memo (2019) 12:196–199
https://doi.org/10.1007/s12254-019-00529-4

memo
magazine of european medical oncology

CML at the 2018 ASH meeting—selected presentations

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Published online: 20 September 2019

Summary Treatment recommendations in chronic myeloid leukemia (CML) treatment have not changed substantially since treatment-free remission (TFR) has become a therapeutic option. Hence, allowing more patients to enter TFR is gaining significance. Although, Asciminib as a first-in-class new type of tyrosine kinase inhibitor (TKI) is in clinical development, currently combination treatment with TKIs and Interferon-alpha2b appears the best option to deepen molecular response and broaden the basis of potential TFR candidates. Improving the chances of a first successful TFR has to be the primary goal in TFR optimization as even re-induction of a deep molecular response after TFR failure using second generation TKIs shows disillusioning results.

Keywords Treatment · TKI, tyrosine kinase inhibitor · Interferon · TFR, treatment-free remission · Asciminib

Take-home message

- Combination therapy of nilotinib and interferon-alpha2b increases the depth of molecular response compared with tyrosine kinase inhibitor (TKI) monotherapy.
- Early data from the TIGER trial support a higher probability to remain in TFR after TKI-interferon combination treatment
- Using a second-generation TKI for re-induction of deep molecular response after TFR failure does not relevantly improve the moderate chances for a successful second TFR.

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Treatment for chronic myeloid leukemia (CML) has been standardized by the introduction and further development of the European Leukemia Net (ELN) [1–3], National Comprehensive Cancer Network (NCCN) [4], and European Society for Medical Oncology (ESMO) [5] recommendations for tyrosine kinase inhibitor therapy. These guidelines focus on molecular response kinetics as measure of treatment efficacy from which timelines and milestones were derived.

The mainstay of this approach is a continuous TKI treatment until molecular relapse occurs. By blocking BCR-ABL1 activity, a well-controlled state of minimal-residual disease can be achieved in most patients treated. The high level of efficacy of this approach is reflected in a statistically normal life expectancy for TKI-treated CML patients [6–8]. Upon treatment failure or intolerability issues, the five approved TKIs are used sequentially. However, owing to a lack of prospective trials there is no consensus on the optimal TKI sequence. Imatinib is generally considered the TKI with the best safety profile and is in many settings still preferred for front-line therapy [9]. Pharmacoeconomic reasons might contribute to this pattern of usage since imatinib is available as a generic drug. Second-generation TKIs with higher potency are often chosen for front-line treatment in high-risk settings or for second- and later-line therapy after treatment failure or intolerability of imatinib. In those cases, the choice of TKI is based on a risk–benefit assessment of the TKI-specific safety profiles and the comorbidity spectrum of the individual patient.

The concept of continuous treatment has been challenged by a considerable number of trials demonstrating that about half of patients who have reached a deep molecular response (DMR, as defined by MR 4.0 or deeper) do not relapse with overt leukemia even if treatment is discontinued. In some patients remaining in treatment-free remission (TFR), BCR-

ABL1 transcripts seem to fluctuate below the level of MR3 [10, 11], which supports the idea that after TKI discontinuation an endogenous and still unknown mechanism is sufficient to control CML at such a low level of residual disease. Treatment-free remission has since been incorporated in CML treatment recommendations as an option for patients who have reached and maintained a deep molecular remission under TKI treatment. Therefore, one issue in current clinical research in CML is to define the optimal prerequisites for TFR and improve TKI treatment in order to increase the number of potential TFR candidates. Analyses of TFR trials identified several prognostic factors for successful TFR approaches such as time of TKI treatment, level of molecular response, and time in deep molecular remission [12, 13].

Regarding the chances of a successful second TFR after failing a first one, Legros and colleagues [14] had shown earlier that the probability for a successful TFR is considerably lower in the second attempt than in the first. However, in this trial imatinib was used in the majority of cases for re-induction of a DMR while a minority of patients received second-generation TKIs (nilotinib $n=13$, dasatinib $n=7$). The importance of a successful first attempt for TFR was corroborated by the results of the TRAD trial [15] presented at the 2018 ASH meeting. A total of 155 patients were enrolled in this trial. Of these patients, 131 discontinued imatinib treatment after a median of 9.18 years (3.01–17.53 years) and a median duration of deep molecular response (MR 4.5) of 5.08 years (2.16–11.80). At 12 months, 69.9% of patients were still in MMR (MR 3.0), while 57 patients lost it and 55 of those were treated with dasatinib to re-induce DMR. The majority ($n=47/49$) of patients achieved again a DMR (MR 4.5) and 26 attempted a second TFR. Only 21 of 26 (21.5%) remained in at least MMR at month 6 after discontinuation of dasatinib. Similar results, namely, a second TFR rate of 35.7% of patients remaining in MMR after a median time of 5.3 months (range, 2–42 months), were reported earlier by Legros et al. Therewith, the chance of a patient to successfully remain in a second TFR after failure of a previous one is only half that of the initial chance. TFR is of particular interest for young CML patients who by remaining in TFR would be spared many years of treatment and potential adverse effects. However, these rather disillusioning data on successful second TFR attempts support that all efforts should be undertaken to optimize the chances for a first TFR. Since duration of DMR is a prognostic marker for TFR and success rates increase further with every year in DMR, patience to start TFR could be a simple approach to improve TFR success rates.

Driven by the notion that some interferon-treated patients in the pre-TKI era had shown long-lasting remissions, several clinical trials investigated both depth of molecular response reached and the proportion of patients reaching DMR under a combined TKI and interferon treatment.

Two trials, the Australian ALLG CML 11 Pinnacle study [16] and the German TIGER study [17], were presented at the 2018 ASH meeting. Both studies combined interferon and nilotinib. The Australian design incorporated a 21-month combined treatment period between an initial 3-month nilotinib monotherapy prior to a continuing single nilotinib treatment. The German TIGER trial randomized a continuous nilotinib first-line treatment for 36 months against a 24-month combination therapy followed by a 12-month interferon maintenance. Nilotinib dosing was 300 mg bid in both trials, and interferon-alpha2b was given at doses of 30–50 mcg per week and 50 mcg per week in the Pinnacle trial and the TIGER trial, respectively. The patient cohorts were well comparable regarding the Sokal risk score: 56% and 56.6% of patients had an intermediate or high Sokal score in the Pinnacle and TIGER trial, respectively. While both trials investigated the depth of response (TIGER trial: MMR at 18 months, Pinnacle trial: MMR at 12 months and MR 4.5 at 24 months), the TIGER trial had an optional discontinuation phase included to determine the rate of successful TFR in both arms after maintenance. Several clinical trials using nilotinib as frontline therapy had shown a high level of efficacy and its superiority to imatinib. In the ENEST series of studies, molecular response rates ranged from 55% to 70.8% for MMR rates at 12 months and from 25% to 38.6% for MR 4.5 at months 24. The combination treatment in the PINNACLE trial reached an MMR rate at 12 months of 78.3% and a DMR of 50.9% (MR 4.5 at month 24). The calculated probability for remaining in TFR at month 18 was 75% in the TIGER trial cohort. This compares favorably with 48.9% and 51% of patients remaining in TFR at 24 months in the ENEST Freedom trial [18] and the EURO-SKI study [12], respectively.

In an earlier phase II trial, 30% of patients achieved a DMR level of MR 4.5 after 12 months of combined dasatinib with interferon-alpha2b treatment in frontline CML therapy [19]. In view of 3% and 16% of patients reaching the same response level in the DASISION [20] and SPIRIT2 trials, respectively, the dasatinib–interferon combination appears to be superior to a monotherapy (cited in; [21]). Prior to combining interferon with second-generation TKIs, an imatinib–interferon-alpha2a combination was investigated against the imatinib monotherapy by Preudhomme and colleagues [22]. At 12 months, MMR rates in the combination therapy cohort were clearly higher (57% vs. 38%) than in the imatinib-only cohort and the benefit translated into higher rates of undetectable BCR-ABL1 levels at 24 months in the combination treatment arm (16% vs. 9%). While adverse effects led to discontinuation of the interferon-alpha2a combination treatment in the majority of cases in this early combination trial, the profile in the dasatinib–interferon-alpha2b combination was assessed to be manageable with 6/40 treatment discontinuations and most adverse events (AEs) being of grade 2–3. The recently presented data on nilotinib–interferon-alpha2b combination showed a discontinuation rate of 10.6% and required interferon dose reduction in 50% of cases.

The future role of interferon in CML will depend on whether or not a good management of interferon dosage and AEs will allow for successful combination treatment in a such a proportion of patients that the number of TFR candidates considerably increases and thus outweighs the interferon-related risks. The potential to reduce adverse events associated with continuous TKI treatment (vascular events, pleural effusions, low-level AEs, potentially relevant renal dysfunction [23]) further supports TFR as an important aim in CML treatment.

The primary goal in treatment of any malignancy is disease eradication. However, in CML no such approach is close to clinical development. Asciminib is a first-in-class new type of TKI, which provides a different mutation resistance profile and, thus, complements the mutation-resistance profiles of conventional TKIs. While all of the approved TKIs target the ATP-binding site of the BCR-ABL1 fusion protein, asciminib interferes in an allosteric manner with the myristate-binding site. Therewith, the fusion molecule is kept in an inactive conformation. At the 2018 ASH meeting, early efficacy data on asciminib monotherapy in T315I-mutated CML patients were presented [24]. A total of 32 patients enrolled in this single-arm trial were treated with 200 mg asciminib bid and 75% of patients achieved a complete cytogenetic response after 24 weeks of treatment. However, molecular response rates dropped from 61.5% to 17.6% when comparing ponatinib-naïve and -pretreated patients, respectively. The safety profile was considered to be well tolerable as reflected in a low discontinuation rate of only 3/32 patients. Registered AEs were mostly of grade 1–2. Asciminib might become an alternative to ponatinib for T315I-mutated CML patients and could provide a second-line approach after ponatinib failure for some of these patients.

Funding The author received research grants and/or honoraria from Incyte, Pfizer, BMS, AOP, Novartis.

Conflict of interest S. Schmidt declares that he has no competing interests.

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