Efficacy of combining dasatinib and intensive chemotherapy for patients with chronic myeloid leukemia in blastic transformation

by Dragan Milojkovic, Amr Ibrahim, Alistair Reid, Letizia Foroni, Jane Apperley, and David Marin

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Efficacy of combining dasatinib and intensive chemotherapy for patients with chronic myeloid leukemia in blastic transformation

The prognosis of patients with chronic myeloid leukemia (CML) has improved considerably over the last ten years with the introduction of ABL tyrosine kinase inhibitors (TKI) into clinical practice. TKIs induce complete cytogenetic remissions (CCyR) in 10-45% of patients who are treated with these drugs in advanced phase with minimal toxicity, unfortunately these remissions are typically short lasting.\textsuperscript{1,2} Dasatinib alone induces CCyR in 20-40% of patients,\textsuperscript{2,3} however the majority relapse within 1 year and the median survival is 8 months.\textsuperscript{2} Conventional chemotherapy regimens such as FLAG-IDA can induce CCyR in 30-40% of patients who have progressed to blastic phase, but again most patients relapse within 6 months and the survival is poor.\textsuperscript{4} A logical approach might be to combine both strategies in order to improve the outcome. The proposed schedule of combination TKI and chemotherapy is supported by two clinical observations: a number of chemotherapeutic agents commonly used in the management of blastic phase CML have been shown to have synergism with a TKI (e.g. cytarabine)\textsuperscript{5-8} and TKIs have been used successfully in combination with conventional chemotherapy for the therapy of Ph+ ALL.\textsuperscript{9} We report our experience of dasatinib/FLAG-IDA chemotherapy in 4 CML patients who progressed to blastic phase while on imatinib.

The four patients received first-line imatinib for 11, 7, 26 and 10 months respectively, before progressing to blastic phase. Table 1 shows the patient characteristics. Patients received two courses of FLAG-IDA (G-CSF 300μg/day sc days 0 to 6, fludarabine 30mg/m\textsuperscript{2} iv days 1 to 5, cytarabine 2g/m\textsuperscript{2} iv days 1 to 5 and idarubicin 12mg/m\textsuperscript{2} iv, days 1 to 3) together with dasatinib 100 mg daily. Dasatinib was administered continuously from day 0 of the first course of chemotherapy. The combination was fairly well tolerated (see table) and all patients recovered a neutrophil count >1 x 10\textsuperscript{9}/L within 30 days of the start of combination therapy.

After the first course of chemotherapy all patients achieved morphological remission (95CI 40-100%); one achieved major cytogenetic response and the remaining three achieved both CCyR and major molecular response (MMR). The patients who failed
to achieve CCyR after the first course of chemotherapy achieved CCyR and MMR after the second cycle. Currently all four patients are alive; Patients 1, 2 and 3 have undergone allogeneic stem cell transplantation (continuing remission 3, 12 and 13 months post transplant) and patient 4 is scheduled to do so shortly. Dasatinib was reintroduced on day +30 after the transplant in all 3 patients with good tolerance. We have shown that dasatinib can be safely combined with conventional chemotherapy and although this approach should be tested in a larger number of patients the combination seems to induce deep remissions in patients with CML in blastic phase allowing for further therapeutic strategies to enable a continuing response.

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Conflict of interest

The authors declare no conflict of interest.
References


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<th>Cytogenetics</th>
<th>BCR-ABL/ABL (%)</th>
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*Patient 2 harboured the ABL kinase domain mutation E459K at the time of starting chemotherapy. Dasatinib was permanently discontinued on day +16 of the first course of chemotherapy due to HRCT chest abnormalities later attributed to a fungal infection.

# Dasatinib was interrupted during the second cycle of chemotherapy due to the development of pleural effusions but was uneventfully reintroduced at a reduced dose of 70mg after three weeks.