American Journal of Leukemia Research

Editorial
Published: 24 Jun, 2017

Back to Normal Life: Pregnancy and CML

Elisabetta Abruzzese, Malgorzata Monika Trawinska, Pasquale Niscola and Paolo de Fabritiis*

Hematology, S. Eugenio Hospital, Tor Vergata University, Italy

Editorial

Since the introduction in the new century of the tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia, the whole approach to the illness has changed very quickly.

In twenty years, the communication of the diagnosis in chronic myeloid leukemia (CML) patients moved from the awareness of an invariably fatal disease and many side effects during Interferon therapy, being allogeneic transplant the only curative approach [1], to an illness treated at home with a targeted drug, able to restore a normal hemopoiesis but requiring a lifelong therapy that could never be stopped [2], to a condition whose survival might be comparable to the normal same age population, for which multiple targeted drugs are available, able to induce deep molecular responses that could allow discontinuation of treatment [3]. For this category of patients, in both male and female, conception/pregnancy can be planned and successfully accomplished.

Having the possibility to block the protein responsible for the onset of CML, the developed tyrosine kinase inhibitors (TKI) provided a very powerful arm in fighting the illness. This brought to the necessity of standardize behavior and objectives to be reached. A panel of expert, therefore, defined the aims complete hematologic remission (CHR), complete cytogenetic remission (CCyR) and major molecular responses (MMR, e.g., standardized BCR-ABL transcript ratio <0.1%, defined as MR3, <0.01% as MR4, and <0.0032% as MR4.5) to be obtained within specific time-points. The worldwide known European Leukemia Net (ELN) recommendations were first published in 2006. With the advent of newer, more potent TKIs, the goals have become more ambitious and the same were updated in 2009 and 2013.

The two hottest subjects nowadays in CML management are the discontinuation of treatment and the pregnancy, both strictly related to each other.

In the latest ELN update, for the first time, pregnancy was officially mentioned together with discontinuation [4]. Although the median age at diagnosis for patients with CML is around 60 years, the GIMEMA registry of CML has reported that more than 50% of patients at diagnosis are in reproductive age (Table 1) [5]. This has addressed issues relating fertility and pregnancy and physicians are frequently asked for advice on this subject.

While it seems that fertility, conception and delivery of female partners of male patients are not affected (even if for some TKIs very few data are available), female patients should not be exposed to TKIs during pregnancy, as it is well known both for *in vitro* and *in vivo* (animal model) preclinical studies that TKIs are not genotoxic but could be teratogenic, resulting in bone, vascular and organ defects when administered during pregnancy [6]. This has been confirmed in pregnant women treated with TKIs, mainly with imatinib, and exposed during the 1st trimester and over, since in approximately 20% of them the same defects described in animal model could be found in the product of conception [7].

At present, there are 5 TKI inhibitors available for the treatment of CML or other Ph+ leukemias [8]. Imatinib has been the first targeted drug to be introduced in 2001 [9]. Since then more than 300 cases of pregnant woman have been reported. Abnormalities reported in patients variably exposed during pregnancy include stillbirths, exencephaly, encephalopaties and abnormalities of the skull and bones, primum atrial septal defect, hypospadias, hydrocephalus, microcephalus, and clinodactily.

Dasatinib, Nilotinib and Bosutinib were introduced after 2005 and are known as second generation TKIs. Fewer data are available for these drugs, since few more than 50 female patients treated with Nilotinib have been described so far, in which 2 serious events were described: omphalocele and transposition of great vessels. Similar number of pregnancies was described for Dasatinib, and 10 events described. The molecule crosses the placenta and can induce arm in all

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Correspondence:
Elisabetta Abruzzese, Hematology, S. Eugenio Hospital, Tor Vergata University, Piazzale dell'Umanesimo 1000144 Rome, Italy, Tel: +39-06-51008984; Fax: +39-0651002390; E-mail: elisabetta.abruzzese@uniroma2.it

Received Date: *04 Jun 2017*
Accepted Date: *14 Jun 2017*
Published Date: *24 Jun 2017*

Citation:
Abruzzese E, Trawinska MM, Niscola P, de Fabritiis P. Back to Normal Life: Pregnancy and CML. Am J Leuk Res. 2017; 1(1): 1003.

Table 1: Gimema CML registry (2008-2012): patients in reproductive age at diagnosis.

Age	Males	Females	Total
18-29	7%	6.7%	13.7%
30-39	8.9%	8.9%	17.8%
40-49	9.6%	9.7%	19.3%
50-55	3.7%	--------	3.7%
Total	29.2%	25.3%	**54.5%**

stages of pregnancies. Encephalocele with premature fusion of the cranial vault sutures, hydrops fetalis, lung hypoplasia, were among those. As of our knowledge, no cases have been described using Bosutinib and Ponatinib, introduced in 2011 and referred as third generation drugs.

Considering the significant proportion of female/male patients diagnosed with CML in reproductive age, and the substantial normal lifespan of those patients when treated and responding, it became mandatory to address issues relating to fertility and pregnancy. The management of fertility begins at diagnosis: the patient in reproductive age should be informed of the risk of unplanned pregnancies in terms of fetal problems and/or the risk of uncontrolled disease in the case of stopping therapy, but also on the possibility that a controlled pregnancy can be carried out when the treatment has being started, and the response is optimal.

There are no consensus/guidelines regarding the best behavior in case of pregnancy. Certainly, different situations can occur: CML discovered during pregnancy, pregnancy discovered during TKI treatment for CML, planned pregnancy after stabilization of the CML response. In the first two cases behaviors should be individualized, taking into consideration two principal variables concerning the patient (her willing, the parity, the week of gestation, the exposure compared with the age of gestation) and the CML (chronic versus more advanced stage, remission status…).

No TKI should be use during pregnancy; Imatinib and Nilotinib, that do not seem to cross the placenta, can be considered only after the 16th week (placenta mature and organs already formed), while Dasatinib should not be used at any time. Interferon has been extensively used in S both CML and other hematologic and non hematologic conditions and can be used safely [10].

Treatment can be with hold while patient have achieved a stable deep molecular response. Published data confirmed the possibility to successfully discontinue therapy in 40% to 50% of patients. The remaining 50% to 60% tend to lose MMR (suggested point at which treatment can be safely resumed in recent discontinuation studies) within the first 3-6 months [11]; in this group of patients, therefore, a very early interruption of treatment when pregnancy is discovered should allow to go through the critical organ formation period, while in non relapsing patients the whole pregnancy and also breast feeding sometimes can be allowed.

In summary, in female CML patients conception should be planned and TKI therapy discontinued during pregnancy; individual risks and personalized clinical management should be considered when an unplanned pregnancy occurs.

National italian (GIMEMA) [12] and international (ELN) registries of conception/pregnancies in CML are ongoing in order to collect data and suggest in the future the most appropriate measure of support and counseling. Certainly, the developed TKIs have allowed a tremendous progress in CML treatment and a survival comparable to the healthy population of the same age can be proposed to CML patients; further progress must concern the quality of life in all of his aspects and the ability to conceive is one of the most important.

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