SPECIAL EDITION

Treatment free remissions are feasible in patients with chronic myeloid leukemia who obtain a deep molecular response on dasatinib

T. Feys, MSc, MBA

A current area of intensive research in chronic myeloid leukemia (CML) is the achievement of a sustained, deep molecular response (DMR) with tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL fusion protein. The ultimate goal of this approach is to discontinue therapy with the TKI and enter a phase of treatment-free remission (TFR).[1] Several clinical studies are evaluating TFR in patients with chronic phase CML (CML-CP) and a stable deep molecular respons (DMR) on TKI therapy.[2] These studies indicate that roughly 40 to 60% of patients discontinuing TKIs maintain their molecular responses and almost all patients who relapse after stopping the TKI regain their response when the treatment is restarted.[2] Dasatinib is an established, second-generation TKI that induces high rates of early, deep, and sustained molecular responses.[3] This makes dasatinib an interesting option for health care professionals who are considering TFR for their patients. During the 2017 annual meeting of the American Society of Hematology (ASH), *Shah et al.* reported the results of the DASFREE study, a trial investigating TFR in patients with CML-CP and a sustained deep molecular response (DMR) for at least 1 year, discontinuing dasatinib in the first line and beyond.[4]

(BELG J HEMATOL 2018;9(1):26-7)

DASFREE is a phase 2, open-label, single-arm study in adults with CML-CP on dasatinib for at least 2 years as 1st-line or subsequent therapy. To be eligible for the study, patients had to be in a dasatinib-induced DMR ($MR^{4.5}$ or BCR-ABL1 ≥0.0032% on the International Scale) for at least 1 year prior to enrollment. During the screening phase, $MR^{4.5}$ was confirmed at a central lab twice within 3 months prior to dasatinib discontinuation. BCR-ABL1 was monitored centrally after discontinuation every month during the 1st year and every 3 months thereafter. If a major molecular response (MMR) was lost, patients resumed their dasatinib treatment at the previous dose. The primary endpoint of the trial was the rate of MMR 1 year after the dasatinib discontinuation, while secondary objectives included BCR-ABL1 kinetics, event-free survival (EFS or MRFS defined as survival without loss of MMR), relapse-free survival (RFS; defined as survival without loss of MMR, complete cytogenetic response [CCyR], or complete hematologic response [CHR], or progression to accelerated/blast phase [AP/BP] CML), AP/BP transformation rate, progression-free survival (PFS), and overall survival (OS).[4]

The study enrolled a total of 84 patients and at the time of the analysis, all patients had at least 1 year of follow-up. The median age of patients in the trial was 52 years, 56% was male and 81% had an ECOG performance score (PS) of 0. Forty-four percent of patients received dasatinib as first-line therapy and the median time from diagnosis to treatment discontinuation was 69 months (ranging from 29 to 244 months). The median dasatinib dose at the time of treatment discontinuation was 100 mg. In total, 5 patients (6%) discontinued the study: 2 while maintaining a MMR off treatment due to relocation and 3 while being on treatment after restarting dasatinib.[4]

One year after stopping dasatinib, 48% of patients maintained a MMR. Of the patients who received dasatinib as first line therapy, 54% retained their MMR 1 year after stopping

Ariez International, Ghent, Belgium

Please send all correspondence to: T. Feys, Ariez international, Oude Houtlei 118, 900 Ghent, E-mail: t. feys@ariez.com, Tel: 0479/567890

Conflict of interest: The selection of the abstracts discussed here is the sole responsibility of the publisher and was not influenced by third parties.

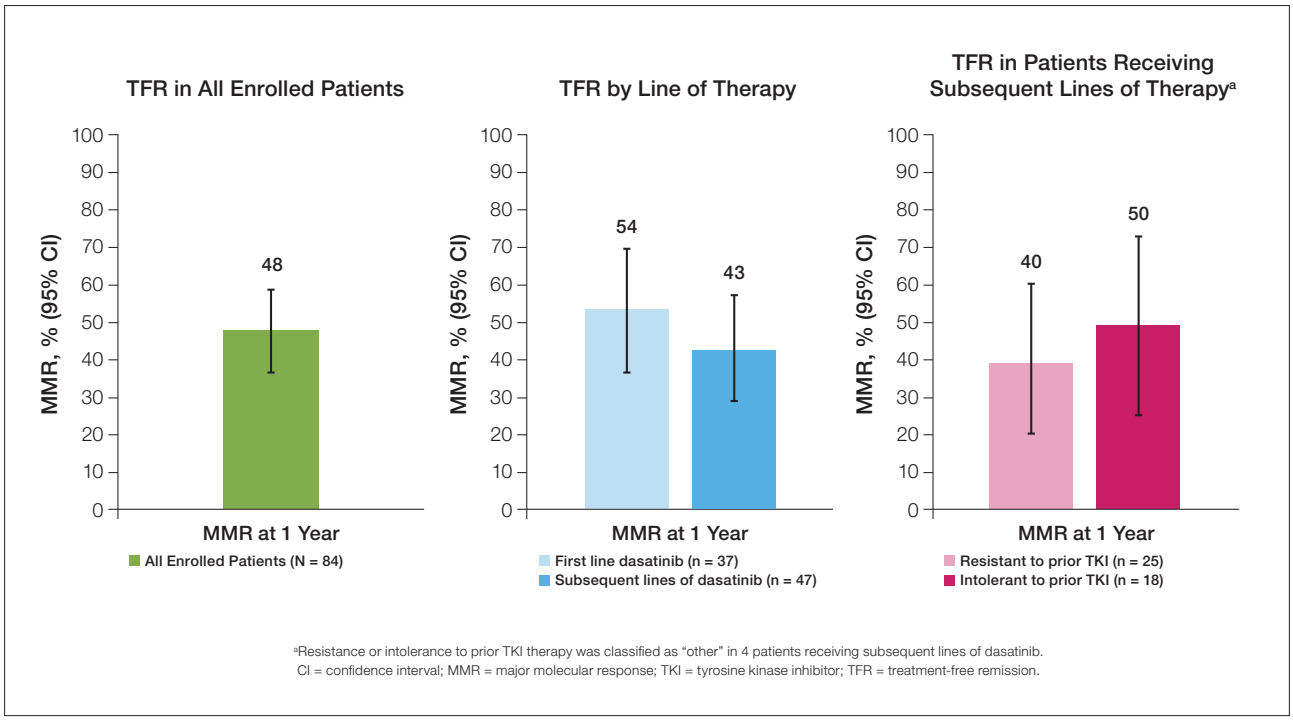

FIGURE 1. TFR 1 year after stopping dasatinib in the DASFREE trial.[4]

therapy as compared to 43% of the patients who received dasatinib in a subsequent treatment line (*Figure 1*).

The molecular RFS rate at 1 year was 49% (54% among 1st line cohort and 45% in subsequent group). Loss of CCyR, or CHR was not seen and not a single case of AP/BP transformation or death was reported. The median time from TKI discontinuation to loss of MMR was 3.93 months. In total, 43 of the 44 patients who lost their MMR restarted treatment with dasatinib. All evaluated patients (N=42) regained a MMR and in 90% (38/42) of the cases a MR[4.5] was achieved after restarting dasatinib. The median time to regain a MMR, or MR[4.5] was 1.89 and 3.25 months, respectively.

In a next step, researchers evaluated the effect of the time on TKI prior to dasatinib discontinuation. This analysis revealed that the range of time on prior TKI was similar for patients who lost or maintained a MMR, regardless of the treatment line in which dasatinib was given. Additional statistical analyses also revealed no significant association between RFS and sex, age, prior therapy line or Sokal score.[4]

Most adverse events (AEs) occurred off-treatment, although not all were attributable to withdrawal events. Musculoskeletal disorders were reported in 19 patients (23%) off-treatment. In 8 patients (with a total of 15 events) these were considered to be withdrawal syndrome. Withdrawal events occurred after a median of 3 months (range <1 – 6 months) after discontinuation. Nine of these events resolved after a median of 3 months (range 1-9), 4 prior to restarting dasatinib and 5 on, or after restarting therapy. Seven of the nine resolved withdrawal events resolved spontaneously without the use of medication (other than TKI). At the time of analysis, all 6 unresolved withdrawal events were grade 1 and did not require therapy. Interestingly, hypertension occurred in 6 pts (7%) off-treatment. There were no AEs leading to discontinuation from the trial.[4]

In summary, in the presented study, 48% of patients with CML-CP in DMR on dasatinib who discontinued TKI therapy maintained a TFR 1 year after discontinuation. The MMR rates at 1 year were similar for patients on first-line (54%) and subsequent lines of dasatinib (43%). Importantly 100% of evaluable patients who lost MMR quickly regained their response after therapy was reinitiated (median time to regain MMR was 1.9 months). Only 9.5% of patients reported symptoms of dasatinib withdrawal, and most of these events resolved without concomitant therapy. As such, this dasatinib discontinuation trial strongly supports the feasibility of TFR in patients with CML-CP in DMR treated in first line and beyond.

REFERENCES

1. Hughes T, et al. Blood. 2016; 128:17-23.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Chronic Myelogenous Leukemia (Version 2.2018).
3. Cortes JE et al. J Clin Oncol. 2016;34:2333-2340.
4. Shah N, et al. Presented at Ash 2017; Abstract 314.