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POSTER ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Treatment Free Remission (TFR) "for" Pregnancy. Overview and Outcome of Pregnancies Reported in the Italy-Tfr Registry

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TFR is a consolidated practice and the goal to be reached for all CML patients. In Italy only a few centers participate in TFR clinical trials, while, in clinical practice, many patients discontinue TKIs for intolerance, pregnancy, or other reasons. A cohort of 467 Italian patients who underwent discontinuation outside of clinical trials were collected in the Italy TFR registry. This cohort showed a mean TFR rate of 73% at 12 months.

Italy-TFR is an observational study, both retrospective and prospective, with the purpose of collecting data on patients with Ph+, chronic phase CML who discontinue TKIs in an off-protocol setting. Eligibility criteria include patients treated with TKI monotherapy or in association with other drugs (IFN, BCR:;ABL1 peptidic vaccine, and others) and those who discontinued therapy for any reason. Deep Molecular Response (DMR) defined as MR4 (BCR::ABL ratio $\leq$ 0.01% IS), MR4.5 ($\leq$ 0.0032%) or MR5 ($\leq$ 0.001%) was confirmed at least three times before TKI discontinuation.

Data from patients discontinuing in less than DMR were collected and analyzed separately.

Molecular responses were assessed by qPCR; tests were performed by the GIMEMA Laboratories Network (LabNet). TFR was assessed using the Kaplan-Meier method and 95% confidence interval, from the date of TKI discontinuation to the date when therapy was reinitiated.

Patients discontinuing for pregnancy were analyzed in this sub-analysis. Thirty patients and 33 pregnancies (3 patients had 2 pregnancies) were entered from 8/32 participating centers.

Main data are reported in Table 1. Median age at diagnosis was 28 years (range 19-36), and 35 years at pregnancy (range 29-41). Fifteen patients switched from 1st to 2 ndG TKI before pregnancy due to intolerance or resistance/unsatisfactory responses. Only one patient switched to another TKI to deepen the response before attempting a second pregnancy (imatinib to nilotinib).

Not all patients at TKI interruption were in DMR, however, they were all treated with the last TKI for a median of 60 months (range 18-151), and exposed to any TKI for a median of 89 months (range 44-186). Specifically, 9/33 pregnancies started in MMR ($\leq$0.1% transcript), 13 in MR4, 6 in MR4.5, and 5 in MR5. Three patients stopped TKI therapy before conception, two at 5 months and 1.5 months, respectively, before pregnancy. The third patient, in TFR after the first pregnancy, conceived a second child while still in TFR. These 3 patients were in TFR for 9, 9 and 5 years after treatment stoppage.

During pregnancy 4 patients were treated after losing MMR. One patient, in MR5 with imatinib for 4 years rapidly lost MMR and was treated with a peptidic vaccine, maintaining complete cytogenetic remission until delivery; 2 patients were treated with IFN, and 1 restarted nilotinib at 23 weeks.

All 33 pregnancies were carried to term, with unremarkable outcomes for mothers and babies. No CML progression was recorded. Breastfeeding was allowed for patients with stable transcript levels.

With a median follow-up of 40 months, 11 patients were still in TFR (33%; 48% at 12 months), with no differences for patients treated with imatinib or a 2 ndG TKI. The lower number of patients maintaining TFR compared with the general population of patients studied can be explained by 3 main considerations.

First, 9/33 pregnancies started in MMR, which is not a criteria that allows for discontinuation, the kinetics of transcript rise are often not correlated with molecular remission. Second, the biological clock in women can rush conception attempts before the appearance of a consolidated response (also resistant patients). Third, as demonstrated in the main study, older age is the only statistically significant positive prognostic factor, with a higher risk of relapse for younger patients.

Indeed, all patients restarting treatment regained at least MMR within 3 months. Except for the patient described earlier, and a patient who had a suboptimal response to the 2nd line and switched to bosutinib 3rd line, patients recommenced the same TKI discontinued before pregnancy.

There was no significant difference in TFR between patients who discontinued imatinib 1 st versus 2 nd lines (Fig.1) and also in patients who discontinued 2 ndG TKI frontline versus 2 nd line for intolerance/resistance unsatisfactory response.

The Italy-TFR protocol is still enrolling in the prospective cohort and updating. We plan to include more cases and present an exhaustive analysis.

Disclosures Abruzzese: *Incyte:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy; *Takeda:* Consultancy; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Trawinska:** *novartis:* Membership on an entity's Board of Directors or advisory committees. **Cavazzini:** *Novartis:* Honoraria; *Incyte:* Honoraria; *Pfizer:* Honoraria.

TABLE 1	N	TKI di 1a generazione	TKI di 2a generazione	Overall	Test Statistic
Age at CML diagnosis	30	(N=18)	(N=12)	(N=30 patients/33 pregnancies)	F1,23=1.93, P=0.183
Median (interquartile range)		30.0 (25.0—31.3)	25.5 (23.4—29.0)	28 (24—31)	
Range		21—32	19—36	19—36	
Age at pregnancy TFR	33				F1,23=0.49, P=0.493
Median (interquartile range)		35.0 (33.7—37.0)	33.5 (30.4—38.0)	35.0 (31.7—37.3)	
Range		30—39	29—41	29—41	
Sokal Score	24				X_2=0.58, P=0.752
High		1/13 (7.692)	1/11 (9.091)	2/24 (8.333)	
Intermediate		3/13 (23.077)	4/11 (36.364)	7/24 (29.167)	
Low		9/13 (69.231)	6/11 (54.545)	15/24 (62.500)	
ELTS	16				X_2=0.74, P=0.692
High		0/6 (0.000)	1/10 (10.000)	1/16 (6.250)	
Intermediate		1/6 (16.667)	1/10 (10.000)	2/16 (12.500)	
Low		5/6 (83.333)	8/10 (80.000)	13/16 (81.250)	
Transcript type	22				$X_{2\text{-}1}$=0.00, P=1.002
b2a2		2/11 (18.1818)	2/11 (18.1818)	4/22 (18.1818)	
b3a2		9/11 (81.8182)	9/11 (81.8182)	18/22 (81.8182)	
e1a2		0/11 (0.0000)	0/11 (0.0000)	0/22 (0.0000)	
Last TKI before pregnancy	33*				X_2=25.00, P<0.012
Imatinib generator		10/11 (90.909)	0/19 (0.000)	10/33 (30.303)	
Imatinib generico		1/11 (9.090)	0/19 (0.000)	1/33 (3.030)	
Nilotinib		0/11(0.000)	14*/19 (73.684)	14/33 (42.424)	
Dasatinib		0/11 (0.000)	6/19 (36.842)	7/33 (24.242)	
TFR at pregnancy		0/11 (0.000)	na	1/33 (3.030)	
Therapy line, at pregnancy	33				X_2=12.75, P<0.012
1		11/11 (100.000)	4/19 (21.052)	15/33 (45.454)	
2		0/11 (0.000)	14/19 (73.684)	14/33 (42.424)	
3		0/11 (0.000)	1/19 (5.263)	1/33 (3.030)	
TFR at pregnancy		0/11 (0.000)	2/19 (10.526)	3/33 (9.090)	
Molecular response (MR) at TFR	33				$X_{2\text{-}3}$=3.20, P=0.362
< MMR		0/11 (0.000)	0/22 (0.000)	0/33 (0.000)	
MMR		3/11 (27.272)	6/22 (27.272)	9/33 (27.272)	
MR4		4/11 (36.363)	9/22 (40.909)	13/33 (39.393)	
MR4.5		2/11 (18.181)	4/22 (18.181)	6/33 (18.181)	
MR5		2/11 (18.181)	3/22 (13.636)	5/33 (15.151)	
Time of administration of last TKI	25				F1,23=4.39, P=0.053
Median (interquartile range)		70.0 (58.3—93.3)	45.0 (26.8—77.5)	60.0 (40.0—91.0)	
Range		32—151	18—143	18—151	
Time of exposure to any TKI	10				F1,8=0.25, P=0.633
Median (interquartile range)		79.5 (70.0—89.0)	93.5 (61.0—126.9)	89.5 (67.0—112.4)	
Range		70—89	44—186	44—186	
Time to DMR	19	V			F1,17=2.70, P=0.123
Median (interquartile range)		11.0 (6.3—22.5)	19.0 (13.2—38.2)	15.0 (8.2—27.2)	
Range		2—33	5—43	2—43	
Lenght of DMR	14				F1,12=5.86, P=0.033
Median (interquartile range)		54.5 (29.8—79.2)	25.0 (19.1—38.6)	30.5 (23.8—59.6)	
Range		27—82	0—66	0—82	

N is the number of non-missing value. 1Kruskal-Wallis. 2Pearson. 3Wilcoxon.
* total number includes second pregnancies
*One patient switched from Imatinib to Nilotinib for the second pregnancy

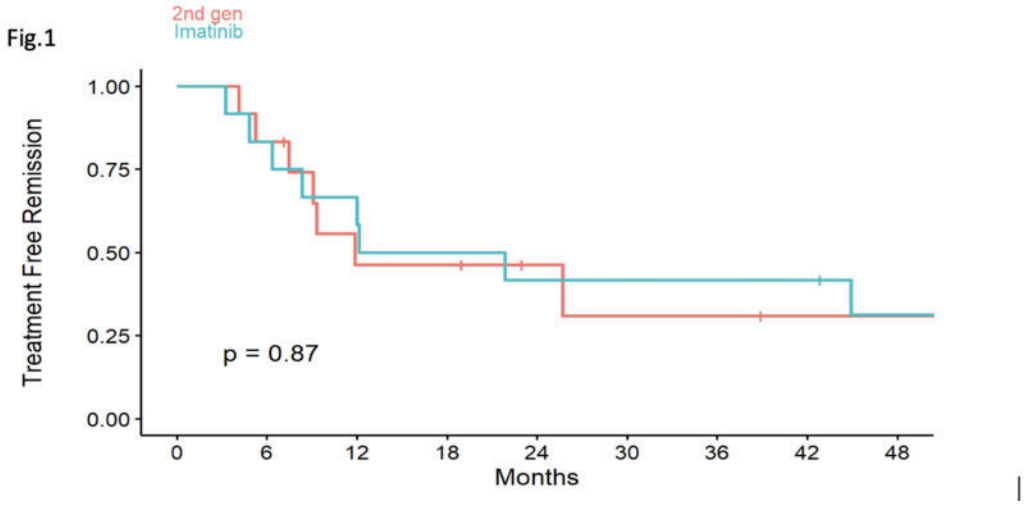

Figure 1

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