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Review/ Praca poglądowa

Efficacy and safety of bosutinib in the second and third line of treatment in chronic myeloid leukemia

Skuteczność i bezpieczeństwo bozutynibu w leczeniu drugiej i trzeciej linii linii przewlekłej białaczki szpikowej

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder that comprises approx. 10% leukemia cases in adults. CML is characterized by the presence of reciprocal translocation between the long arms of chromosomes 9 and Q2 22, which leads to the formation of Philadelphia chromosome (Ph, shortened chromosome 22), that results in expression of fusion oncogene BCR-ABL1 consisting of BCR located on chromosome 22 and ABL1 gene derived from chromosome 9 [1–3]. BCR-ABL1 encodes a protein kinase Bcr-Abl that is responsible for the impairment of regulatory processes in the cell, including cell cycle and DNA repair regulation [1, 3–6]. This leads to increased proliferation rate and reduced apoptosis of myeloid cells.

The majority of CML cases are diagnosed in the chronic phase (CP) that may progress to accelerated phase (AP) and subsequent blastic phase (BP) or directly to BP (tri- or biphasic course of the disease, respectively).

Introduction of tyrosine kinases inhibitors (TKIs) significantly improved the prognosis of CML patients and has become a paradigm of effective targeted therapy [7, 8]. Imatinib was the first TKI used in the treatment of CML [9, 10]. Dasatinib and nilotinib are second generation TKIs (TKI2G) [11–14]. Despite the effectiveness and long-term safety of imatinib, approx. 40% of patients require switch to other TKIs due to the development of resistance or intolerance [15, 16]. Approx. half of them achieve complete cytogenetic response (CCyR) when treated with TKI2G [17, 18]. In addition, TKI2G in first line of CML-CP treatment allow to achieve deep molecular responses faster and in a larger number of patients, however, they do not improve overall survival in this group [19, 20]. The choice of a specific TKI for the treatment of CML depends on its side effects profile, disease phase, ABL kinase domain mutations, concomitant diseases, as well as the costs and the possibility of treatment reimbursement [21, 22].

Bosutinib (SKI-606) is another TKI2G that is selective against both Bcr-Abl and Src family of kinases. Bosutinib

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was approved by the European Medicines Agency in 2013 for the treatment of adult patients with CML in all phases, who were previously treated with one or more TKI, who cannot be treated with imatinib, nilotinib or dasatinib [23]. The aim of this paper is to provide pharmacological data regarding efficacy and toxicity of bosutinib in the treatment of CML (on-label use).

Pharmacodynamics

Bosutinib (SKI-606) was identified in 2001 by Boschelli as a potent inhibitor of non-receptor, protein Src kinases involved in various signaling pathways, including surface receptor- and Bcr-Abl kinase pathways [24–26]. The Src family kinases are involved in malignant transformation, tumor progression, and formation of metastases [25]. It is believed that these interactions are responsible for the progression of CML to AP and BP [25, 27]. Active sites of Src and c-Abl kinases are structurally related [28–30]. In 2003, Golas et al. showed that bosutinib (1–20 nmol/l) exerts more potent antiproliferative and proapoptotic efficacy in CML cell lines (K562, KU812, Meg-01) than imatinib [30]. Moreover, in murine and human myeloid cells bosutinib was active against imatinib-resistant, mutated forms of Bcr-Abl (Y253F, E255K, and D276G) [25, 40]. No activity in patients with T315I and V299L mutations was observed [25, 29, 31, 32, 27, 33]. Bosutinib also inhibits a number of other kinases involved in the promotion stage of carcinogenesis in myeloid leukemia cells. These include thyrosine kinases, serine-threonine kinases, and two calmodulin-dependent protein kinases [32, 34]. Unlike other TKIs, bosutinib is only minimally active against c-Kit and platelet-derived growth factor receptor (PDGFR), which play a role in normal hematopoiesis [24, 25, 34, 35]. Activity profile of bosutinib may explain its relatively low myelosuppressive potential in comparison to other TKIs [35]. Further studies performed by Konig et al. showed that bosutinib does not exert any significant effect on quiescent progenitor CML cells [36].

Pharmacokinetics

The pharmacokinetic parameters of bosutinib do not depend on age, weight, gender or ethnicity. The absorption of the oral forms of bosutinib from the gastrointestinal tract is slow, dose-dependent, and might be influenced by simultaneous consumption of food, and a pH of gastric acid [37, 38]. In phase I clinical trials, median maximal serum concentration (C_{max}) was achieved after 4–6 h of the administration of a single dose of the drug. Area under the curve (AUC) (serum concentration to time) after oral administration of bosutinib was 1.6–1.7 times higher if the drug was administered with food compared to the administration on an empty stomach [37, 38]. Bosutinib administered with food (200–600 mg) was safe and well tolerated, while doses greater than 400 mg administered on an empty stomach were associated with increased risk of adverse events, including diarrhea and nausea. At 400 mg/day diarrhea was observed in 83% of patients who took the drug on an empty stomach and 33% of patients who took the drug during a meal [38]. Simultaneous food intake increase the solubility of bosutinib and increase the absorption and tolerance of the drug. Volume of distribution of bosutinib is 5000–7000 L, what translates into a significant penetration and accumulation of the drug in the tissues. The absorption of bosutinib is lower if pH of gastric acid exceeds 5. Therefore, patients requiring antacid treatment should use short-acting H_2-blockers instead of proton pump inhibitors. H_2-blockers should be administered at least 2 h apart from bosutinib [23].

Bosutinib binds strongly (96%) to plasma proteins. It inhibits glycoprotein P (Pgp) and is metabolized in liver to inactive metabolites by cytochrome P450 isoenzyme 3A4 (CYP3A4) with "first pass effect" [39, 40]. Simultaneous administration of CYP3A4 inhibitors, such as ketoconazole or grapefruit juice, as well as inducers (e.g. rifampicin) may increase or decrease plasma concentration of bosutinib, respectively [40, 41]. In addition, simultaneous administration of Pgp inhibitors may increase plasma concentrations of bosutinib [23]. Such drug combinations should be avoided.

Bosutinib is contraindicated in patients with liver failure because of 2-fold increase of AUC and C_{max} of the drug in this group [23, 39]. Moderate (creatinine clearance 30–50 ml/min/1.73 m^2) or severe (creatinine clearance <30 ml/min/1.73 m^2) renal failure leads to 35% or 60% increase in AUC, respectively, in comparison to patients with normal kidney function [23]. In patients with renal failure bosutinib dose should be reduced. Elimination half-life of bosutinib is 22.5 h and in consequence, the drug is administered once daily [23, 37, 38]. Approx. 91% of inactive metabolites of bosutinib is excreted in faces [23, 39].

Clinical trials of bosutinib – results

Study evaluating SKI-606 (Bosutynib) in Philadelphia Chromosome Positive Leukemias (NCT00261846) was an open, multicenter, I/II phase clinical trial evaluating efficacy, safety and pharmacokinetics of bosutinib in CML-CP, AP and BC patients resistant or intolerant to imatinib. The results of these trials are shown below, including the efficacy of the second-line, third-line and subsequent lines of treatment in chronic phase as well as AP and BC.

Primary TKI resistance was defined as lack of hematologic response after 4 weeks of treatment, lack of complete hematologic response (CHR) after 12 weeks, lack of any cytogenetic response after 24 weeks or lack of major cytogenetic response (MCyR) after 12 months [35, 42]. Acquired resistance was defined as a loss of any hematologic response or MCyR [35, 42]. TKI intolerance was defined as the inability to continue the treatment due to 4 grade hematologic toxicity for longer than 7 days, non-hematologic toxicity grade ≥3, persistent grade 2 toxicity that do not respond to dose reduction or symptomatic treatment, loss of response to low dose TKI treatment if dose increase is not possible due to TKI toxicity [35, 42]. In total 17 patients in CP and 1 patient in AP was enrolled to phase 1 trial. Clinical benefits have been observed at all administered

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