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26th Congress of the European Hematology Association

ABSTRACT BOOK

EP671 OUTCOMES BEFORE AND AFTER DOSE REDUCTION IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA RECEIVING BOSUTINIB OR IMATINIB

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Background: Bosutinib is approved for patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML), at a starting dose of 400 mg once daily (QD) in newly diagnosed patients in chronic phase (CP).
Aims: This analysis evaluated the impact dose reduction has on the outcomes of bosutinib and imatinib in patients with CP CML.
Methods: In the open-label BFORE trial, 536 patients with newly diagnosed CP CML were randomized to receive 400 mg QD bosutinib (N=268) or imatinib (N=268; 3 untreated). Dose could be reduced to 300 mg QD for toxicity. Following sponsor approval, dose reduction to bosutinib 200 mg QD was permitted for 4 weeks maximum; after this time, dose escalation or treatment discontinuation was required. Maintenance of response after dose reduction was defined as having a response >6 months after the first reduction. Database lock: June 12, 2020, 5 years after the last patient enrolled.
Results: In the bosutinib arm, dose reduction to 300 (without further reduction) or 200 mg QD was seen in 82 (31%) and 33 (12%) patients, and median time to dose reduction was 85 and 205 days. In the imatinib arm, 50 (19%) patients had a dose reduction to 300 mg QD, and median time to dose reduction was 92 days. Most common (≥2% of patients) treatment-emergent adverse events (TEAEs) leading to dose reduction were increased alanine aminotransferase (8%), thrombocytopenia (7%), diarrhea (7%), increased lipase (6%), increased aspartate aminotransferase (4%), nausea (4%), neutropenia (3%), rash (3%) and abdominal pain (2%) with bosutinib, and neutropenia (4%) with imatinib.
Of the patients who remained on 400 mg QD bosutinib (n=153) or imatinib (n=214), respectively, 120 (78%) and 139 (65%) achieved major molecular response (MMR). Among patients who had a bosutinib dose reduction to 300 mg QD, 51/82 (62%) had MMR >6 months after dose reduction: 14 (17%) maintained MMR before and after dose reduction and 37 (45%) achieved MMR for the first time after dose reduction. Seven (9%) patients had MMR before dose reduction but discontinued treatment before the next >6 months assessment. In the imatinib arm, 32/50 (64%) patients had MMR >6 months after dose reduction: 9 (18%) maintained MMR before and after dose reduction and 23 (46%) achieved MMR for the first time after dose reduction. One (2%) patient had MMR before dose reduction but discontinued treatment before the next >6 months assessment and 1 (2%) patient lost a previously attained MMR after dose reduction. Among patients who had a bosutinib dose reduction to 200 mg QD, 12/33 (36%) had MMR >6 months after dose reduction: 7 (21%) maintained MMR before and after dose reduction and 5 (15%) achieved MMR for the first time after dose reduction. Six (18%) patients had MMR before dose reduction but discontinued treatment before the next >6 months assessment. Similar trends were seen for complete cytogenetic response.
Summary/Conclusion: Management of TEAEs through bosutinib or imatinib dose reduction enabled patients to continue treatment, with a substantial number of patients achieving MMR for the first time after dose reduction.

EP672 SECOND-LINE BOSUTINIB FOR PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA: FINAL 10-YEAR RESULTS OF A PHASE 1/2 STUDY

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Background: Bosutinib is approved for patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant/intolerant to prior therapy and newly diagnosed Ph+ chronic phase (CP) CML. In a phase 1/2 study, second-line bosutinib showed durable efficacy and manageable toxicity in patients with imatinib-resistant (IM-R) or imatinib-intolerant (IM-I) Ph+ CP CML.
Aims: The final efficacy and safety analysis of this phase 1/2 study and its extension study (NCT00261846 and NCT01903733) is presented.
Methods: Patients with Ph+ CP CML who received bosutinib starting at 500 mg/day after prior treatment with imatinib only were included. This analysis was based on ≥10 years of follow-up.
Results: 19% of patients were on treatment with bosutinib at year 10, and 13% were still receiving bosutinib at study completion after ≥10 years; 19% completed ≥10 years of follow-up. Median duration of treatment and follow-up were 26 and 54 months, respectively. Median (range) dose intensity was 436 (87–599) mg/day. The most common primary reasons for permanent treatment discontinuation were lack of efficacy (unsatisfactory response or disease progression; 27%) and adverse events (AEs; 26%). In patients with a valid baseline assessment, cumulative complete cytogenetic response (CCyR), major molecular response (MMR) and MR[4] rates were 50%, 42% and 37%, respectively (Table). Responses were durable, with estimated probabilities of maintaining CCyR, MMR and MR[4] >50% after ≥10 years (Table). At 10 years, cumulative incidence of on-treatment progression/death was 24% and Kaplan-Meier (K-M) overall survival 72% (Table). 55 deaths (IM-R: n=41; IM-I: n=14) occurred on study; causes of death were disease progression (n=30), AEs (n=16; none bosutinib-related), other (n=5) and unknown (n=4). Any grade treatment-emergent AEs (TEAEs) occurring in ≥40% of patients were diarrhea (86%), nausea (46%) and thrombocytopenia (42%). Pleural effusion, cardiac and vascular TEAEs occurred in 13%, 12% and 11% of patients, respectively. 28% of patients had AEs leading to permanent treatment discontinuation; the most common (≥2% of patients) were thrombocytopenia (6%), neutropenia (2%) and alanine aminotransferase increased (2%).

Outcome after ≥10 years[a]	IM-R N=195	IM-I N=89	Total N=284
Patients with CCyR, n/N	88/182	42/80	130/262
Cumulative CCyR rate, % (95% CI)	48 (41–56)	53 (41–64)	50 (43–46)
Probability of maintaining CCyR, % (95% CI)[b,c]	61 (49–73)	52 (32–73)	58 (48–69)
Patients with MMR, n/N	58/127	25/70	83/197
Cumulative MMR rate, % (95% CI)	46 (37–55)	36 (25–48)	42 (35–49)
Probability of maintaining MMR, % (95% CI)[b,c]	55 (39–70)	54 (15–93)	56 (41–71)
Patients with MR[4], n/N	50/127	23/70	73/197
Cumulative MR[4] rate, % (95% CI)	39 (31–48)	33 (22–45)	37 (30–44)
Probability of maintaining MR[4], % (95% CI)[b,c]	55 (38–73)	52 (8–96)	56 (39–72)
Cumulative incidence of on-treatment progression/death, % (95% CI)	29 (23–36)	14 (8–23)	24 (20–30)
Overall survival, % (95% CI)[b]	71 (63–79)	73 (60–87)	72 (64–79)

Molecular data not on International Scale and not available for patients in China, Russia, South Africa and India. CCyR imputed from MMR in extension study if valid cytogenetic assessment not available on a specific date.
[a]Outcomes reported after ≥10 years: few events (e.g., initial response, loss of response and death) occurred after year 10.
[b]K-M estimates.
[c]Among responders.

Summary/Conclusion: These 10-year data are consistent with prior results of durable efficacy and manageable toxicity with second-line bosutinib and support long-term bosutinib use in patients with CP CML after imatinib failure.

EP673 TREATMENT-FREE REMISSION IN CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH LOW-DOSE TKIS. A FEASIBLE OPTION ALSO IN THE REAL-LIFE SETTING?

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Background: Long-term use of TKIs may expose patients (pts) to significant adverse events (AEs) that may affect quality of life. In recent years, treatment-free remission (TFR) has become a new therapeutic goal and is considered feasible also by international expert guidelines. Most clinical trials have indeed demonstrated that this approach is safe in CML pts who have gained a sustained DMR during treatment at a standard dose. In the real-life practice, TKI dose reductions are often required to reduce AEs but their impact on the possibility of attempting a TFR is still a matter of debate.
Aims: To explore the attitude of Italian hematologists towards the prescription of TKIs at a reduced dose and its impact on TFR attempts in CML pts.
Methods: In September 2020 a questionnaire was sent to the 54 centers participating in the Campus CML. This interactive network connects Italian Hematology specialists active in the field of CML with the aim of sharing experiences and updates for the diagnosis and treatment of this disease, the identification and prevention of specific toxicities of the drugs used and also on possible future therapeutic approaches. The online survey consisted of questions regarding the use of reduced doses of TKIs in the clinical practice and the physicians' propensity to offer a TFR to these pts.
Results: The survey was completed by 45 centers (83%). All declared to have CML pts in treatment with low-dose TKIs (total number = 1.579). More in detail, this occurred in 22.4% of pts treated with imatinib, 24.2% with nilotinib, 34.0% with dasatinib, 70.3% with bosutinib and 74.5% with ponatinib. Dose reduction was due to AEs in most cases (70%), while only in the remaining pts TKIs were de-escalated after achieving molecular milestone. Most involved hematologists believed that reduced doses of TKIs should not influence TFR attempts; indeed, this approach was offered to 117 pts. The TKI most frequently used at reduced doses prior to a TFR attempt was imatinib (60 pts), followed by nilotinib (32 pts), dasatinib (22 pts) and, to a lesser extent, by ponatinib (2 pts) and bosutinib (1 patient). Before attempting TFR, 77 pts had received only one TKI, while 33 and 7 pts were, respectively, treated in second or later lines of therapy, with a median TKI duration of 121.8 months (range 16-221.9). At the time of TFR, all pts had already achieved a DMR, with a median treatment duration of 72 months. After a median follow-up from TKI discontinuation of 25 months (range 1.6-128.7), 88 pts (75.2%) were still in TFR. The median time to molecular recurrence (≥MMR) in the entire cohort was 3.9 months (range 1.6-29.6), and a MMR or a DMR was rapidly achieved in all cases after resuming TKI therapy (median time 5.8 months, range 1–25.8).
Summary/Conclusion: In this large series of real-life CML patient management in Italy, treatment with low-dose TKI represents an important reality and, as expected, bosutinib and ponatinib are the drugs more frequently used in this setting. While a third of Italian hematologists still has some uncertainties on the feasibility of attempting a TFR after using reduced doses of TKIs outside of clinical trials, TFR is most often considered a safe option also in the real-life practice in pts treated with TKIs at a reduced dose either because of AEs or due to an optimal response already achieved. Interestingly, only about 25% of our series experienced a molecular recurrence, less than reported in pts treated at a standard dose. Consequently, TFR was not impaired by low-dose TKI regimens. Updated results will be presented.

EP674 COVID-19 IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: DISEASE OUTCOMES AND FIRST VACCINATION DATA IN RUSSIAN FEDERATION

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Background: Due to the challenge of COVID-19 pandemic the prognosis for patients (pts) with hematologic (hem) tumors, including chronic myeloid leukemia (CML), was difficult to make. With the data accumulation and vaccination start in early 2021, a view of the problem begins to change.
Aims: We aimed to describe the disease course of COVID-19, treatment and first vaccination data in pts with CML in Russian Federation.
Methods: A total of 113 CML pts were analyzed: 106 pts with lab-confirmed or suspected COVID-19 and 7 pts vaccinated against COVID-19. Registration of COVID-19 cases was done prospectively during in person or remote consultations from March 2020 till February 2021. The pts were participants of CHRONOS19, a nationwide observational cohort study of adult (≥18 y) pts with wide spectrum of hem diseases (NCT04422470). We performed a sub-analysis for CML and COVID-19 cohort with the data of 3 hem clinics regarding diagnostics, disease course, treatment and outcomes. Additionally, we evaluated the tolerability and first vaccination results in 7 CML pts (Sputnik V in civil vaccination).
Results: Case registration corresponded to incidence in the country with clear 2 "waves": 1st one in March-August (n=35) and 2nd starting from September 2020 (n=71) (fig1). COVID-19 was clinically and/or lab diagnosed and treated according to current national recommendations. CML was newly diagnosed during COVID-19 in 8(8%) pts, while 86(81%) were on treatment and 12(11%) were in treatment-free remission (TFR). One case was in pregnant pt. CML phases were chronic(CP)/accelerated/blast crisis in 95(89,6%), 6(5,4%) and 5(5%) pts respectively. Median (Me) age of pts was 52 years (range 22-75), 58(55%) were male. No CML therapy during COVID-19 was in 34 (32%) pts (interrupted or not started), therapy was held in 67 (63%), no data in 5 (5%). Disease course of COVID-19 was asymptomatic, mild, moderate and severe in 5 (5%), 59 (56%), 29(27%) and 13(12%) pts respectively. No therapy for COVID-19 was in 30 (28%) pts, symptomatic therapy (fever relief, anti-cough, decongestants, vitamins etc) - in 73 (69%) pts, antiviral drugs and antibiotics were used in 28 (26%) and 44 (42%) pts respectively. Anticoagulants, corticosteroids and IL-6 inhibitors were introduced mainly during 2nd wave while hydroxychloroquine was abandoned (fig.1). Hospitalization was in 33(31%) pts, oxygenation was applied in 12 (11%) pts. The outcomes were as follows: 101(95%) pts alive (98 recovered, 3 not yet), 4 (3,7%) pts died (2 due to COVID, 2 to CML progression), 1(1,3%) –no data. No COVID reinfection was detected so far. No factors connected with moderate/severe vs asymptomatic/mild COVID-19 were found when analyzing gender, CML phase, TFR, comorbidities, 1st and 2nd wave, except age≥52 years (p=0,039). A trend of mild disease was in pts taking TKI vs without TKI (p=0,065).
Seven CP CML pts with Me age 63 years (range 50-70) were vaccinated against COVID-19 since December 2020: 2 had the 1st shot and 5 pts completed vaccination. All 7 pts tolerated the procedure well, with no adverse effects. One pt was checked for antibodies 21 days after the 2nd shot and revealed a high level of anti-SARS-CoV-2 IgG with coefficient of positivity 6,2 (reference range 0-0,9).

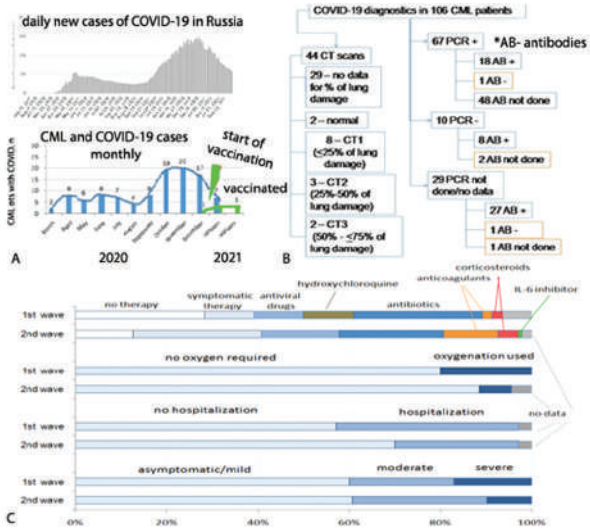

Figure 1. Incidence (A), diagnostics (B) and treatment (C) of COVID-19 in CML patients

Summary/Conclusion: The incidence, disease course and COVID-19 dependent mortality rates in CML pts seem to be similar to common population. Older age is a factor of moderate/severe disease course. The