inclusion criteria that was used for the selection of studies for this review paper involved patients over the age of 18 who suffer from CML. Comparisons are made against newly diagnosed patients with CML, patients who are resistant or intolerant to TKI, and the use of aprepitant while administering bosutinib.

OUTCOMES: This review examined patient monitoring for adverse effects and questionnaires for assessing health-related quality of life. Common adverse effects that were monitored throughout various studies were gastrointestinal disorders, including abdominal pain, nausea, vomiting, and diarrhea.

RESULTS: Bosutinib has been shown to have an increase in therapeutic response at 12 months while decreasing disease progression to accelerated or blast phase and decreasing death rates. Patients who were administered aprepitant while receiving bosutinib had a significant decrease in gastrointestinal side effects such as nausea and vomiting. Overall health-related quality of life surveys indicated that patients who were treated with bosutinib showed a consistent improvement from baseline and their quality of life was not decreased while being treated with bosutinib.

CONCLUSION: Bosutinib has had recent FDA approval and can be used as first line treatment for patients who are newly diagnosed with Ph+ CML. Bosutinib has shown to decrease disease progression and death rates. Co-administration with aprepitant can help decrease common gastrointestinal side effects. Further research needs to be completed on long term side effects and variations in dosage.

KEYWORDS: bosutinib and leukemia; bosutinib; chronic myeloid leukemia; Philadelphia chromosome; tyrosine kinase inhibitors.

INTRODUCTION

Chronic myeloid leukemia (CML) is cancer of the myeloid cells located in the bone marrow that affects adults greater than 50 years old. A genetic mutation occurs between BCR on chromosome 22 and ABL1 on chromosome 9 causing the two chromosomes to fuse together and produce a translocation on chromosome 22, creating a new chromosome identified as the Philadelphia chromosome (Ph). This new chromosome is now considered an oncogene and is a specific finding for CML. The Philadelphia chromosome creates its own BCR-ABL1 protein which is responsible for creating another protein known as tyrosine kinase. Tyrosine kinase is responsible for the proliferation of CML cells, most notable neutrophils, but also basophils and eosinophils. There were an estimated 8,430 new cases of CML and 1,090 deaths due to CML in 2018.¹ An estimated 1/526 people will get CML in their lifetime and approximately 15% of all new cases of leukemia are CML.¹

CML occurs in three stages and is considered an unstable disease. In the absence of treatment, the disease can progress from chronic, to accelerated, to terminal blast crisis. During chronic phase, signs and symptoms can be absent or very mild with the median duration of this phase lasting 5-6 years. During the accelerated phase, neutrophil differentiation becomes increasingly impaired and white blood cell counts are more difficult to control with treatment. A patient is most likely to experience fatigue, low-grade fever, diaphoresis, lymphadenopathy, anorexia, splenomegaly, hepatomegaly, and anemia. The median duration of this phase is 6-9 months. A blast crisis is most severe and presents similar to acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled rate; it is the hardest phase to enter remission and the median survival is 3-6 months. Patients with CML have an average of 55 outpatient visits per patient per year, 1 inpatient visit per patient per year, and 2 emergency visits per patient per

year.¹ The average cost of outpatient care is \$24,391, while the average cost of inpatient care is \$24,462.²

Current treatment methods for CML consist of tyrosine kinase inhibitors (TKI), interferon, chemotherapy, radiation, surgery, and stem cell transplant. Currently, the oldest TKI imatinib is first line treatment because it has been shown to be very effective.³ TKIs target the tyrosine kinase protein and decrease the proliferation of CML cells. The average cost of TKI therapy is \$92,000 - \$138,000 a year.² Traditionally, bosutinib has been used as a second line treatment option if a patient becomes resistant to TKI or if imatinib has stopped working, however, in recent studies, “bosutinib is now being considered as a first line treatment”³ for patients who are newly diagnosed with CML Ph+. This new method is being proposed because bosutinib may lead to a faster drug response and higher rates of achieving major molecular response (MMR) and complete cytogenetic response rate (CCyR).³ MMR measures the amount of BCR-ABL1 protein in a patient’s bone marrow and CCyR measures the amount of Ph in the bone marrow.³ Therefore, if MMR and CCyR levels are achieved, the amount of BCR-ABL1 and Ph in the bone marrow are low, thus preventing CML from progressing into an accelerated or blast phase and can lead to an increase in overall survival of patients who suffer from CML. Bosutinib has also been shown to have decreased gastrointestinal (GI) side effects such as nausea, vomiting, and diarrhea compared to the leading TKI, imatinib.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not bosutinib is effective and safe enough to be used as a first line treatment option for patients who suffer from chronic myeloid leukemia.

METHODS

Two randomized control trials and one cohort study were chosen for this review. All selected articles were published in peer-reviewed journals between 2016 and 2018, written in English, and searched via PubMed and OVID. Articles were selected based on their relevance to my clinical question and if they had patient-oriented outcomes. Keywords that were used were bosutinib and leukemia; bosutinib; chronic myeloid leukemia; Philadelphia chromosome; tyrosine kinase inhibitors.

Inclusion criteria that was used for the selection of studies for this review paper involved the patient population which included patients over the age of 18 who suffer from CML. Comparisons are made against patients who are newly diagnosed with CML Ph+, those who suffer from chronic phase CML, and those who suffer from chronic phase CML and are resistant to one or more TKI such as imatinib, dasatinib, and nilotinib. The comparison of adding the use of aprepitant while being treated with bosutinib was also measured. Aprepitant is a receptor antagonist used to prevent nausea and vomiting caused by chemotherapy. Both aprepitant and bosutinib are primarily metabolized by cytochrome P450 (CYP) 3A4 enzyme. Outcomes that are being measured are any adverse effects patients may experience and drug effectiveness based on the progression to the next stage of leukemia.

Exclusion criteria included patients under the age of 18 and patients who did not display the Philadelphia chromosome when diagnosed with CML. Detailed inclusion and exclusion criteria, as well as other individual study characteristics, are provided in Table 1. The statistics reported in the studies and utilized for the review were NNT, NNH, ARI, ABI, RRI, RBI, and p-values.

Table 1 – Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cortes³ (2018)	RCT	536	>18 yrs	<ul style="list-style-type: none"> - Diagnosed with Chronic Phase CML within 6 months. - Eastern Cooperative Oncology Group performance status of 0 or 1. - Ph- pts with typical BCR-ABL1 	<ul style="list-style-type: none"> - Ph- or unknown Ph status. - Inadequate bone marrow, hepatic, or renal function. 	96	400mg bosutinib once daily OR 400mg imatinib once daily
Hsyu⁴ (2016)	RCT	20	>18 yrs	<ul style="list-style-type: none"> - Weight: >45kg - BMI: 17.5-30.5 kg/m² 	<ul style="list-style-type: none"> -Any condition potentially affecting drug absorption -BP >140/90 -+Urine drug test for illicit drugs -Consumption of Alcoholic or tobacco products ≤24hrs before 1st dose - history of sensitivity to heparin 	2	Bosutinib 100mg x5 in 1 period followed by bosutinib 100mg x5 + single-dose aprepitant (125mg) in period 2
Kantarjian⁵ (2017)	Cohort	403	>18 yrs	<ul style="list-style-type: none"> - Confirmed diagnosis of CML Ph+ or Ph+ acute lymphocytic leukemia with resistance or intolerance to Imatinib. - Eastern Cooperative Oncology Group performance status of 0 or 1. 	Inadequate bone marrow, hepatic, or renal function	101	The influence of health-related quality of life when treated with bosutinib.

OUTCOMES MEASURED

This review examined patient monitoring for CML disease progression and patient monitoring for adverse effects while using bosutinib compared to patients taking imatinib while also comparing the use of bosutinib with an aprepitant. Common adverse effects that were monitored throughout various studies GI disorders consisting of abdominal pain, diarrhea, nausea, and vomiting.^{3,4} Questionnaires for health-related quality of life based on EuroQol 5-Dimensions Questionnaire (EQ-5D) and Functional Assessment of Cancer Therapy-leukemia (FACT-leu) were used to monitoring patient's overall well-being.⁵

RESULTS

The randomized control trial conducted by Cortes et al., consisted of 536 patients who were newly diagnosed with chronic phase CML. Patients were randomly assigned to receive daily treatment with 400mg bosutinib or 400mg imatinib. Patients who received bosutinib had higher therapeutic response rates after 12 months compared to those who received imatinib.³ Disease progression from chronic phase to accelerated or blast phase was seen in both therapy groups; four patients who were receiving bosutinib and six patients receiving imatinib.³ Only seven patients died while enrolled in the study, one patient who received bosutinib and six who received imatinib.³ These results indicate that for every 10 patients receiving bosutinib, 1 less patient experienced disease progression and for every 7 patients, 1 less patient died while being treated with bosutinib compared to imatinib. See Table 2 for more details.

The most common side effects seen in the Cortes study were GI side effects consisting of diarrhea, nausea, vomiting, and abdominal pain.³ Diarrhea and nausea were most commonly seen in patients who were administered bosutinib whereas vomiting was more common in patients who received imatinib.³ This study indicates that for every 6 patients being treated with bosutinib, 1 more will experience GI symptoms, for every 30 patients treated with bosutinib, 1

less will experience nausea, and for every 22 patients treated with bosutinib, 1 more patient will discontinue treatment compared to imatinib. See Table 3 for more details.

Table 2 – Treatment Status³

	RBI	ABI	NNT
Disease Progression	-73.3%	-11%	-10
Death Rate	-100%	-15%	-7

Table 3 – Adverse Effects, Cortes³

	RRI	ARI	NNH
Gastrointestinal (total)	32.3%	19.8%	6
Diarrhea	108%	36.5%	3
Nausea	-8.83%	-3.4%	-30
Vomiting	1.7%	1.7%	59
Abdominal Pain	148%	10.7%	10
Discontinuation of Treatment	51.6%	4.7%	22

The randomized control trial performed by Hsyu et al. was a randomized, 2-sequence, 2-period crossover study consisting of 20 patients who received bosutinib alone or co-administered with aprepitant.⁴ This study demonstrated how the use of aprepitant can decrease vomiting as a side effect. Vomiting was reported by five patients who received bosutinib alone and zero patients who received bosutinib plus aprepitant,⁴ indicating that for every 10 patients treated with bosutinib and aprepitant, 1 less patient will suffer from vomiting. For overall GI side effects, for every 20 patients treated with bosutinib and aprepitant, 1 less patient will experience GI symptoms compared to bosutinib alone. See Table 4 for more details.

Table 4 – Adverse Effects, Hsyu⁴

	RRI	ARI	NNH
Gastrointestinal (total)	-8%	-5%	-20
Diarrhea	10%	5%	20
Nausea	-29%	-10%	-10
Vomiting	-100%	-20%	-5
Abdominal Pain	-100%	-5%	-20

EQ-5D is a survey to help aid in the assessment of the patient's general health status. The survey asked about a patient's ability to ambulate, take care of themselves, whether or not they were able to perform their usual activities, their levels of pain and discomfort, and levels of anxiety and depression.⁵ Patients responded by selecting whether or not they had "no problems," "some problems," and "extreme problems."⁵ FACT-Leu summary scales included questions about the patient's well-being, including factors such as physical, family and social, emotional, and functional well-being.⁵ Both surveys were asked before treatment began in order to establish a baseline and at weeks 4, 8, and 12.⁵ Surveys continued every 12 weeks until treatment was completed or if there was suspicion of disease progression.⁵

Health related quality of life was assessed through questionnaires based on EQ-5D and FACT-Leu. They were completed on 403 patients who had already received ≥ 1 dose of bosutinib and who were already resistant or intolerant to ≥ 1 TKI. Only 284 patients were resistant or intolerant to one TKI (CP2L cohort) and 119 patients were resistant or intolerant to ≥ 1 TKI (CP3L cohort).⁵ At baseline, 87% of EQ-5D assessments were collected in both cohorts with mean scores resulting in 0.83 (95% CI, 0.80 – 0.85) in CP2L and 0.80 (95% CI, 0.76 – 0.85) in CP3L.⁵ Results remained relatively stable for CP2L throughout treatment and showed improvements from baseline in weeks 36, 96, 192, and 360.⁵ After treatment was completed, 59-91% of patients in CP2L reported "no problems" on all 5 dimensions of the EQ-5D. Likewise, 55-92% of patients in CP3L reported "no problems."⁴ Less than 37% of patients in CP2L reported "some problems" in any 1 dimension compared to less than 41% of the patients in CP3L.⁵ Less than 5% of patients in both cohorts reported "extreme problems."⁵

Similar to the EQ-5D assessment, 86-87% of FACT-Leu assessments were collected in both cohorts at baseline and represented a 95% CI.⁵ Consistent improvement from baseline was observed in the CP2L group, especially when monitoring their physical well-being at weeks 60,

120, and 168. After completion of treatment, the CP2L cohort showed decline in family well-being and emotional well-being.⁵ There weren't any distinct trends observed in the CP3L cohort, however improvement in emotional well-being was observed in week 168, whereas, declines were observed in social well-being and family well-being at week 60, and another decline in family well-being after treatment completion.⁵

DISCUSSION

As of December 2017, the FDA has approved 400mg bosutinib for patients who are newly diagnosed with Ph+ CML. There are currently no black box warnings on this product. Results from the Cortes study indicates that patients who were treated with 400mg bosutinib had a higher therapeutic response after 12 months of therapy, a decreased chance of entering an accelerated or blast phase, and a decreased chance of dying compared to patients treated with imatinib.³ The additional use of aprepitant with bosutinib decreased the common GI side effects and eliminated the action of vomiting.⁴ Decreasing GI side effects can have a positive impact on health-related quality of life because patients are more likely to continue treatment. However, the cost of bosutinib is extremely high and poses as a significant barrier to treatment. A 120-day supply of bosutinib costs approximately \$15,592 and a 90-day supply of imatinib costs approximately \$8,807 depending on the pharmacy. Insurance companies are not likely to cover the cost of these drugs; if they do, copays are still considered relatively expensive.

Due to its recent FDA approval, most studies that are currently being conducted are proving whether or not bosutinib is effective and how much more effective bosutinib is compared to imatinib. There has been limited research on the immediate and long-term side effects of bosutinib. Other limitations throughout these studies are lack of variation of dosage amounts and side effects associated with the dosage, for example, the Cortes' study used 400mg,³ Hsyu's study used 100mg,⁴ and Kantarjian's study used 600mg.⁵ All studies concluded

the same side effects, but severity of side effects and dosage amount are not taken into consideration. There is also no mention as to why specific doses were chosen.

CONCLUSION

All of the studies used for this review, along with recent FDA approval, indicate that bosutinib is safe and effective enough to be used as first line therapy for patients who are newly diagnosed with chronic phase CML Ph+. In order to increase tolerability, it may be essential to consider the use of aprepitant in order to decrease common GI side effects. However, it is also important to consider the patients personal preference as to whether or not they can handle the side effects, whether or not it will impact their overall health-related quality of life, and whether or not it is cost effective. Since bosutinib has been recently approved by the FDA, most studies are proving its effectiveness to increase therapeutic response and more research needs to be done exploring its side effects and dosage tolerability.

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