Predictors of Success in Treatment-Free Remission: A Single Centre Experience

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Background

- For patients meeting specific clinical criteria, a trial of TKI cessation is a safe option if regular quantitative RT-PCR (qRT-PCR) monitoring is performed and TKI recommencement is prompt in the event of molecular relapse [Mahon, *Lancet Oncology* 2010; Ross, *Blood* 2013].
- While the safety of TFR has been established [Mahon, *Lancet Oncol* 2010; Ross, *Blood* 2013], the ability to predict success following attempted TFR remains limited.
- Recent publication of Euro-Ski [Saussele, *Lancet Oncol* 2018], the largest tyrosine kinase inhibitor (TKI) cessation study to date, demonstrated that duration of MR4 (BCR-ABL1 <0.01% IS) prior to attempted TFR was the main factor predicting TFR success.

Aims

- To determine the proportion of patients becoming eligible for a TFR attempt.
- To determine the proportion of patients attempting TFR.
- To identify predictors of successful TFR.

Patients and Methods

- All adult patients receiving their primary CML management at the Royal Adelaide Hospital were included.
- History of blast crisis, allogeneic stem cell transplantation and non-quantifiable atypical BCR-ABL1 transcripts precluded TFR qualification.
- Clinical and molecular data from January 2008 to March 2018 were analysed.
- Minimum criteria at our centre for qualifying for a TFR attempt was:
 - TKI therapy of ≥ 3 years
 - Sustained deep molecular response (DMR) ≥ 2 years (BCR-ABL1 <0.0032% IS; MR4.5).

Figure 1: Cumulative incidence of TFR qualification, TFR attempts and durable TFR

Figure 2: Forest plot of multivariate analysis of factors predicting TFR success at 12 months

Table 1: Characteristics of patients attempting TFR (n = 96)

Variable	Median (%/range)
Age at diagnosis	53 (24-76)
Age at TFR attempt	61 (34-90)
Sex	
Male	53 (55%)
Female	43 (45%)
Time from diagnosis to TFR attempt (yrs)	8.1 (3.1-21.0)
Duration of TKI therapy (yrs)	7.45 (3.0-15.8)
Transcript	
e14a2	42 (44%)
e13a2	35 (36%)
Both transcripts	18 (19%)
e1a2	1 (1%)
Sokal score	
Low	38 (40%)
Intermediate	38 (40%)
High	14 (15%)
Early molecular response (EMR; BCR-ABL1 <10% at 3 months)	72 (75%)
Major molecular response (MMR) at 12 months	72 (75%)
Duration of MR4 prior to TFR attempt (yrs)	4.7 (2.3-11.6)
Duration of MR4.5 prior to TFR attempt (yrs)	3.3 (2-10.8)
Time to MR4 from TKI commencement (yrs)	1.5 (0.2-11.0)
Time to MR4.5 from TKI commencement (yrs)	2.6 (0.2-13.5)
Halving-time of BCR-ABL1 from baseline to 3 months post TKI commencement (dys)	14.5 (6.2-128.9)

- Monthly BCR-ABL1 was instituted for a minimum of 12 months for all patients embarking on a trial of cessation.
- Molecular relapse was defined as a loss of major molecular response (MMR) as per current recommendations (single BCR-ABL1 value $\geq 0.1\%$ IS).
 - Twenty patients were enrolled in the TWISTER trial where restart criteria was presence of detectable rising BCR-ABL1 levels in 2 consecutive tests.
- Durable TFR was defined as no molecular relapse ≥ 12 months after TKI cessation

Results

- 298 patients were treated at our institution within the defined time frame; 280 patients qualified for inclusion into our retrospective analysis.
- TFR eligibility was attained in 114 patients and 96 (84%) attempted TFR.

- Of the 82 patients with >12 months of follow-up, 52% (n=43) remain off TKI at 12 months in MMR.
- The demographics of patients attempting TFR are detailed in **Table 1**.
- An increasing proportion of patients became eligible for TFR with longer duration of TKI exposure, from 16% at 4 years compared to 61% at 14 years (see **Figure 1**).
- Variables were assessed by univariate Cox proportional hazards regression analysis for their association with TFR.
- The most significant finding was that patients attempting TFR with e14a2 BCR-ABL1 transcripts were more likely to remain in TFR at 12 months (65%; n=24/37) in comparison to the e13a2 transcript (34%; n=10/29), p = 0.008.
- This advantage also translated to patients with both e14a2 and e13a2 transcripts when grouped with the e14a2 cohort and compared with e13a2 alone, p = 0.006.
- The negative effect of the e13a2 transcript was further confirmed on multivariate analysis (see **Figure 2**).
- Patients with sustained MR4.5 >3.4 yrs prior to cessation were more likely to remain in TFR at 12 months (42 vs. 64%, p = 0.014).
- Cumulative incidence curves of all 280 patients in our analysis demonstrated that by 6 yrs of TKI therapy, 70% of patients with e14a2 transcripts achieved MR4.5 whereas only 52% of patients with e13a2 transcripts attained MR4.5; confirming that patients with e14a2 transcripts are more likely to achieve DMR earlier. Furthermore by 8 yrs, 48% of patients with e14a2 transcripts became eligible for a TFR attempt compared with only 32% of e13a2 transcripts. While patients with e13a2 transcripts eventually achieve the same frequency of MR4.5 as the e14a2 group, the earlier achievement of MR4.5 in e14a2 patients may have contributed to the difference in TFR success.

Conclusion

- TFR in published literature is achieved in 40-50% of cessation attempts for patients who meet the qualification criteria and these figures are in line with our real-world experience.
- The factors that we identified as most predictive for TFR success were duration of MR4.5 and the presence of the e14a2 transcript.
- We also observed earlier achievement of MR4.5 in the e14a2 cohort, consistent with other studies [Jain, *Blood* 2016]. These observations, taken together, raise important questions about the impact of transcript type on disease biology, drug sensitivity, and immunological response which warrant further investigation.
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