Possible alternative strategy for stage I imatinib-sensitive testicular seminoma; lessons from a case associated with Philadelphia chromosome-positive acute lymphoblastic leukemia

KIT is a member of the type III receptor tyrosine kinase family, which is widely expressed in a variety of human malignancies. It is a potential target for imatinib because its constitutive activation, which is mostly caused by gene mutations, induces tumorigenesis, such as gastrointestinal stromal tumor (GIST) [1]. In this study, the first case of primary Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) associated with imatinib-sensitive testicular seminoma expressing KIT is described.

This is the case of a 49-year-old man, who presented with painless left testicular enlargement and lumbago in October 2008. The serum levels of human chorionic gonadotrophin-β and lactate dehydrogenase were 1.0 ng/ml (normal value <0.1 ng/ml) and 1448 IU/l (115–217 IU/l), respectively; hence, testicular germ-cell tumor was initially suspected. Thereafter, pancytopenia and disseminated intravascular coagulation progressed promptly. Bone marrow aspiration revealed a hypercellular marrow with 92% blasts, which were positive for CD10, CD13, CD19, CD34, and human leukocyte antigen-DR by flow cytometry. Real-time quantitative RT-PCR also revealed positive for minor bcr/abl transcript. Under the diagnosis of Ph+ ALL, induction chemotherapy containing imatinib was started. The patient achieved complete molecular remission in the bone marrow. After imatinib administration (600 mg/day) from day 8 of induction therapy, the left testicular tumor started to decrease in size, but magnetic resonance imaging showed only 50% reduction (Figure 1A and B). In December 2008, orchietomy was carried out for diagnostic purpose. The specimen was pathologically confirmed as pure testicular seminoma without leukemic cell infiltration (Figure 1C). Moreover, it was strongly positive for KIT by immunohistochemistry (Figure 1D). In March 2009, the patient underwent myeloablative cord blood transplantation (CBT) following two courses of consolidation therapy containing imatinib. During follow-up 6 months after CBT, no recurrence in Ph+ ALL as well as KIT-positive seminoma, were noted.

KIT expression is commonly seen in testicular seminoma, wherein, approximately a quarter of cases has activating mutations in the kinase domain, exon 17 [1, 2]. Although a tyrosine kinase inhibitor for KIT, such as imatinib, is expected to be an ideal molecular targeting drug for testicular seminoma, as well as for GIST, the clinical efficacy remains to be clarified. The KIT-mediated tumorigenesis and the sensitivity to imatinib might depend not only on the presence and/or type of activating mutations but also on other mechanisms, such as an autocrine/paracrine loop [3]. In this case, any known mutations in the KIT could not be

Figure 1. Imatinib-sensitive testicular seminoma expressing KIT. Swollen left testis, which measured 55 mm and 33 mm (A) before imatinib administration, was reduced to the size of 35 mm and 23 mm (B) after the treatment. Hematoxylin and eosin staining (C) and immunohistochemistry staining (D) with a Dako polyclonal rabbit antibody for KIT (A4502; Dako Corp., Carpinteria, CA) were carried out in the orchietomy specimen (×400 magnification). The KIT expression was strongly positive.
detected. Currently, imatinib is being examined for refractory KIT-positive germ-cell tumors in a salvage setting with or without chemotherapy after the third line \cite{4, 5}. To date, orchiectomy followed by either adjuvant irradiation or single-dose carboplatin is the standard treatment of stage I testicular seminoma. The present case has raised a possibility that imatinib might be useful for stage I KIT-positive seminoma as neoadjuvant and adjuvant therapies for orchiectomy. Further randomized controlled trials are necessary to confirm this alternative strategy.


Hematology/Oncology, Department of Medicine, Kobe University
Graduate School of Medicine, Kobe, Japan
(*E-mail: atsuo@med.kobe-u.ac.jp)

disclosure

There is no conflict of interest for any of the authors.

references


doi:10.1093/annonc/mdp607
Published online 15 January 2010