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POSTER ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Use of Ponatinib Alone or Combined with Other Therapies in Relapsed/Refractory Ph-like Acute Lymphoblastic Leukemia. a Campus ALL Real-Life Study

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Introduction. Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) employed in relapsed/refractory (R/R) and, more recently, also in newly diagnosed Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Ph-like ALL is a genetically heterogenous subgroup that shares a common transcriptional profile, similar to that of true Ph+ ALL, though lacking the *BCR::ABL1* rearrangement. Ph-like ALL is characterized by a poor prognosis, a high relapse rate and a worse overall survival if treated with standard chemotherapy. Several molecular pathways are involved, including *JAK/STAT*, *CRLF2* and *ABL*-class mutations, providing a heterogeneous genetic landscape with very limited data on the subsequent clinical outcome. Few isolated cases of successful treatment of R/R Ph-like ALL with ponatinib have been reported, including also patients with lesions different from *ABL*-class mutations. Currently, ponatinib prescription in Italy is not allowed for Ph-like ALL.
Patients and Methods. Between January 2019 and July 2023, 17 patients were candidate to receive ponatinib on a nominate compassionate use basis; data were collected in the context of the Campus ALL network in Italy. The criteria for inclusion were a diagnosis of Ph-like ALL, with either hematological or molecular evidence of disease, and a treatment period of at least 28 consecutive days of ponatinib. The Ph-like signature was based on the BCR/ABL1 like-predictor (Chiaretti et al, BJH 2018) and, whenever possible, targeted RNA sequencing. Final data were collected for 15 patients (2 patients were excluded due to a treatment period <28 days) treated with ponatinib either as a single agent or in association with immuno and/or chemotherapy.
Results. All patients had common ALL. Eight of the 15 cases were classified as high risk or very high risk ALL at diagnosis; 10 were males, the median age was 28 years (14-66) and the median white blood count at diagnosis was 25.6 x10 ^{9}/l (2.7-317 x10 ^{9}/l). Targeted RNA sequencing was carried out in 10/15 cases: 7 presented gene fusions (*ABL*-class mutations in 2, *JAK2* mutations in 2, and *CRLF2::P2RY8*, *IKZF1::DDC* and *RB1::RCBTB2* in 1 case each); 2 additional cases had a *CRLF2*

rearrangement, evaluated by FISH. Copy number aberrations analysis by multiplex ligation-dependent probe amplification (MLPA) technology was performed in 12/15 cases: 5 cases had a *IKZF1 plus* signature, 6 had a *IZKF1* loss, while 1 case was *IKZF1* wild type.

Ponatinib was started in first (n=2) or second (n=5) hematologic relapse in 7 patients (46%), with 3 also having an extramedullary disease; 7 additional patients (46%) were treated in first (n=5) or second (n=2) minimal residual disease (MRD) persistence/recurrence; finally, 1 patient was refractory to 3 subsequent lines of treatment. In 8/15 patients ponatinib was used as single agent or in association with steroids or intrathecal chemotherapy only, in 4 it was administered in combination with chemotherapy and in 3 with blinatumomab; 7 patients started ponatinib after having failed an allogeneic transplant (6 hematologic relapses and 1 molecular relapse). A complete hematological and molecular remission (MRD- CR) was achieved in 6 patients (40%); notably, 4 of these 6 cases carried a gene fusion (1 *JAK2* rearrangement, 1 *ABL*-class fusion, 1 *IKZF1::DDC* and 1 *RB1::RCBTB2*); 2 further patients in hematologic relapse at the start of treatment achieved a MRD+ CR (1 patient had a *ABL*-class gene fusion). Thus, the overall response rate was 53%. Four patients were refractory, while 2 maintained a stable disease. After ponatinib-based treatment, 6 patients were allografted and 1 received a CAR-T cell infusion. The toxicity profile was mild: 3 patients developed a transaminitis, 1 also had a fungal pneumonia, and 1 an increase in pancreatic enzymes. At a median follow-up of 3 months (1-5), 10 patients are alive, 8 being in continuous complete remission.

Conclusions. Treatment with ponatinib showed promising results in terms of CR achievement in a heavily pre-treated population of Ph-like ALL patients, with an acceptable toxicity profile. In a pre-transplant setting, ponatinib was effective as a bridge to cellular therapies in 7 out of 8 patients as intention-to-treat (ITT), thus suggesting that this strategy may represent an effective bridge to further therapies. To our knowledge, this is the largest cohort of adult Ph-like ALL cases treated with ponatinib so far reported.

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