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Should You Be Afraid of the Big Bad Wolf? A Practical Real-world Review for the Comfortable Use of Bosutinib in the Therapy of Chronic Myeloid Leukemia

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Abstract

Bosutinib is a second generation (2G) tyrosine kinase inhibitor (TKI) for the therapy of chronic myeloid leukemia (CML). It is effective, as other 2g TKIs and long term, is likely the safest, with few significant issues. Short term adverse events which have inhibited their use in the past can be overcome with some simple maneuvers which will be reviewed here. The background for bosutinib, patient selection, and a process for successfully starting patients on therapy will be outlined.

Keywords: Adverse events, Bosutinib, Chronic myeloid leukemia, CML

Introduction

In this review, the author would like to look at the most recent rationale for the use of bosutinib in the treatment of chronic myeloid leukemia (CML)—when to use it, practical real world options for reducing adverse events without impacting efficacy, examining studies in the literature which support its use and studies which have perhaps had inappropriate conclusions about efficacy and adversity of its use, and describe those situations where the use of bosutinib should be thought about before considering it as an option. The author will not go into detail on "ancient history" of the drug but try to keep the references current and in many cases, reviews summarizing the issues to be discussed. The author hopes to convince the reader that bosutinib is not the "big bad wolf" of CML therapy but should be considered along with other drugs or perhaps even instead of other drugs. Bosutinib use has been limited because of side effects from in retrospect were poorly conceived protocols, ongoing use of those results which fed their way into product monographs and more recent studies with other drugs, and unfortunately the word of mouth fear of the side effects which have been passed on, even by individuals who have never used the drug. The author wants to present here a review, which is concise, practical, relevant and easy to read, without the pages of review of previous studies. The author hopes it will be useful in sorting through the morass of data and salesmanship that is out there and be of value to the physician on the front line.

Background on CML Management

The therapy and management of CML has evolved tremendously over the last quarter century and there are a number of recent publications to review this [1–3]. Not only are there new drugs, but the whole field of understanding the biology of CML and the science of monitoring have changed the way we look at the disease [4,5]. This whole story at three levels—biology, therapy, monitoring—has been the poster child for how to manage malignant diseases in a logical manner.

The results have truly been impressive. From a disease where the median survival was somewhere between 4 and 5 years unless a stem cell allograft, limited to younger individuals with related donors, was possible, the survival of patients of all ages now is virtually the same as age-matched individuals if CML is diagnosed and treated in chronic phase [6] and patients are compliant. In fact, the best and deepest molecular response is not even necessary to achieve this survival result [2,7].

After survival, the concept of treatment-free remission (TFR) or the ability to successfully discontinue treatment is felt to be a major goal of therapy [8,9]. Although noble in its intent, it is not an option for many patients because they do not reach the target for an attempt, the appropriate resources for safe monitoring are not available, or in fact, around half will recur with their CML after coming off therapy [10]. The latter is not a relapse, as prompt re-initiation of therapy almost always restores the response. What is important here as well is that the appropriate trials for TFR have only been conducted using three drugs—imatinib, dasatinib, and nilotinib. Although bosutinib is a second generation drug like nilotinib and dasatinib and TFR results given drug response are felt to be the same, there are no large study data to confirm this [4,11–13]. There are also no study TFR data, other than case reports, for third generation drugs such as ponatinib or asciminib or newer drugs when used even in first line.

Imatinib was the first generation drug used for CML therapy. It has been followed by three widely used second generation drugs—dasatinib, nilotinib, bosutinib—although there are others that have limited global distribution. Bosutinib, originally marketed by Pfizer as Bosulif, and now off patent in most of the world, was the third to become available. It has approval in many countries for use and reimbursement beyond first-line, although first-line therapy is also approved and reimbursed in some jurisdictions.

Cut to the Chase Background on Bosutinib

The phase 2 studies that proved the efficacy of bosutinib in CML therapy in second, third line therapy and beyond. They are all discussed in the papers listed here and the author will not dwell in detail [14,15]. Bosutinib pharmacokinetics and dosing are well established [16] and there are no significant effects related to body mass [17].

TKI studies and long term follow up have revealed new side effects that are not listed in product monographs [18–20]. Although bosutinib is as effective as other medications, the big issues over the years have related to the acute adverse events, namely diarrhea and liver dysfunction [21]. These have caused some issues with previous studies. The front-line randomized BELA study [22] did not meet its primary cytogenetic response end point, although it did meet its secondary molecular response end point because of patient drop out due to adverse events, primarily the diarrhea. We now can appreciate that the original 500 mg dose of bosutinib was high, particularly in some populations such as Asian patients, resulting in unwanted side effects. Reducing the starting dose at least in new patients to 400 mg daily rectified part of the problem, but not all. In a subsequent randomized study BFORE [23], the lower dose resulted in fewer discontinuations and a superior outcome of bosutinib versus imatinib, such has been seen with other second generation TKIs. In addition, it was seen that some patients easily gained and sustained their responses with even lower doses of 200-300 mg daily! Population modeling has shown good response at the lower doses [24] and in fact studies at lower doses show efficacy [25].

Generally, early diarrhea or liver dysfunction occurs in the first few weeks of therapy. For the most part diarrhea is limited to a few days, controlled with hydration, anti-diarrheals in most patients [21]. This is unlike the diarrhea associated with imatinib, which is chronic and not time limited. The biggest side effect of bosutinib induced diarrhea is patient and/or clinician patience in managing the problem, often resulting in a drug switch and a bad reputation. What has also come to light over the last few years is something called the "ramping up" or "dosing up" or "stepping in" effect [26,27]. We have now seen that starting bosutinib at a lower dose of 100-200 mg daily and increasing it to the target dose whether for first line or subsequent therapy, greatly reduces the incidence and severity of the problem. In fact, in some cases, it is found that lower doses of bosutinib are all that are required for good disease control [23] and the package monograph recommended dose is not necessary. Doses can often be reduced after response is obtained [28]. Side effects are greatly reduced and tolerance greatly improved. It should be pointed out that without exception, the dose of all TKIs that is used is not the dose determined from phase 1 or 2 studies but is less either as a lower starting dose or an ability to dose reduce once a response is achieved. In fact, this concept of dose reduction has now been applied to all TKIs and very few are being dosed at the level determined by the earlier studies [25,29].

An unfortunate and somewhat misleading side effect of this problem has been the issues related to the use of bosutinib as the control arm of other studies [30]. Reasonable for FDA requirements, but not realistically, the product monograph dose of bosutinIb 500 mg was used and no ramping up was permitted. This resulted in the obvious and "desired" early adverse events that resulted in early discontinuation of the bosutinib control arm patients and a switch to the study arm. As an aside, the arms were not truly balanced with more resistant patients in the bosutinib arm and more having had a greater number of TKIs. It is well known that intolerant patients are more likely to respond to a new drug than resistant patients. The bosutinib response rate was also in fact, inferior to that seen with other recent bosutinib studies for patients

in third line [31]. Survival for all patients was about the same, but then depth of response and speed of response which were endpoints of the study, generally have minimal impact on survival. Treatment-free remission eligibility is currently not routinely on the table with patients who have had beyond two lines of therapy.

Long term side effects of most TKIs have been documented although there is not lot of data for newer drugs such as asciminib and olverembatinib. Long term side effects of bosutinib are minimal but some are noteworthy. For a comparison of these with all other TKIs, please refer to rather extensive reviews [9,20]. The most recent ELN CML Recommendations just published comment on the transaminitis and diarrhea, but long-term mention a few relatively uncommon issues. The author will go over the ones of which to take note and to watch. The first is hypertension often seen in patients with other risks, but easy to control. Elevated creatinine is the second [32,33], but this appears to be an event reversible on holding or discontinuing drug [34]. This decision should be based on severity. Rash can be seen but is usually limited and not severe [35]. Pleural effusion, which is an autoimmune phenomenon and not cardiac, have been seen. This is an extremely uncommon event but can be seen in patients on any TKI but more common with patients who have been on dasatinib [36]. Given the similarity of action of bosutinib and dasatinib, it can occur in patients who have been switched from dasatinib to bosutinib. The most serious side effect is pulmonary arterial hypertension or pulmonary hypertension. This uncommon event is seen most again in patients previously on dasatinib where it is a little more common and in extremely rarely in cases of first line bosutinib where it is reportable [37–39]. Compared to other drugs as can be seen in a table in the ELN publication, long term events are very uncommon making bosutinib perhaps the safest drug that is out there. Significantly, cardiovascular side effects are also very rare [40] making bosutinib a good drug for older individuals [41,42]. Asciminib appears at least as safe, but the long term follow up data will need to be seen.

The problem with side effects that are listed in the product monograph that comes out subsequently after a drug is marketed, is that most are collated from early studies and when they appear later, does not for the most part transfer over to the product monograph. That is where the review previously to which the author alluded comes in [20]. We know that some side effects such as pleural effusions with dasatinib can occur at any time, cardiac events with nilotinib can increase with time and many of the imatinib chronic effects such as edema or MSK issues persist. Looking at these, it makes a good case for using bosutinib, where late events are rare.

Bosutinib has one of the best quality of life follow up profiles that has been documented. Obviously, this is for patients who have remained on therapy and especially have a good response [43]. Patients can report issues [44] and actually guide dosing as a consequence [45].

Bosutinib has been shown to be a cost effective therapy [46] and with the dose adjustment findings and the recent appearance of generics, makes it a good option. Patient selection is important [47], and approaches should be individualized taking patient preference into account [48]. This can include age adjusted dosing which comes into play in the pediatric and older patient groups [49]. These findings make it an appropriate choice when a second generation TKI is required.

Special Circumstances

Pediatrics

The author has considered this as a unique circumstance only because CML is an extremely rare disease in the pediatric population [50–52]. Bosutinib has recently been approved for use in this group [53] and is effective with a toxicity profile similar to adults and is used [54]. Long term issues need to be followed. Whether the src targeting of bosutinib will have an impact on growing children has not been seen. Growth retardation in children on other TKIs has been observed [55]. Bosutinib does fit into the therapy of pediatric CML when appropriate [56].

Fertility and pregnancy

Management of CML in women during childbearing age has significant issues [57]. Not only are there fertility concerns [58] but also potential pregnancy problems [59].

There is not a lot of data on bosutinib in the fertility area [58,60] with no significant problems noted albeit with few patients reported. As well, no problems have been reported if the male is on bosutinib as appears true for most TKIs [61]. What has been seen with some TKIs is a lower sperm count, but this has not been reported with bosutinib.

Bosutinib should be treated in the pregnant woman or in the woman desiring pregnancy in the same way as other TKIs [57,58]. Although there are no reported cases of bosutinib related birth defects, TKIs are teratogenic and should be avoided in the first and probably second trimesters. Bosutinib may be safe in the third trimester. Safety would suggest that unless absolutely necessary, TKIs should be avoided during pregnancy.

Dialysis and renal dysfunction

Bosutinib is liver metabolized and hence drug interactions with other cytochrome P450 metabolized medications are a possibility. There is almost no renal excretion. Bosutinib may increase creatinine in patients on the drug long term, but this

appears to be reversible on holding or discontinuation. Dialysis does not seem to impact bosutinib blood levels and therefore can be used with close observation in chronic kidney failure patients [62].

Gastric bypass and stomach acid blockade

There is almost no data here for bosutinib or for most TKIs in fact. Gastric by-pass (Roux-en-Y) appears to decrease absorption of some TKIs and may reduce efficacy [63,64] and this is particularly the case with dasatinib [65] and perhaps bosutinib which is similar. Theoretically, sleeve use reduces stomach volume but should have less of an effect on absorption. Patients with these procedures should be monitored closely for efficacy if they need to be started on TKI therapy. If on TKI therapy and by-pass is necessary, then sleeve may be preferable, with monitoring. Loosening of a gastric banding has been associated with better absorption. Obesity is a problem with the management of CML [66]. Semaglutide therapy which is being used for weight reduction has replaced much of by-pass therapy. A single case of safe/effective use of imatinib with semaglutide being used for diabetes, has been reported [67].

A single study of the impact of a proton pump inhibitor on the absorption of bosutinib has been reported [68]. As with some TKIs such as dasatinib [65], PPIs and H2 blockers seem to reduce absorption, and patients need to be monitored for efficacy. Bosutinib is probably not the drug of choice if there are other options in this scenario.

HIV

CML TKI therapy appears to be safe in HIV patients [69,70]. Dose adjustments may be required, but also this may yield some benefit [71]. There is also a theoretical suggestion that dasatinib [72,73] and bosutinib [74] may also have a positive impact on HIV therapy by their interference with NK cell activity. As with other TKIs and metabolism, the impact of potential drug interactions on organ toxicity needs to be monitored.

Who Should Use Bosutinib?

Bosutinib is a valuable TKI for any CML patient who is in first, second or third line therapy or beyond.

Who Should Not Use Bosutinib?

1. Any patient with a previous adverse event to bosutinib, including allergy.
2. Any patient with a history of gastrointestinal problems with symptoms of colitis unless there are no other options and then informed consent and close monitoring are required.
3. Any patient with a history of hepatitis of any cause, unless there are no other options, and then informed consent and close monitoring are required.
4. Any patient with a bcr::abl1 mutation that has been shown to be resistant to bosutinib.
5. Any patient with a comorbidity that would suggest that a different drug is safer.
6. Any patient with a history of pulmonary hypertension/ pulmonary arterial hypertension.
7. Any patient who has failed another second generation TKI for reasons other than intolerance or a directing resistant mutation that would be bosutinib sensitive. Patients failing a second generation drug for any other reason have less than a poor chance of responding to any other second generation drug [75] and should be considered for a third generation drug or stem cell allografting.

Who Could Use Bosutinib with Appropriate Work-up and Close Observation

1. Any patient with hypertension.
2. Any patient with renal dysfunction or other risk factors for renal dysfunction, e.g. diabetes.
3. Any patient previously on dasatinib who has a history of pleural effusion and only if the dasatinib related pleural effusion has completely resolved.

How to Work up a Patient to Start Bosutinib (Common Sense but Necessary)

1. Review of CML history to be sure there are no mutations that are resistant to bosutinib. Mutations with no directing drug sensitivity data can be tried but reassessment should be done within 3 months to determine efficacy.
2. Get a thorough medical history to become aware of other conditions that may impact therapy.
3. Get a complete medication history including prescription, naturopathic, herbal and recreational drugs, as they may interact with any TKI, not just bosutinib.
4. Get a complete physical exam to rule out unsuspected diagnoses.
5. Get bloodwork to look for pre-existing organ dysfunction.
6. Get a baseline electrocardiogram.
7. Get additional testing such as CXR or echocardiogram if there is any suspicion of problem or risk.

8. Get specialist consultation for other problems such as cardiac, renal, pulmonary etc.

How to Start a Patient on Bosutinib

1. Informed consent.
2. Agreement on a co-management strategy where the patient will inform you of any issues regardless of how serious they think they are and without self-management and where you will be available to answer all questions and deal with problems.
3. Start bosutinib at a lower dose than target—100–200 mg daily and ramp up over a couple of weeks to the final dose. You may find response before you even get there.

How to Follow a Patient Taking Bosutinib

1. Regular follow up looking for early side effects.
2. Regular follow up even if a patient is doing well to check for changes in health or other new medications that may interact with bosutinib.
3. Regular physical exam.
4. Appropriate molecular monitoring following guidelines.
5. Appropriate bloodwork to rule out any organ toxicity.
6. A deep dive into compliance if there is any suggestion of loss of response.
7. If TFR is considered, remembering that there are no formal studies for bosutinib, be sure that the appropriate baseline response criteria have been met, and that the appropriate regular frequent guideline molecular monitoring is done. A loss of response is common in about half of patients, but resumption of the original TKI is almost always effective if started promptly.

Conclusion

Bosutinib can be a very long term safe and effective option for newly diagnosed or beyond first line CML patients. Appropriate dosing methodology and monitoring can prevent or ameliorate common early side effects. The "big bad wolf "of history for many or even most patients may just be a fairy tale.

Disclaimer

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