Response of prostate cancer during imatinib therapy in a patient with chronic myeloid leukemia

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Imatinib mesylate is a specifically designed selective inhibitor of bcr-abl tyrosine kinase, significantly active against Philadelphia (Ph)-chromosome-positive chronic myeloid leukemia (CML) and Ph positive acute lymphocytic leukemia (ALL).[1-2] Imatinib also inhibits c-kit and PDGF-R and has been shown, both *in vivo* and *in vitro*, to be effective in different tumor models expressing these oncogenic tyrosine kinases, including glioblastoma, chronic myelomonocytic leukemia (CMML), dermatofibrosarcoma, and prostate cancer. Furthermore, it seems also exert inhibitory effect on vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF) induced angiogenesis and tumor growth.[3-5] Recently, several studies have demonstrated the potential of imatinib as an alternative to conventional therapy in prostate cancer, yet the safety and efficacy of this drug have never been investigated *in vivo*.[5-6]

We describe a patient with Ph-positive CML and concomitant prostate cancer who was treated with imatinib. The results show that imatinib induced a positive effect, possibly via different signalling pathways, with the patient achieving both complete hematological remission (CHR) and complete cytogenetic remission (CCR) of CML, and reduction in the size of the solid tumor.

In November 1999, we diagnosed a 67-year-old man with CML in chronic phase, with leukocytosis (60×10^9/L) and thrombocytosis ($1{,}500\times10^9$/L). Standard cytogenetics and interphase FISH analysis showed the presence of a variant Ph translocation, t(1;9;22) (q23;q34;q11), and molecular studies revealed the bcr-abl rearrangement with coexpression of p210 and p190 transcripts. Following cytoreduction with hydroxyurea (HU), therapy with interferon alpha (IFNγ) was begun (January 2000). After one month of IFNγ therapy, the patient experienced acute urinary retention. An elevated level of prostate-specific antigen (PSA) ratio (i.e., 15 ng/mL) was found and PSA level was 0.440 ng/mL; the digital rectal examination revealed that the right lobe of the prostate was enlarged and hardened. Transrectal scan displayed an hypoecogenic nodule on the right lobe (dimensions 20×10×18 mm). An adenocarcinoma was diagnosed after transrectal biopsy, with the following features: Gleason grade score,[7] c-kit negative, EGFR-Her 1 expression. The patient was considered not eligible for surgery and/or radiation therapy for the concomitance of CML. IFNγ therapy was discontinued, and the patient recommenced HU therapy. Testosterone level was 0.182; flutamide and subsequently biclutamide (Casodex®) were started and continued until September 2002, yet with no apparent effect on the tumor. According to the oncologist, treatment with imatinib alone (400 mg per day) was begun after an informed consent; at the time, the size of the tumor was unchanged and the PSA ratio had increased to 38.75% with a PSA level of 0.482 ng/mL.

At week 13, he achieved CCR (20/20 Ph- metaphases), with the only apparent side effect being minimal periorbital edema; the PSA level was 0.144 ng/ml. At week 26, while in CCR (FISH analysis on 150 nucleis negative), the PSA ratio decreased to 18% with a PSA level of 0.021 ng/ml and the solid hypoecogenic nodule had decreased in size (11×7×14 mm). Testosterone examined level was 0.222. At week 59, PSA ratio was decreased to 12% with a PSA level of < 0.010 ng/mL; a transrectal scan showed a further decrease of the tumor size (10×6×12 mm). At the time of this writing (week 62 of therapy), the patient's biological (still in CCR) and clinical conditions are stable under imatinib at 400 mg per day with a stable conditions of prostate cancer without any other cancer treatment.

The finding that CML in our patient promptly responded to imatinib treatment, with CHR obtained in 2 weeks and CCR in 13 weeks, is consistent with the high remission rates reported for this drug. In fact, CML patients with a new diagnosis or refractory to antecedent γ-IFN therapy, have shown to achieve high response rates, with 60-85% of major cytogenetic remission and 40-70% of CCR 2.

At present, there are no data available in the literature on the *in vivo* use of imatinib for prostate-cancer patients, and patients with two concomitant neoplastic diseases generally undergo only conservative therapy. Prostate cancer usually develops as an androgen-dependent hyperproliferation of prostate gland epithelial cells and it is generally treated with anti-androgen therapy. Molecular mechanisms that sometimes render prostatic cancer insensitive to androgenic deprivation are yet not know and activation of pathways that stimulate the cells proliferation even in the absence of androgens, have been proposed.[7] In our patient, the mechanism underlying the effect of imatinib on prostate cancer remains to be clarified. Different signalling pathways may have been involved: expression of PDGF and activation of its receptor (PDGF-R) have been found to be associated with the growth of prostate cancer cells, and there is strong evidence that the pro-angiogenetic factor VEGF is involved in the development of this type of cancer. In vitro experiments have shown that imatinib blocks PDGF-R autophosphorilation, resulting in the suppression of tumor growth, and that it inhibits neo-angiogenesis by blocking the effects mediated by PDGF, VEGF and BFGF.[6,8]

Furthermore, c-kit and PDGF-R are expressed in the testis and involved in testosterone production and are inhibited by imatinib. A reduction in testosterone levels has been very recently reported in patients with CML under imatinib treatment, indicating a relationship between this drug and androgen hormones.[9] Thus, the possibility of a hormonal mechanism in the improvement of prostate cancer by androgens deprivation in our patient cannot be excluded, even though the low levels of androgens as detected both before and during imatinib treatment does not support this idea.

In conclusion, in our patient imatinib might have exerted its anti-tumor activity on both CML and prostate cancer by inhibiting multiple signalling pathways, including proliferative and neo-angiogenetic functions and possibly trough hormonal mechanisms.

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