TREATMENT OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA DURING PREGNANCY ACCORDING TO SCHEME CONSIDERING THE LEUKEMIC BURDEN AND TERM OF PREGNANCY (THE LET SCHEME)

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Background

Finding out an optimal balance between risks both for mother and child and developing the safe treatment schemes in patients with chronic myeloid leukemia (CML) during pregnancy is a challenge .

Objective

To evaluate the results of treatment in CML pts with pregnancy in accordance with the Leukemic burden and Term of pregnancy (the LET scheme) developed by hematologists and obstetricians and used during years 2011-2017.

Materials & Methods

The main principles of the LET scheme:

At early pregnancy stage

• stop TKI immediately after pregnancy confirmation if they have been used and avoid TKI till 15th week of pregnancy

• use interferon alpha (IFN) if there is no complete hematologic response (CHR).

At late pregnancy stage (after 15th week)

• allow the use of imatinib (IM) or nilotinib (NIL) in case of no CHR and MR2 loss (BCR-ABL>1% IS) to benefit for the mother.

At any pregnancy stage

• observe without treatment or use IFN if a CHR and at least MR2 remains (BCR-ABL≤1% IS)

• do not use dasatinib (DAS)

Rationale for the scheme:

1) *IM has a moderate placental transfer[1,2];*
2) *fetal abnormalities on IM were predominantly associated with the use in 1st trimester[2];*
3) *safe IM use during late pregnancy has been reported[3,4];*
4) *no teratogenicity of NIL in preclinical studies [4]*
5) *DAS has a high placental transfer, severe fetal abnormalities irrespective of pregnancy stage[5].*

The results were collected within CML Pregnancy Registry of Russian Hematology Society together with data of other treatment schemes.

Results

The outcomes of 125 pregnancy cases in Russian CML pregnancy registry were: labor n=83(66%), artificial abortion n= 34(27%), miscarriage n=8 (7%). The LET scheme was used in 45 patients with chronic phase CML including 49 subsequent pregnancy cases which ended in labor (*table1).*

A deep molecular response (DMR or BCR-ABL<0,01%) at pregnancy onset was in 14 (29%) patients, a spectrum of BCR-ABL levels was in other cases; no CHR was in 13(27%) patients *(table 2).*

No treatment or IFN at early pregnancy was in 41(84%) and 7(14%) cases respectively; 1(2%) woman stopped imatinib at week 17th. No treatment, IFN, imatinib 400 mg QD and nilotinib 400 mg QD were used at late pregnancy in 16(38%), 3(6%), 26(53%) and 4(8%) of cases respectively. Me time of TKI cessation and TKI restart was 4th week (range 3-17) and 19th week (range 15-35) respectively (*table3).*

The newborns (n=49) were healthy including 30 infants who underwent TKI exposure at late pregnancy *(table 4)*, Seven of 30 children who were under TKI exposure were born preterm with a low birth weight (<2500 g), other children were born at term.

No birth abnormaliries were found except 1(2%) infant with hypospadia which usually is frequently observed in common population (1:150-180 cases). There was no association of this abnormality with TKI use as the mother had only IFN therapy throughout pregnancy.

A CHR was in 47(96%) within 1 year after labor; DMR, major molecular response (MMR) and no MMR was in 17(35%),15(30%) and 17(35%) cases respectively.

Table 1. Clinical and demographic data of the patients

Characteristics of the patients (n=45)	
CML phase – CP/ AP, n (%)	44 (98%) / 1 (2%)
Sokal score low/ intermediate/ high, n (%)	31 (70%) / 7 (16%) / 6(14%)
Age at pregnancy onset, Me (min-max)years	29 (20-43)
CML diagnosed at pregnancy, n(%)	7 (16%)

.Table 2. Molecular response (MR) at pregnancy onset , at delivery and after labor in 49 cases

Response to treatment	At pregnancy onset	At delivery	within 1 year after labor
	Pregnancy cases, n (%)		
No CHR	13 (27%)	3* (6%)	2* (4%)
CHR	36 (73%)	46 (94%)	47 (96%)
BCR-ABL ≥10%	10 (20%)	11 (22%)	2 (4%)
No MR2	7 (14%)	16 (33%)	4 (8%)
MR2	6 (12%)	7 (14%)	11 (22%)
MMR	5 (11%)	3 (6%)	15 (30%)
DMR	14 (29%)	9 (18%)	17 (35%)
No data	7 (14%)	3 (6%)	-

.Table 3 Therapy by LET scheme in 49 cases

Therapy	at pregnancy onset	at 15th week	after 15th week
	Pregnancy cases, n (%)		
IM	28 (57%)	1 (2%)	26 (53%)
NIL	4 (8%)	0 (0%)	4 (8%)
DAS	1 (2%)	0 (0%)	0 (0%)
IFN	2 (4%)	7 (14%)	3 (6%)
no therapy	14 (29%)	41 (84%)	16 (33%)

Table 4. Characteristics of the children (n=49)

Characteristics	
Male/female ratio , n (%)	30 (61%) / 19 (39%)
Me weight, g (min-max)	3545 (1800 - 4540)
Low weight* at birth <2500g, n(%)	8 (16%)
Me height, cm (min-max)	59 (44 - 56)
Me Apgar score, (min-max)	8 (2-9)
No birth abnormalities	48 (98%)
Abnormality at birth (hypospadia)	1 (2%)

Summary

- The LET scheme shows effectiveness and safety in different clinical situations of CML patients during pregnancy though the case number is limited;
- Collaboration with obstetricians, accurate analysis of cases and data accumulating are needed furthermore.

References

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