

Mini-Review

Tyrosine Kinase Inhibitor and Fertility

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Abstract

Treatment options for Chronic Myeloid Leukemia (CML) have changed dramatically during the last decades. Imatinib became the first line treatment of chronic myeloid leukemia in chronic and accelerated phase. Several clinical trials with imatinib have largely demonstrated the drug to be well tolerated in humans and common side effects usually manageable. With longer follow-up we are able to evaluate rarer toxicities, and to report the clinical experience with male fertility and pregnancy outcome. This review attempts to identify the best management strategy for patients with CML who desire to have healthy children.

Keywords: Tyrosine kinase inhibitor; Chronic myeloid leukaemia; Fertility

Introduction

The treatment of CML has been revolutionized with the use of competitive inhibitor of the Bcr-Abl tyrosine kinase, imatinib mesylate, for about two decades in chronic and accelerated phase [1]. Durable response to imatinib is now achievable in a significant number of patients with CML (#51) [2], which are also tolerable and safe [3]. Imatinib inhibits several tyrosine kinases associated with disease, selectively BCR/ABL in CML patients, c-kit in patients with gastrointestinal stromal tumors, and platelet derived growth factor receptor (PDGF-R) in patients with certain myeloproliferative disorders and dermatofibrosarcoma protuberans [4,5]. Most patients appear to tolerate imatinib well, but the potential consequence of the drug on developing fetus is still obscure.

Male Fertility

One of the important problem in male with imatinib therapy for CML is its effect on spermatogenesis, the other aspect is the effect of imatinib in fetus and child health is also important; therefore; if the effect on spermatogenesis will be acceptable, we need to prove its safety on fetus and child health, then to justify the cryopreservation. Also the patient's age and dose of imatinib are also may be important factor in the effect of imatinib.

Certain signaling pathways that up-regulated in many type of tumor cells also have some effect on normal cells, especially during development. C-kit tyrosine kinase receptor and its ligand, the stem cell factor plays an important role in testicular development by regulating of migration, proliferation and survival of the germ cells. In addition, PDGF is an important mediator in testis organogenesis, the development of Leydig cells, steroidogenesis, and spermatogenesis

especially in prepubertal. Therefore inhibition of these signal pathways could give rise the side effects in growing individuals [5].

In the study by Nicolini et al. [6], the authors describe male sperm parameters at CML diagnosis and on imatinib mesylate, and to compare these results to those of a cohort of normal sperm donors. Their study highlights significant and unexpected sperm alterations in CML patients at diagnosis, alterations that are surprisingly not restored by imatinib treatment and they also reported that many normal children have been fathered by patients on imatinib. They suggest that whether pre-therapeutic sperm analysis and cryopreservation recommendation is valid for patients receiving TKI, remains to be determined in the near future.

Several studies also confirm the reduction of circulating testosterone and gynaecomastia in men who are treated with imatinib or other multitargeted tyrosine kinase inhibitors, such as solitinib and dasatinib. The hypotheses of the mechanism by which drugs reduce testosterone production are the PDGFR and c-kit blocks in the testes. (#49) [7].

Chang et al. [8], in their study suggests that imatinib crosses the blood-testis barrier and reduces sperm density, sperm count, survival rates, and activity in CML-CP patients. However, imatinib did not affect the sex hormone levels or structure of reproductive organs.

Ramasamy et al. [4] report on five uneventful pregnancies in partners of patients who were on prolonged high-dose TKI, imatinib therapy for CML. In spite of the successful conception in four patients, several data suggest that use of imatinib can be injurious to spermatogenesis. Also they suggest appropriate pharmacovigilance must be done and patients while on imatinib should be advised to take contraceptive precautions [4]. Hensley and Ford [9] reported four normal pregnancies with one spontaneous abortion, two therapeutic abortions, and one fetal death in 13 week of pregnancy in 8 men patients on therapeutic imatinib trial. Ault et al. [10] study showed pregnancies in eight men at median dose of imatinib 700 mg/d and exposure period of 20 month were done. There were seven successful pregnancies, one spontaneous abortion and one baby born with gut malrotation [10].

When new molecularly designed cancer therapies, such as several inhibitors of tyrosine kinases, are introduced into treatment strategies for children, the latent effects on testicular development should be

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taken into consideration. The roles played by these agents in some of the specific physiological signal cascades modulated may be varying with age and maturational status. The pharmacokinetics, effectiveness and undesirable side-effects of these therapeutic agents in children and adults may be different. In one case report, semen analyses showed severe oligozoospermia after long-term administration of imatinib started before puberty and the complete maturation of the testis. The inhibin-B/FSH ratio was reduced in their patient [7].

There are some studies that show the sterility and oligospermia caused by loss of function of c-kit that is a one of target of imatinib. In some animal studies have showed that imatinib induce teratogenesis and dose related effect on spermatogenesis. In a case series evidence showed that conception in CML male patients receiving imatinib may result in normal pregnancies even if androgen production have been reported to be decreased by studies in which oligospermia and gynecomastia were documented. They suggested that patients who are on high dose imatinib treatment, testosterone level are reduced due to a possible role of imatinib on inhibition of c-kit and PDGF-R in testicular tissue [11].

Therefore pregnancy and family planning for CML patients are increasingly important [12]. There are no special precautions for male CML patients receiving treatment with imatinib, in contrast Imatinib is not recommended for female CML patients during pregnancy because of the potential harm to the fetus [13]. We think that the advantage and disadvantage of TKI therapy for male CML patients who desire to have children must be evaluated on an individual basis [2]. Specific studies into the male fertility, fetus abnormalities, the dose-effect relationship, testosterone production and age of patients are warranted.

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