Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT)

Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumor (TGCT), is a rare pathological entity affecting the synovium in young adults [1, 2]. Initially considered as an inflammatory reactive process, recent observations have shown that this disease may actually be a benign neoplastic process with specific genetic alterations [3, 4]. Indeed, a specific t(1;2) translocation, involving the collagen 6A3 gene (on 2q35) and the macrophage colony-stimulating factor (M-CSF) (also known as CSF1) gene (on 1p13), is present in a fraction of tumor cells in PVNS/TGCT. This fusion gene expressed by a fraction of the cells encodes for a fusion protein which attracts non-neoplastic cells expressing Macrophage colony stimulating factor (M-CSFR), through a paracrine—‘landscape’—effect [3, 4].

PVNS/TGCT is generally treated by surgery alone. However, relapses may occur, and re-excision may be needed, with possible important functional impairment [1, 2]. In addition to its inhibitory activity on BCR-ABL, KIT, and platelet derived growth factor receptor alpha, imatinib has recently been reported to block M-CSFR activation at therapeutic concentration [5]. These observations prompted us to evaluate imatinib in a patient with recurrent and symptomatic PVNS/TGCT following surgery, in whom surgical re-excision would have had important functional consequences.

A 34-year-old right-handed female was referred to us for a rapid painful relapse of PVNS/TGCT of the right elbow 3 months after surgical removal of the lesion. Imatinib was initiated at a dose of 400 mg/day on 18 September 2006 (Figure 1). A partial response was observed at month 2 (08 November 2006) and complete remission was observed at month 5 (28 February 2007). Treatment was interrupted at month 7. In June 2007 (month 9), a symptomatic painful relapse of the tumor was diagnosed both clinically and on magnetic resonance imaging. Imatinib was reintroduced at the same dose and a second complete remission was observed in September 2007 and confirmed in December 2007 at month 14.

The rationale for imatinib treatment in this observation came out from the hypothesis that imatinib may disrupt the paracrine loop found responsible for PVNS/TGCT growth [3, 4, 6]. In this patient, the rapid response observed with imatinib,
the relapse at discontinuation, and the secondary response obtained at imatinib reintroduction, as reported in GIST [7], show that imatinib targets an essential biological mechanism responsible for tumor growth in this locally invasive tumor. Although a potential contribution of the blockade of other tyrosine kinases by imatinib cannot be ruled out, the frequency at which the col6A3/CSF1 fusion gene is observed in PVNS/TGCT as compared with other pathological synovial process strongly indicates that imatinib activity involves M-CSFR blockade in this disease, despite recent observation showing limited biological activity of the product of the fusion gene [6]. This observation further illustrates the efficacy of targeted oncogene treatment when applied to the causing molecular alteration responsible for a neoplastic process.

These results show that imatinib may induce complete responses in relapsing PVNS/TGCT and offer an option in patients in whom surgery is not feasible or would result in significant functional impairment. This is the first report of the activity of imatinib in an M-CSF/M-CSFR-dependent solid tumor. The optimal duration of the treatment in this disease is not known.

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J.-Y. Blay1,2, H. El Sayadi2, P. Thiesse2, J. Garret3 & I. Ray-Coquard2

1UJOMM Pavillon E, Hopital Edouard Herriot, 2INSERM U590, Department of Medicine, Department of Radiology Centre, Léon Bérard, 3Clinique du Parc, Lyon, France

Correspondence to: Prof. J.-Y. Blay, INSERM U590 Centre Léon Bérard, 28, rue Laennec, 69008 Lyon, France. E-mail: blay@lyon.fnclcc.fr

references


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