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Asciminib: Its Place in Current Therapy of Chronic Myeloid Leukemia

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Abstract

The treatment options for patients receiving third-or later line (≥3L) tyrosine kinase inhibitors (TKI) therapy, include alternative TKIs that might not have been previously used. Patients who fail to respond to multiple TKIs may show lack of durable response to alternative second generation TKI as ≥3L therapy. Asciminib is a third-generation TKI that specifically targets the myristoyl pocket (STAMP) of the ABL1. A novel mechanism that is completely distinct from that of the conventional TKIs. The safety profile of asciminib is very promising, compared to existing TKIs due to its limited off-target activity and being inactive against other kinases including PDGFR, c-KIT, CSF1R, and the Src family.

Keywords: Asciminib; Third- or later line; Tyrosine kinase inhibitors; Chronic myeloid leukemia; Asciminib resistance

Abbreviations: AEs: Adverse Events; ≥3L: Third- or Later Line; TKIs: Tyrosine Kinase Inhibitors; STAMP: Specifically Targeting the Myristoyl Pocket; MMR: Major Molecular Response

Introduction

The optimal treatment recommendations and current guidelines pathways in chronic myeloid leukemia patients receiving third- or later line (≥3L) tyrosine kinase inhibitors (TKIs) therapy are unclear. Furthermore, treatment options in later lines are limited due to the development of intolerance or resistance to multiple TKIs [1]. The treatment options for patients receiving ≥3L TKI therapy include alternative TKIs that might not be previously used, such as dasatinib, nilotinib, bosutinib, ponatinib, and asciminib. Patients who failed to respond to multiple TKIs may show lack of durable response to alternative 2G TKI as ≥3L therapy [1]. Most people having third line and later treatment would have bosutinib. Ponatinib would be appropriate in bosutinib resistant people [2]. However, ponatinib use is associated with life-threatening cardiovascular events that require potential dose reductions. The safety profile of asciminib is very promising, compared to existing TKIs due to its limited off-target activity and being inactive against other kinases [1].

Asciminib

Asciminib is a third generation TKI that works through a novel mechanism completely distinct from that of the conventional TKIs which bind to the catalytic domain of BCR-ABL1. It allosterically inhibits the overactive kinase activity by specifically targeting the myristoyl pocket (STAMP) of the ABL1 [3]. Because the myristoyl domain is not readily found in other kinds of kinases including PDGFR, c-KIT, CSF1R, and the Src family, this inhibitor is highly selective for BCRABL1 [4]. It receives FDA approval in 2021 for the treatment of CML-CP after resistance and/or intolerance to two or more previous TKI or in the presence of T315I mutation [3]. Because of its different mechanism of action, asciminib is combined with other conventional TKIs in ongoing investigational trials. The addition of asciminib to ponatinib in this setting has merit and should be investigated. This approach should not be carried into the standard practice since such combinations may be associated with unexpected longer-term synergistic toxicities and may increase the cost of care significantly [5].

Comparing asciminib with bosutinib and ponatinib

All the TKIs except for imatinib are potential comparators, for asciminib, but the main comparators are bosutinib and ponatinib [2].

Comparing asciminib with bosutinib

ASCEMBL (NCT03106779) trial (Novartis 2021) is an open-label, randomized, phase III trial that compares asciminib with bosutinib in CML-CP patients on a ≥3L therapy. The

primary endpoint was to assess the superiority in achieving major molecular response (MMR; BCR: ABL1≤0.1%) at week 24 [1]. Results showed that asciminib had better molecular and cytogenetic response rates compared with bosutinib [2]. Asciminib showed significantly higher MMR rates at 6 months (25% versus 12%) and a higher MMR rate at 2 years (38% versus 16%) but the 2-year OS was similar (97% with asciminib and 99% with bosutinib) [3]. At a 96-week follow-up, phase 3 ASCEMBL study, showed superior MMR rate together with a favorable safety profile in asciminib compared to bosutinib [6]. Asciminib at the higher dose (200 mg BID) used for treatment of T315I-mutated CML showed lower all grade and ≥ grade 3 AEs than bosutinib in the ASCEMBL trial. However, longer follow-up on a larger number of patients is still needed for better defining of its safety [3].

Comparing asciminib with ponatinib

Both asciminib and dose modified ponatinib are excellent options. Both asciminib and ponatinib would be efficacious for T315I mutation and for non-T315I kinase domain mutations except for mutations at the F359 residue [5]. The higher doses of asciminib required to achieve response against T315I mutation is associated with increased toxicity [5]. There are no trials that compare head-to-head the efficacy of ponatinib and asciminib [5]. Trials that compare the efficacy and toxicity profiles of ponatinib (response dose-adjusted) and asciminib in second- or ≥ third-line therapy of CML are needed [5].

It is likely that one drug will be a better option over the other in specific settings.

i) Asciminib may be the preferred agent in the third line setting in the "pan-intolerant" patient including ponatinib without frank TKI resistance [5].

ii) Ponatinib may be more suited to patients with panTKI resistance, especially in patients who have never demonstrated molecular response to prior TKIs, with the view of dose de-escalation once a BCR-ABLIS of ≤1% is achieved [5].

iii) Asciminib can serve as an alternative treatment option to ponatinib, especially in those with cardiovascular risk factors preventing ponatinib use for e.g. following a 2GTKI failure in a ponatinib-naive patient [7].

iv) The outcomes of patients with T315I-mutated CML appear to be better with ponatinib than with asciminib in prospective trials [3].

Asciminib Administration [6]

a. Food should be avoided for at least 2 hours before taking the dose and for at least 1 hour after taking the dose. If vomiting occurs within the first hour after taking the drug, re-dosing is allowed before the next scheduled dose.

b. Patients should avoid prolonged exposure to sunlight and sunbeds and use of sunscreen. Asciminib may have phototoxic properties (phototoxicity was seen in mice at doses much higher than the doses licensed for humans).

c. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose--galactose malabsorption should not take this medicine.

d. Dose adjustments should be made for hematologic and non-hematologic toxicities, such as absolute neutrophil count less than 1.0×10^9/L, platelets less than 50×10^9 / L, elevated serum amylase and/or lipase, hypertension, hypersensitivity and cardiovascular toxicity [6].

Asciminib Interactions [8]

Caution should be exercised during concomitant administration of asciminib with strong CYP3A inducers, CYP3A4 substrates with a narrow therapeutic index, CYP2C9 substrates with a narrow therapeutic index, P-gp substrates with narrow therapeutic index and certain medicinal products. Dose adjustment of asciminib is not required in such cases.

i) Strong CYP3A inducers, including carbamazepine, phenobarbital, phenytoin may decrease the plasma concentration of asciminib.

ii) Asciminib administration increase plasma concentrations of the following: CYP3A4 substrates with a narrow therapeutic index, including, fentanyl, alfentanil, dihydroergotamine or ergotamine, CYP2C9 substrates with a narrow therapeutic index, including phenytoin or warfarin and P-gp substrates with narrow therapeutic index (e.g dabigatran or digoxin).

iii) Concomitant use of medicinal products including, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide cause QT prolongation and/or torsades de pointes.

Side effects

Conventional TKIs frequently show off-target effects because they are not specific for targeting BCR: ABL1 but bind also other tyrosine kinases, including PDGFR, c-KIT, CSF1R, and the Src family. As against conventional TKIs, asciminib has fewer off-target effects because of the limited number of tyrosine kinases containing myristate-binding sites [9]. Thrombocytopenia and neutropenia are the main reported adverse events [6].

Asciminib Resistance

New mutations involving the myristoyl pocket (site of asciminib binding) are emerging [3]. More than 100 ABL1 KD mutations have been reported on asciminib therapy [3]. Point mutations in BCR: ABL1 within or near the myristoyl pocket,

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including A337V, P465S, V468F, F359C/I/V, and C464W, have been reported to confer asciminib resistance in several preclinical studies. In addition to the BCR: ABL1 mutation, ABCG-2 mediated drug efflux was found to be a major driving mechanism of resistance [9].

Conclusion

Longer follow-up on a larger number of patients is still needed to define better the safety of asciminib treatment. In addition, trials comparing the efficacy and toxicity profiles of ponatinib and asciminib in second- or ≥ third-line therapy of CML are also required.

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