Triplet therapy for advanced BCR::ABL1 positive myeloid leukaemias

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Main text:

Most patients presenting with chronic myeloid leukaemia (CML) are diagnosed in chronic phase (CP). With the widespread use of tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib and nilotinib, patients with CP-CML achieving optimal treatment responses can expect normal life expectancy;[1] a minority may even be able to successfully discontinue therapy.[2] However, 2-3% of patients present with de.novo blast phase (BP)-CML and a further 5% will progress to BP on treatment.[3] BP-CML is a poor prognosis myeloid, lymphoid or bi-phenotypic acute leukaemia.[4] Median overall survival (OS) from diagnosis of BP-CML is less than 12 months, and novel, effective treatment strategies are urgently sought.

Myeloid BP-CML is more common with a worse prognosis than lymphoid BP. Current treatment recommendations for myeloid BP-CML are either TKI alone or TKI with AML-type chemotherapy such as fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin (FLAG-IDA) followed by consolidation with allogeneic stem cell transplantation (alloSCT),[2] which is important for achieving an optimal response.[4]

Preclinical studies provide a strong rationale for combining TKIs with hypomethylating agents and venetoclax, with epigenetic dysregulation and abnormalities of the intrinsic apoptotic pathway seen with progression to BP-CML.[5] Recent small studies indicate that combining a hypomethylating agent (azacitidine or decitabine) with a second generation TKI or ponatinib may be effective in advanced CML, with complete cytogenetic response rates of 33-43% and median OS of 14-27 months.[6,7] However, both studies demonstrated grade 3 or higher haematological toxicity in many patients; Abaza et al, 93%,[6] and Ruggiu et al, 50%.[7]

In this issue, Short and colleagues report the results of a prospective, single centre, single arm, phase 2 clinical trial including 20 patients, combining ponatinib with decitabine and venetoclax for accelerated phase (AP; n=4)) and myeloid BP-CML (n=14) and Philadelphia chromosome-positive acute myeloid leukaemia (Ph+AML; n=2).[8] Median age at study entry was 42 years (IQR 32-58 years) with 5 patients >60 years.

14/20 patients had at least one high-risk additional cytogenetic abnormality (ACA) or complex karyotype at study entry, and 8/20 had a BCR¿¿ABL7 kinase domain mutation, including 2 patients with a T315I mutation. The starting dose of ponatinib was 45mg once daily, with standard AML dosing of decitabine and venetoclax, including venetoclax dose reductions for CYP3A4 inhibitors. Prior ponatinib wasn't an exclusion. The primary endpoint was complete response (CR) or complete response with incomplete haematological recovery (CRi) in the intention-to-treat population within two cycles of treatment. Ponatinib dose reductions were allowed according to response; reduce to 30mg on achievement of CR/CRi and 15 mg with undetectable BCR¿¿ABL7 transcripts.

The median number of cycles received was 2.5 (IQR 1-3.5). The CR/CRi rate was 50% (5% CR and 45% CRi). Neither patient with Ph+AML responded. In the myeloid BP cohort, median OS was 10.8 months. The most common grade 3-4 non-haematological adverse events were febrile neutropenia (40%), infection (30%) and elevated transaminases (25%). No haematological or non-haematological adverse events met the criteria for a dose-limiting toxicity. Ten patients (50%) required at least one dose reduction of at least one study drug (decitabine n=3, venetoclax n=8, and ponatinib n=3; excluding protocol-mandated ponatinib dose reductions) due to toxicity. Eight patients proceeded to alloSCT, and of these 4 received post-transplant maintenance ponatinib 15mg. Four patients were alive at last follow-up in continuing remission and of these, 3 were post-transplant.

Since the clinical trial by Short et.al completed recruitment, the WHO classification of CML has been revised with the removal of AP-CML, making CML a bi-phasic rather than tri-phasic disorder.[9] AP-CML patients with 10-19% blasts or high-risk ACAs are now classified as high-risk CP-CML. Although only a minority of patients in this trial (n=4/20), these patients had a better outcome (1 CR and 3 CRi) as compared to myeloid BP-CML (n=14/20; 0 CR and 6 CRi). Given the good outcomes for AP-CML patients, it should be considered whether these patients would have been candidates for TKI alone, limiting treatment-related toxicity.

Despite differences in the study populations and definitions of response, the median OS of 10.8 months for this study is similar to that of MATCHPOINT which combined ponatinib with FLAG-IDA chemotherapy (median OS 12 months).[10] It remains clear that alloSCT is an effective consolidation therapy for BP-CML, and should be considered in all eligible patients. Post-transplant maintenance TKI looks to have utility, but further studies with longer follow-up are required.

In conclusion, results from Short et.al suggest that a triplet of hypomethylating agent, venetoclax and ponatinib holds promise for patients with myeloid BP-CML. It improves treatment choice, especially for older, frailer patients and will be attractive to patients as can be delivered as out-patient therapy, but haematological and cardiovascular toxicity remain a concern. A further study of ponatinib with azacitidine (PONAZA; NCT03895671 www.clinicaltrials.gov), currently in follow-up will perhaps delineate the added benefit of venetoclax in myeloid BP-CML.

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