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Case Report

Chronic Myeloid Leukaemia and Gastrointestinal Stromal Tumour in a Single Individual - the Choice of Therapy is a Shoo-In

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ABSTRACT

Chronic myeloid leukaemia and gastrointestinal stromal tumours are rare diseases that, despite different genomic lesions, are sensitive to tyrosine kinase inhibition with imatinib. We report a case of a patient with both diagnoses and discuss the rationale for treatment.

Keywords: CML; GIST; BCR-ABL; c-kit; Imatinib

BACKGROUND

Gastrointestinal stromal tumours (GIST) are rare neoplasms of the gastrointestinal tract with an incidence of 10-15 per million per annum [1]. They typically involve the stomach and proximal small intestine though can affect other sites within the abdomen. Their clinical presentation is variable. Some tumours are identified incidentally while others result in abdominal pain, bleeding or, in some cases, bowel obstruction. First recognised in 1941, the main stay of treatment for these tumours was surgical resection. Unresectable, recurrent or metastatic disease was challenging to treat and traditionally considered as chemotherapy and radiation resistant. The identification of recurrent activating mutations in c-Kit (stem cell factor receptor, CD117) in these tumours [2] paved the way for targeted therapy. Chronic myeloid leukaemia (CML) is a clonal stem cell disorder caused by a balanced translocation between the long arms of chromosomes 9 and 22 [i.e. t (9;22) (q34; q11)] [3]. This translocation juxtaposes the 3' segment of the c-ABL oncogene on chromosome 9 next to the 5' region of the BCR gene on chromosome 22. This fusion gene is translated into a functional protein, BCR-ABL, which possesses constitutive tyrosine kinase signalling activity. This signalling confers a proliferative and survival advantage over normal haemopoietic progenitors. This eventually results in clinical characteristics of CML, namely splenomegaly, myeloid hyperplasia (manifesting as marked leucocytosis and thrombocytosis), anaemia and, in some cases, catabolic symptoms. Imatinib is a tyrosine kinase inhibitor (TKI) that inhibits the BCR-ABL fusion tyrosine kinase. This blockade results in apoptosis of cells dependent on ongoing BCR-ABL signalling. Imatinib also acts on platelet-derived growth factor receptors (PDGFR-α and PDGFR–β) and c-Kit and serves to inhibit the downstream effects mediated by signalling through these receptors. It has thus served as a mainstay of therapy for both CML and GIST.

CASE PRESENTATION

A 56 year old man presented in 2014 with melena and pre-syncopal symptoms. He was found to have normocytic anaemic (haemoglobin 70g/L); leucocyte count, differential and platelet count were normal. He commenced therapy with a proton pump inhibitor and underwent endoscopic examination which demonstrated a large ulcerated mass on the posterior wall of the stomach. Appearances were suggestive of a GIST though biopsies demonstrated only necrotic mucosa and inflamed gastric mucosa. Follow-up computed tomography (CT) demonstrated only this lesion; metastatic disease was not identified. Laparoscopic partial gastrectomy was performed electively. The procedure was uncomplicated and our patient recovered well. Tissue pathology confirmed the diagnosis of gastrointestinal stromal tumour, mixed subtype. The tumour itself was 4 x 3.4 x 3cm in size with a low mitotic rate (2 mitoses/50 high power fields) and clear resection margins. c-Kit (CD117) immunohistochemistry was positive; DOG-1 immunohistochemistry was not performed. Molecular studies for KIT mutations were not performed. Overall this tumour was evaluated as being low risk for recurrence. Follow-up endoscopic examination was unremarkable and, given the tumour size and mitotic rate, it was felt likely that he was cured with surgical therapy. Adjuvant tyrosine kinase inhibitor therapy was not utilised. Approximately 18 months later, routine blood tests performed for monitoring of dyslipidaemia demonstrated leucocytosis. His hemoglobin was 158g/L, white cell count 31.1 x 10^9/L and platelet count 235 x 10^9/L. Smear review demonstrated basophilia alongside circulating metamyelocytes and myelocytes. Blasts were not evident. Liver and renal biochemistry was normal. Beyond scars consistent with prior abdominal surgery, clinical examination was unremarkable. Abdominal CT did not demonstrate hepatosplenomegaly. Bone marrow examination demonstrated marked hypercellularity with left shifted granulopoiesis. Blasts were not increased representing only 1% of all cells. Polymerase Chain Reaction (PCR) analysis of peripheral blood demonstrated the BCR-ABL transcript at diagnostic levels. Other molecular tests (JAK2 V617F and CALR mutation analysis) were negative. Accordingly a diagnosis of chronic myeloid leukaemia was made. Given the history of GIST we recommended treatment with imatinib 400mg daily. Our patient had no notable side effects from imatinib and achieved haematologic remission after 2 months of therapy. Quantitative PCR monitoring at 12 months showed a 3.2 log reduction in transcript (0.067% by International Scale) and, 3 months later, he had achieved a 3.7 log reduction (0.019%).

DISCUSSION

The majority of gastrointestinal stromal tumours have activating mutations in either c-Kit or PDGFRA [4]. The recognition of these driving mutations has allowed targeted therapy with tyrosine kinase inhibitors. Effective agents interrupt signalling through the involved receptor pathways, impairing proliferation and promoting apoptosis within the malignant cells. A multi-centre phase III clinical trial evaluated relapse-free survival (RFS) of 713 patients treated with complete resection of a primary GIST at least 3cm in size and expressing c-Kit protein [5]. Participants received either imatinib 400mg daily or placebo. The study was terminated early after a planned interim analysis demonstrated significant prolongation of RFS in imatinib treated patients (98% vs. 83% at 1 year; overall hazard ratio 0.35; one-sided $p < 0.0001$). Based on these results, imatinib was approved in 2008 by the US Food and Drug Administration (FDA) and in 2009 by the European Medical Agency (EMA) for adjuvant treatment of adult patients following resection of c-Kit-positive GIST. Risk of recurrent was retrospectively assessed based on the recognised prognostic factors of tumour size, mitotic index and tumour location [6]. Imatinib was shown to be effective in groups at moderate and high risk of recurrence. Benefit was not seen in those at very low (as our patient is) and low risk of recurrent disease given the extremely low rates of relapse in these groups. Tyrosine kinase inhibitors also play a critical role in the treatment of chronic myeloid leukaemia. The

landmark IRIS study [7] demonstrated a marked difference in CML outcomes between those treated with imatinib and those receiving combination therapy with cytarabine and interferon. Following routine use of imatinib the rates of allogeneic transplantation for chronic phase CML have declined markedly [8] with this strategy more commonly used in more advanced phases of disease. Since imatinib's success, other tyrosine kinase inhibitors with even higher potency against the BCR-ABL fusion protein have become available. Nilotinib, dasatinib, bosutinib and ponatinib are now therapeutic options. Given the increasing number of effective treatments, first-line therapy in CML is often based on patient preference (including frequency of administration) and potential for long-term risks. A number of discussion papers and review articles may be found on treatment selection [9-11]. Relative resistance to imatinib therapy has been observed in GIST with mutations in exon 9 of KIT. Analysis of this group in a recently published study has demonstrated the superiority of higher (800mg) doses of imatinib [12]. Alternative TKIs with dual activity have also been studied, generally in the setting of imatinib resistance or intolerance. These studies [13,14] have generally demonstrated limited benefit though this might reflect relative resistance to TKI therapy. Of interest, however, are results from a Phase III clinical trial comparing imatinib and nilotinib in recurrent or unresectable GIST [15]. In this study imatinib was clearly superior to nilotinib. Whether this reflects disease biology or pharmacodynamics factors remains unsettled. We elected to treat our patient with imatinib on the basis of long experience with this agent and, while his risk of relapsed GIST is low, therapeutic activity against this tumour. Although second malignancies are not uncommon, the relatively short time from the identification of the GIST to CML diagnosis in this man, coupled with the fact that both diseases are imatinib-responsive, is of interest. In fact, only one other case of CML emerging in a patient with GIST has been reported in the literature [16]. The circumstances in this case report are notably different to our case but likewise serve to highlight the therapeutic efficacy of imatinib.

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