Current and future place of ponatinib in the treatment of chronic myeloid leukemia and Ph+ acute lymphocytic leukemia

Joanna WĄCŁAW
Tomasz SACHA

Katedra i Klinika Hematologii Uniwersytet Jagielloński - Collegium Medicum, Kraków
Kierownik: Prof. dr hab. Aleksander B. Skotnicki

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Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) with potent activity against BCR-ABL1 and all single resistance mutants, including the gatekeeper mutant T315I. Ponatinib is approved for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) who are resistant or intolerant to dasatinib or nilotinib or who have the T315I mutation and for the treatment of adult patients with Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to dasatinib or nilotinib or who have the T315I mutation. In a pivotal phase II PACE study 267 patients with CP-CML, 83 with AP-CML and 94 patients with BP-CML or Ph+ALL were enrolled. T315I mutation were detected in 64, 18 and 46 patients, respectively. Two or more or three or more TKIs were used before ponatinib in 93% and 58% of patients, respectively. The median follow-up was 4 years. Among patients with CP-CML, 4-year rates for progression-free survival (PFS), overall survival (OS), major cytogenetic response (MCyR) and major molecular response (MMR) were 56%, 77%, 82% and 61%, respectively. Median OS for BP-CML and Ph+ ALL was 6.9 months. Efficacy of ponatinib as a first-line treatment for CP-CML patients was suggested in phase II and phase III trials. However, due to serious adverse events, predominantly arterial occlusion, the EPIC trial investigating ponatinib in a first line setting was discontinued. Ponatinib is a valuable agent for patients with CML and Ph+ ALL resistant or intolerant to other TKIs and those with T315I mutation.

Ponatynib jest inhibitorem kinazy tyrozynowej (TKI) BCR-ABL1 trzeciej generacji, aktywnym we wszystkich znanych mutacjach kinazy, również w przypadku mutacji T315I powodującej oporność na działanie pozostałych TKI. Ponatynib jest zarejestrowany do stosowań u dorosłych pacjentów z przewlekłą białaczką szpikową oraz ostrej białaczką limfoblastyczną Ph+: teraźniejszość i przyszłość

Adres do korespondencji:
Joanna Wąclaw
Katedra Hematologii UJCM
31-501 Kraków, ul Kopernika 17
tel: 12 424 76 00
fax: 12 424 74 26
e-mail: joanna.waclaw89@gmail.com

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The introduction of tyrosine kinase inhibitors (TKIs) has dramatically changed the landscape of the chronic myeloid leukemia (CML) treatment. The majority of patients with CML in the chronic phase have a life expectancy comparable with that of the general population. However, imatinib, a first-generation TKI, fails in up to 40% of patients due to disease resistance or intolerance [1]. Moreover, 37 to 52% of these patients do not respond to the second generation TKIs (nilotinib, dasatinib and bosutinib) either [2-6]. Resistance to TKIs is frequently caused by mutations in the BCR-ABL1 kinase domain.

Patients with Philadelphia chromosome positive or BCR-ABL1-positive acute lymphoblastic leukemia (Ph+ ALL), who constitute about 25% of patients with B-lineage ALL have a very poor outcome with systemic chemotherapy, particularly if they did not undergo allogeneic stem-cell transplantation in first remission. The introduction of first- and second-generation TKIs in combination with chemotherapy has revolutionised the treatment of Ph+ ALL, improved the outcome of therapy and became the standard of care for these patients. Despite the high efficacy of this combination, the 3-year event-free survival (EFS) and overall survival (OS) rates of Ph+ adult ALL are roughly only 40% and 60%, respectively [7,8]. These relatively low survival rates can mostly be attributed to TKI resistance. As in CML, TKI resistance in Ph+ ALL might be caused by mutations in the BCR-ABL1 kinase domain.

Ponatinib (Iclusig®) is a third-generation TKI with potent activity against BCR-ABL1 and all single resistance mutations, including the gatekeeper mutant T315I, which is uniformly resistant to other TKIs. In preclinical in vitro experiments, 40 nM of ponatinib (a concentration achieved in patients who receive daily dose of ≥30 mg) suppressed the emergence of any single mutation [9,10]. Ponatinib is approved for the treatment of adult patients with chronic phase, accelerated phase, or blast phase CML who are resistant to or intolerant of dasatinib or nilotinib or who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically indicated, or who have the T315I mutation. The drug is also approved for Ph+ ALL patients who are resistant to dasatinib or who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not appropriate as well as in case of the T315I mutation [11].

We discuss here the current and future place of ponatinib in the therapy of CML and Ph+ ALL based on the reports from the last ASCO and ASH meetings and on the second CML and Ph+ ALL – State of the Art Expert Panel which took place in Budapest on November 24-26th, 2016.

**Ponatinib in chronic-phase CML**

The efficacy and safety of ponatinib were evaluated in a phase 1 trial in 81 patients with resistant/refractory hematologic malignancies. Patients were treated with ponatinib at a starting dose of 2 mg/d – 60 mg/d. In October 2013, dose reduction instructions were provided in response to an observed accumulation of arterial occlusive events (AOEs) with longer follow-up across the ponatinib clinical program. During the 58th ASH Annual Meeting the four-year follow-up data from chronic-phase CML (CP-CML) patients of this trial was presented. The median follow-up was 53.1 months. At baseline, median age was 55 years and median time since diagnosis was 6.6 years. BCR-ABL1 kinase domain mutations were reported in 63% of patients, with T315I confirmed at a central laboratory in 28% of patients. Patients were heavily pretreated, with 37% having received 2 prior TKIs and 60% having received ≥3 prior TKIs. Of 43 CP-CML patients, 22 (51%) remained on ponatinib treatment at data cutoff. Cumulative response rates were: major cytogenetic response (McyR) 72%, complete cytogenetic response (CCyR) 65%, major molecular response (MMR) 56%, molecular response 4 (MR4) 42%, MR4.5, 28% (Tab. I). Responses were durable, the median durations of response were not reached for McyR, CCyR, and MMR. Among patients who received ponatinib at starting doses of ≤30 mg/d (n = 15), McyR was achieved by 67%, CCyR by 53%, and MMR by 47%; ponatinib dose was ≤30 mg/d in all but one of these patients at the time of response. Of the 22 ongoing patients at the time of the presented analysis, 18 (82%) had CCyR and 17 (77%) had MMR or better response. Adverse events (AEs) in 26%, and disease progression in 9% of patients were the most common reasons for discontinuation of therapy. Rash (65%), fatigue (63%), abdominal pain (58%), headache (58%) and arthralgia (53%) were the most common treatment-emergent AEs.

The incidence of AEs (any/serious) was 40%/30% (by subcategory: cardiovascular, 30%/21%; cerebrovascular, 9%/7%; peripheral vascular, 14%/9%) [12].

In a phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias (PACE) 449 heavily pretreated patients with CML or Ph+ ALL with resistance to or intolerance of dasatinib or nilotinib or who had the T315I mutation were involved. Ponatinib was administered at an initial dose of 45 mg once daily. During the 2016 ASCO Annual Meeting the four-year follow-up data from the PACE study was presented. Ponatinib dose reductions were recommended in October 2013 due to increased incidence of grade ≥3 adverse events. The Ponatinib Analysis Group (134/207) of CP-CML patients (median follow-up 48.2 months) remained on study. Estimated 4-year rates for progression free survival (PFS), overall survival (OS), and maintenance of McyR and MMR were 56%, 77%, 82% and 61%, respectively. Common (in ≥30% of patients) AEs (all grades) were: myelosuppression ≥38%, abdominal pain ≥38%, rash ≥42%, constipation ≥37%, headache ≥37%, dry skin ≥36%, fatigue and hypertension ≥30%. AOE rate/serious AOE rate was 23%/19%, including cardio- 13%/9%, cerebro- 9%/7%, and peripheral-vascular 9%/7% adverse events. Of all patients with AOE (n=104), 38% remained on study. Nearly 2 years after recommended dose reductions, 87% (114/131) and 74% (70/95) of CP-CML patients were estimated to maintain McyR and MMR, respectively, and 8% (6/75) of all dose-reduced patients without a prior AOE on trial had an AOE [13].

To establish possible predictive factors of response to ponatinib, 94 patients were included in a post hoc analysis of results among CP-CML patients enrolled in the PACE trial according to the number of TKIs received prior to the study entry. CP-CML patients were evaluated based on previous treatment with 1, 2, 3, or 4 prior TKIs approved for use in CP-CML (ie, imatinib, dasatinib, nilotinib, and bosutinib). Rates of cytogenetic and molecular response to ponatinib were higher with fewer prior TKIs used. The incidence of grade ≥3 AEs appeared to increase with the number of prior TKIs received (68%, 86%, 90%, and 100%, respectively). A similar frequency pattern was observed for serious AEs, which occurred in 58%, 53%, 62%, and 92% of patients who had previously received 1, 2, 3, and 4 approved TKIs, respectively. The frequency of AOE was 32%, 26%, 28%, and 42%, respectively, by increasing number of prior TKIs [14].

Jabbour and colleagues conducted the pooled analysis of ponatinib efficacy and safety in a subgroup of CP-CML patients with the T315I mutation from the aforementioned phase 1 and phase 2 PACE trials. There were 76 T315I+ CP-CML patients included in the analysis (phase 1, n=12; PACE, n=64). At the time of analysis, median duration of follow-up in T315I+ CP-CML patients was 40 (range: 1.5–74) months; 37 patients (49%) remained on study. Median baseline ponatinib dose intensity was 33 mg daily; 25/37 (68%) ongoing patients were receiving 15 mg daily as their current dose as of the data cut-off. Primary reasons for discontinuation in T315I+ CP-CML patients were disease progression [10/76 (13%)] and AEs [9/76 (12%)]. Cumulative response rates in T315I+ CP-CML patients (n=76) were: McyR, 75%; CCyR, 72%; MMR, 61%, and MR4.5, 37%. OS and PFS data were evaluated only for PACE study subgroup. Criteria for disease progression included death, development of advanced phase CML, loss of complete hematologic response (CHR) (in absence of cytogenetic response) and loss of McyR. Estimated 3-year PFS and OS rates for 64 T315I+ CP-CML patients (n=64) were: McyR, 75%; CCyR 72%; MMR, 61%, and MR4.5, 37%. OS and PFS data were evaluated only for PACE study subgroup. Criteria for disease progression included death, development of advanced phase CML, loss of complete hematologic response (CHR) (in absence of cytogenetic response) and loss of McyR. Estimated 3-year PFS and OS rates for 64 T315I+ CP-CML patients (n=64) were: McyR, 75%; CCyR 72%; MMR, 61%, and MR4.5, 37%. OS and PFS data were evaluated only for PACE study subgroup.

Common treatment-emergent AEs (≥40%) in the pooled group of T315I+ CP-CML patients (n=76, phase 1 and PACE) were: rash, 55%; dry skin, 49%; headache, 46%; abdominal pain, 43%; nausea, 41%; and fatigue, 41%. Among these patients, the most common treatment-emergent AEs (≥4%) were: cardiovascular 20%/15%; cerebrovascular 12% /5%, and peripheral vascular 13%/8% events [15].

The Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia
(EPIC) study was a randomised, open-label, phase 3 trial designed to test the efficacy and safety of ponatinib, compared with imatinib, in newly diagnosed patients with CP-CML. Eligible patients were at least 18 years of age, within 6 months of diagnosis, Ph+ by cytogenetic assessment and had not previously been treated with TKIs. 307 patients were randomly assigned to receive ponatinib (45 mg) (n=155) or imatinib (400 mg) (n=152). The trial was terminated early, in October 2013, due to concerns regarding vascular adverse events observed in patients given ponatinib in other trials. The trial termination limited assessment of the primary endpoint of MMR at 12 months, as only 13 patients in the imatinib group and ten patients in the ponatinib group could be assessed at this timepoint. At trial termination median follow-up for the entire trial population was 5.1 months (5.0 for the ponatinib group, and 5.3 for the imatinib group). The proportion of patients achieving MMR at 12 months did not differ significantly between the two groups: eight of ten patients given ponatinib and five of 15 patients given imatinib. For secondary endpoints, the proportion of patients achieving MMR at 3, 6 and 9 months was significantly higher in ponatinib group than in imatinib group: 31%, 62% and 86% vs 3%, 22% and 33%, respectively. Significantly more patients achieved MMR, MR4 and MR4.5 at any time in ponatinib vs imatinib group (41%, 21% and 15% vs 18%, 1% and 0%, respectively). This finding was similar regardless of Sokal risk score. The proportion of patients achieving BCR-ABL1 gene transcript levels of less than 10% (IS; international scale) at 3 months was significantly higher in patients receiving ponatinib than imatinib (94% vs 68%), irrespective of Sokal risk category. Significantly more assessable patients treated with ponatinib (74% and 86% vs 53% and 60%) achieved CCyR at any time and at 6 months, respectively. Eleven (7%) of 154 patients given ponatinib and three (2%) of 152 patients given imatinib had AEs (p=0.05); AEs were designated as serious in 10 (6%) of 154 patients given ponatinib and in 1 (1%) of 152 patients given imatinib. Grade 3 or 4 AEs observed in more than 5% of patients in the ponatinib group were: increased lipase (14% vs 2% with imatinib), thrombocytopenia (12% vs 7% with imatinib), rash (6% vs 1% with imatinib). In the imatinib group, grade 3 or 4 AEs observed in more than 5% of patients were neutropenia (12% vs 3% with ponatinib) and thrombocytopenia (7% vs 12% with ponatinib). Serious AEs that occurred in three or more patients given ponatinib were pancreatitis (n=5), atrial fibrillation (n=3), and thrombocytopenia (n=3). No serious AE occurred in three or more patients given imatinib [16]. Another single-arm, phase 2 trial investigating the activity and safety of ponatinib as first-line treatment for patients with CP-CML was conducted at MD Anderson Cancer Center in Houston, USA. 51 patients with a median age of 48 years (range 21–75) with early diagnosed (<6 months) CP-CML were enrolled. Sokal risk score was low for most patients and EUTOS score was low risk in 41 (81%) of 45 patients evaluated and high risk in four (9%). No previous therapy for CML other than hydroxy-carbamide or 1 month or less of therapy with approved TKIs were allowed. Initially, patients were given a starting ponatinib dose of 45 mg/d. Due to tolerability issues a starting dose was lowered to 30 mg/d. After a warning by the US Food and Drug Administration (FDA) in October, 2013, for vascular complications with ponatinib, all patients were started on aspirin 81 mg daily; the dose of ponatinib was reduced to 30 mg or 15 mg/d for all patients. The study was terminated in June 2014, at the recommendation of the FDA due to concern about the increased risk of thromboembolism with ponatinib. Median follow-up was 20.9 months (IQR 14.9–25.2). 43 patients were started on ponatinib 45 mg/d, eight patients were started on 30 mg/d. The cumulative proportion of patients to achieve CCyR was 96% (48 of 50), MMR was 80% (40 of 50), and MR4.5 was 55% (28 of 50). None of the 50 patients progressed, including no transformations to accelerated or blast phase throughout the observation period, and all patients were alive at the time of last follow up. Estimated EFS, transformation-free survival, and OS at 24 months were 100%. Most frequent toxicities included skin-related effects (n=35; 69%) and elevated lipase (n=32; 63%). Cardiovascular events (mainly hypertension) occurred in 25 (49%) patients. Grade 3–4 myelosuppression occurred in 15 (29%) patients. Five patients (10%) developed cerebrovascular or vaso-occlusive disease. 43 patients (85%) needed treatment interruptions at some time and 45 (88%) needed dose reductions [17]. Since the EPIC trial and the latter study were terminated early, efficacy and safety of ponatinib in the first-line setting remain to be established.

**Ponatinib in advanced-phase CML and Ph+ ALL**

In a phase 1 trial of Ponatinib in Refractory Philadelphia Chromosome–Positive Leukemias, 9 patients with accelerated-phase CML (AP-CML), 8 with blast-phase CML (BP-CML), and 5 with Ph+ ALL were involved. They were treated with ponatinib at a starting dose of 2 mg/d – 60 mg/d. In all trial patients, the disease was relapsed or resistant to approved tyrosine kinase inhibitors (imatinib, dasatinib, or nilotinib). Ninety-one percent of Ph+ patients had received two or more approved TKIs: 40% had received imatinib followed by dasatinib or nilotinib, and 51% had received imatinib followed by both dasatinib and nilotinib. At study entry, 19 of 22 patients (86%) with advanced disease achieved at least one BCR-ABL1 kinase domain mutation; the most frequent mutation was T315I. Median follow-up at the time of analysis was 66 weeks. Of the 22 patients with advanced disease, 8 (36%) achieved a major hematologic response (MaHR), 7 (32%) achieved a McCyR, and 2 (9%) achieved a MMR. Among patients with a MaHR, the median time to response was 8 weeks, and the duration ranged from 0.1 to 64 weeks (median, 16). The most common hematologic, treatment-related AEs were skin disorders (e.g., rash, acneiform dermatitis, and dry skin) and constitutional symptoms (e.g., arthralgia, fatigue, and nausea), most of which were grade 1 or 2. Treatment-related myelosuppression, mostly grade 3 or 4, was common but was also frequently present at baseline, particularly in patients with advanced disease [10]. In a PACE trial 65 patients with AP-CML and resistance to or unacceptable side effects of dasatinib or nilotinib and 18 with AP-CML and the T315I mutation, and 48 with BP-CML or Ph-positive ALL and resistance to or unacceptable side effects of dasatinib or nilotinib and 46 with BP-CML or Ph-positive ALL and the T315I mutation were involved. Ponatinib was administered at an initial dose of 45 mg once daily. The median follow-up was 15 months. Among patients with AP-CML, 55% had a MaHR by 6 months (the primary end point). AM-CyR was noted in 39%, 24% achieved a CyR, and 16% had a MMR. The median time to a MaHR was 3 weeks (range, 2 to 25), and the duration ranged from 1 month to 21 months or more (median, 12 months); the estimated rate of a sustained response of at least 12 months was 48%. The median time to a McCyR was 3.7 months (range, 0.8 to 9.7), and the estimated rate of a sustained response of at least 12 months was 73%. The rate of PFUS was estimated to be 55% at 12 months (median, 18 months), and the rate of OS was estimated to be 84% at 12 months. Like the patients with CP-CML, the patients with AP-CML who received fewer previous tyrosine kinase inhibitors (imatinib, dasatinib, or nilotinib)
higher response rates. High response rates were observed among patients with BCR-ABL1 mutations, including those with the T315I mutation, and among those without.

**BCR-ABL1 mutations.** Among patients with BP-CML, 31% had a MqHR by 6 months (the primary end point), 23% had a MCyR, and 18% had a CCyR. The median time to a MqHR in patients with BP-CML was 4.1 weeks (range, 1.3 to 16.1), the duration ranged from 1 month to 20 months or more (median, 5 months), and the estimated rate of a sustained response of at least 12 months was 42%. The median time to a MCyR in patients with BP-CML was 1.9 months (range, 0.9 to 5.5), and the estimated rate of a sustained response of at least 12 months was 8%. The median time to a CCyR in patients with BP-CML was 1 month (range, 0.9 to 3.7), the median duration was 3.7 months, and the estimated rate of a sustained response of at least 12 months was 32% [18]. In the fo-

**ur-year follow-up data from the PacE study.** The number of patients with 3 mutations in the same allele detected by SS: 27/30 vs. 10/19 cP-cML pts had cP-cML, patients who acquired mutations were observed among patients with Ph+ aLL, 41% (95% CI, 24 to 59) had a MqHR, 47% had a MCyR, and 38% had a CCyR. The median time to a MqHR in pa-

**tients with Ph+ ALL was 2.9 weeks (range, 1.6 to 24), the duration was 2 months to 14 months or more (median, 3 months), and the estimated rate of a sustained response of at least 12 months was 8%.** The median time to a MCyR in patients with Ph+ ALL was 1 month (range, 0.9 to 3.7), the median duration was 3.7 months, and the estimated rate of a sustained response of at least 12 months was 32% [18]. In the fo-

**ur-year follow-up data from the PAC E study median OS for BP-CML and Ph+ ALL was 6.9 months [13].**

Based on data from the PAC E study no single BCR-ABL1 kinase domain mutation was associated with resistance to ponati-

**nib. However, the acquisition of compo-

**und mutations (≥2 mutations in the same BCR-ABL1 gene allele) was sometimes observed in patients with an unsustained MqHR.** Previous studies have shown that certain compound mutations can cause re-

**sistance to ponatinib, but such mutations were found to be rare in CP-CML patients [19].** Pritchard and colleagues utilized a multi-level sequencing strategy combi-

**ning Sanger Sequencing (SS), Next Gene-

**ration Sequencing (NGS), and single mole-

**cule Duplex Sequencing (DS) to profile the mutational mechanisms that may account for the unfavorable survival outcomes ob-

**served in BP-CML/Ph+ ALL patients from the PAC E trial.** The number of BCR-ABL1 mutations in BP-CML/Ph+ ALL patients at baseline, as detected by SS, was not a signi-

**ficant predictor of resistance to ponatinib.** In refractory patients with Odds Ratios (OR) of 1.0 (0.2-4.9 95% CI) for MqHR and 2.4 (0.5-12.5 95% CI) for MCyR. How-

**ever, a larger proportion of BP-CML/Ph+ ALL patients, 30/61, acquired mutations in BCR-ABL1 at end of treatment vs. 19/130 CP-CML patients (OR 7.7 [1.5-53.3 95% CI]).** Nearly all BP-CML/Ph+ ALL, but not CP-CML, patients who acquired mutations had BCR-ABL1 mutations at baseline detected by SS: 27/30 vs. 10/19 CP-CML pts (OR 5.6 [2.7-12.1 95% CI]). At least 19/27 BP-CML/Ph+ ALL patients had compound mutations at end of treatment, including 2 patients with 3 mutations in the same allele. Since the presence of pre-existing mutations from earlier TKI therapy is associated with further gain of mutations on ponatinib treatment, ultra-sensitive DS was used to determine if these resistant clones could be detected at baseline. In 3/18 patients te-

**sted, the resistant clone was directly detec-

**ted, in 3/18 patients tested, the resistant clone was directly detected at baseline in a small minority of cells.** Distinct mathematical modeling strategies suggest that most, if not all, BCR-ABL1 resistance mutations in BP-CML/Ph+ ALL patients that emerge during ponatinib tre-

**atment were pre-existing [20].**

The combination of chemotherapy with a TKI is the standard of care in Ph+ ALL. The efficacy and safety of combining chemotherapy with ponatinib for patients with Ph+ ALL was evaluated in a phase 2 prospective trial. Adult patients with newly diagnosed Ph+ ALL and good perform-

**ance status received 8 cycles of hyper-CVAD alternating with high dose methotrexate/ cytarabine every 21 days.** Ponatinib was given at 45 mg daily for the first 14 days of cycle 1, then continuously for the subsequent cycles. Patients in complete re-

**mission (CR) received maintenance with ponatinib 45 mg daily with vincristine/prednisone monthly for 2 years followed by ponatinib indefinitely.** 37 patients with a median age of 51 years were treated. The overall CCyR, MMR, and complete molecular response (CMR) rates were 32/32 (100%), 35/37 (95%), and 29/37 (78%), respectively. By multiparameter flow cytometry, 35 patients (97%) had no detectable minimal residual disease after a median of 3 weeks of therapy (Tab. II). Grade ≥3 toxicity included infections du-

**ring induction (20 patients), increased liver functional tests (14 patients), thrombotic events (3 patients), myocardial infarction (3 patients), hypertension (6 patients), skin rash (8 patients), and pancreatitis (6 patients). Two potentially related deaths were observed among patients with myocardial infarction were observed. Nine patients underwent allogeneic stem cell transplantation (ASCT). With a me-

**dian follow-up of 26 months (range, 15–39 months), 29 (78%) patients were in CR, with 9 patients (24%) receiving ASCT, for an estimated 2-year survival rate of 80% (95% confidence interval [CI], 63%–90%), CR duration rate of 97% (95% CI, 80–

**99.6%), and an EFS rate of 81% (95% CI, 64–90%) [21].**

The clinical efficacy of hyper-CVAD plus ponatinib has not been compared with that of hyper-CVAD plus dasatinib in a ran-

**domized clinical trial. However, Sasaki and colleagues analyzed 110 patients with newly diagnosed Ph+ ALL who were enrolled in 2 consecutive, prospective, phase 2 clinical trials of frontline hyper-CVAD with either dasatinib (63 patients) or ponatinib (47 patients). Propensity score analysis with 1:1 matching with the nearest neigh-

**bor matching method and inverse proba-

**bility of treatment weighting (IPTW) ana-

**lysis based on the propensity scores were performed to assess response rates, EFS, and OS between the cohorts. Propensity score matching identified 41 patients in each cohort. With propensity score mat-

**ching, the 3-year EFS rates for patients tre-

**ated with hyper-CVAD plus ponatinib and hyper-CVAD plus dasatinib were 69% and 46%, respectively (P=0.4), and the 3-year OS rates were 83% and 56%, respectively (P=0.3). IPTW analysis using prematching cohorts demonstrated that patients treated with hyper-CVAD plus ponatinib had significantly higher rates of minimal residual disease (MRD) negativity by flow cytometry on day 21, CCyR at complete response, MMR at complete response and at 3 months, and complete molecular response at 3 months. IPTW confirmed that treatment with hyper-

**-CVAD plus ponatinib was associated with longer EFS (P=0.003) and OS (P=0.001) compared with treatment with hyper-CVAD plus dasatinib.** Of the 27 deaths reported in the entire cohort, no significant differences with regard to the cause of death were observed between the 2 cohorts (P=0.209) [22].

Philadelphia chromosome is the most frequent recurrent cytogenetic abnormali-

**ty in elderly (aged ≥ 60) aLL patients [23].** Since the introduction of TKIs, two appro-

**aches were developed for this patients’ po-

**pulation: age-adapted chemotherapy plus TKI or solo-agent TKI plus steroids.** The latter approach was proved to be effective and safe [24, 25]. There is an ongoing phase 2 trial by Gruppo Italiano Malattie EMatologiche dell’Adulti (GIMEMA), eva-

**luating the therapeutic effect of ponatinib plus steroid in first-line treatment of Ph+ ALL patients who are ≥ 60 years old, or are

| Table II
| Best overall response for combination of Hyper-CVAD with Ponatinib in frontline therapy of patients with Ph+ ALL [21].
<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
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<tr>
<td>CR</td>
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<tr>
<td>CCyR*</td>
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<td>MMR</td>
<td>35/37 (95)</td>
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<td>CMR</td>
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<td>Flow negativity**</td>
<td>35/36 (97)</td>
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<td>Early death</td>
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* 1 patient in CR at start
** 5 patients were diploidy by conventional cytogenetics at start
*** 1 patient had no sample sent to flow cytometry

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and Ph+ ALL – State of the Art Panel

Therefore the experts of the second panel recommended the use of ponatinib in patients with CML and Ph+ ALL therapy worth considering. The recommended dose of ponatinib in patients with CML and Ph+ ALL is 45 mg/d, with consideration of lower starting doses in patients with selected comorbidities. However, there is evidence suggesting that 15 mg/d is sufficient to suppress the emergence of all clinically relevant single resistant mutations [33]. Another study has shown that dose-intensity correlated with the incidence of AEs, with each 15 mg per day reduction predicted to decrease risk of AEs by ca. 40% [34]. Thus, dose reduction to 15 mg daily should be considered in CP-CML patients who achieved a MCyR based on individual patient risk factors assessment. [11] Two ongoing studies are investigating the effects of 30 mg/d and the 15 mg/d starting doses in CML patients in second-line settings or beyond (NCT02467270 and NCT02627677 ).

In summary, ponatinib is very potent and valuable agent in the therapy of patients with CML and Ph+ ALL resistant or intolerant to other TKIs and those with T315I mutation. Nevertheless, the benefits of the drug have to outweigh the risk of developing AEs. Therefore it is not recommended as a first-line therapy for patients suffering from CP-CML without detected T315I mutation. Current data suggest that ponatinib could yield substantially better reates of cytogenetic and molecular responses when used in third line settings when compared to second generation TKIs. However, its optimal position among the available armamentarium of TKIs is yet to be established.

References


