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CLINICAL RECORD

Complete response in a melanoma patient treated with imatinib

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Abstract

Background: Imatinib therapy has been successful in gastrointestinal stromal tumours containing mutation of the KIT gene. However, there are few reported cases of successful imatinib therapy in patients with melanoma containing KIT gene mutation or c-kit protein expression.

Methods and results: A 52-year-old man developed metastatic melanoma from a primary melanoma in the left side of the nasopharynx. The tumour was positive for c-kit protein, and there was a KIT mutation in exon 11. He was treated with imatinib. A follow-up scan one year later showed a complete response. Treatment targeting the biological characteristics of melanoma proved successful in this patient.

Key words: Melanoma; Proto-Oncogenes; C-kit Protein; Nasopharynx; Antineoplastic Agents

Introduction

Non-cutaneous melanomas are rare compared with cutaneous melanomas: over 90 per cent of melanomas arise from the skin.[1] Only 1.3 per cent of melanomas arise from mucosal sites.[1] Of the small number of mucosal melanomas, the majority are seen in the head and neck.[1] In the UK, the lifetime risk of developing melanoma is one in 77 for women and one in 91 for men.[2] Metastatic melanoma has a poor prognosis, with a median survival of just six to 10 months.[3]

The c-kit protein is involved in proliferation, migration and survival of melanocytes, therefore playing a vital role in melanocyte physiology. In the normal physiological state, the c-kit protein must be activated by stem cell factor; however, in tumours stem cell factor activation is not required for c-kit activation.[4]

Expression of the c-kit protein has been previously reported in melanoma. However, the results of phase II trials of imatinib therapy in melanoma patients have been disappointing, showing little or no efficacy and significant toxicity.[5–7]

Imatinib selectively inhibits protein tyrosine kinases, including c-kit.[8] It has shown to be effective in treating other cancers which express mutant c-kit proteins, such as gastrointestinal stromal tumours.[9]

Case report

A 52-year-old man presented to the ENT department with catarrh and rhinorrhoea. During examination under anaesthesia, a large tumour was seen in the left nasopharynx and a biopsy was taken. Histopathological analysis confirmed a diagnosis of malignant melanoma with no local spread and no nodal metastases. The patient underwent debulking of the tumour and radical radiotherapy via lateral radiation portals to the nasopharynx.

On follow up at 15 months, recurrence in the nasopharynx was treated with local excision.

At 23 months, the patient developed a mass involving the right latissimus dorsi muscle. This isolated mass was proven to be metastatic melanoma, and so the patient received radiotherapy to the right axilla. Molecular genetic testing was carried out on the lesion, which showed it to have a KIT gene exon 11 mutation, c1676T > A.

One month later, the patient developed a lesion on his right thigh. A fine needle aspirate biopsy confirmed this to be metastatic melanoma. This tumour was c-kit-positive. Staging investigations showed widespread cutaneous lesions as well as splenic and widespread abdominal involvement. Molecular genetic testing was carried out on the thigh lesion, showing it to have a KIT gene exon 11 mutation.

In view of this, and following discussion with the patient, imatinib therapy (400 mg daily) was commenced.

After one month of imatinib treatment, the lesions on the patient's neck and lower chest were not palpable on examination, and the lesion on his right thigh was barely palpable. No other abnormalities were detected, and there was no evidence of organomegaly or lymphadenopathy.

Three months after commencement of treatment, a follow-up computed tomography (CT) scan indicated a significant response, as shown in Figure 1.

Nine months after starting treatment, a further CT scan showed a complete response, with no evidence of recurrence.

The patient tolerated imatinib therapy well. The only side effect he complained of was mild peri-orbital oedema, which improved within three months.

At the time of writing, 18 months after commencement of treatment, the patient was continuing on imatinib therapy and remained in remission, with no evidence of recurrence.

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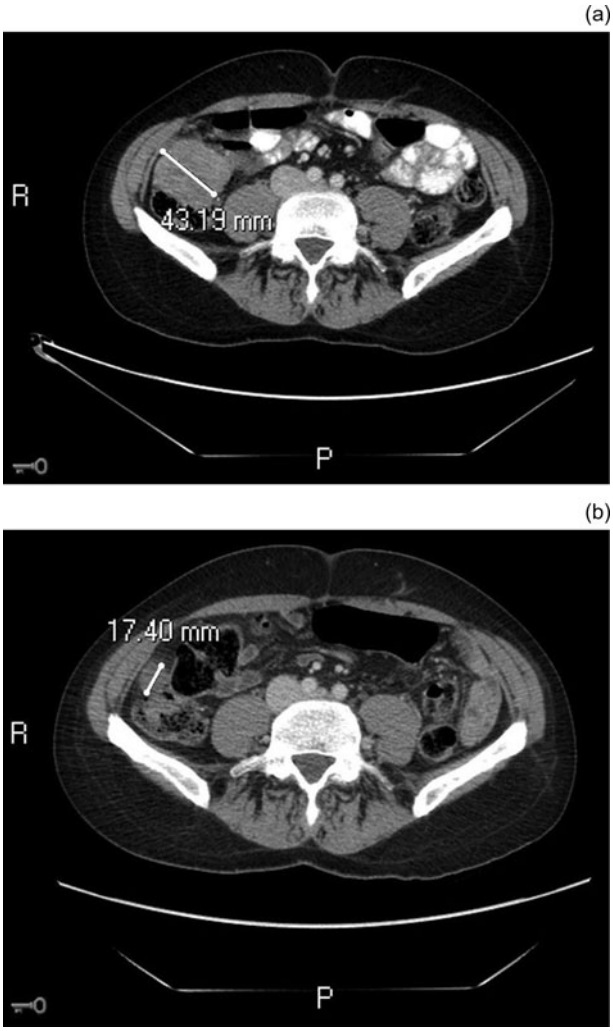

FIG. 1
Axial computed tomography scans taken (a) before and (b) after commencement of imatinib treatment. R = right; P = posterior

Discussion

Imatinib is indicated as treatment for gastrointestinal stromal tumours with a KIT gene mutation, as clinical studies have identified either a response or stable disease in 75 to 90 per cent of patients.[10,11] KIT gene mutations have been identified in 75 to 80 per cent of gastrointestinal stromal tumours, suggesting the importance of such mutations for imatinib efficacy.[12] However, KIT gene mutations are seen in only 15–20 per cent of acral lentiginous or mucosal melanomas.[13–16]

Studies of both gastrointestinal stromal tumours and melanoma have indicated that KIT gene mutation and c-kit protein expression do not always correlate.[15,17] Medeiros *et al.* found that 4 per cent of gastrointestinal stromal tumours did not show c-kit protein expression.[15,17] In this study, all four patients with KIT gene mutation but without c-kit protein expression remained sensitive to imatinib. This suggests that imatinib therapy should still be considered for gastrointestinal stromal tumour treatment even if there is no evidence of c-kit protein expression. If this theory was applied to melanoma, patients should be screened for KIT gene mutation as well as c-kit protein expression, to take into consideration the fact that these may not always correlate.

It is interesting that the KIT gene mutation identified in our patient was in exon 11, as this is the most commonly seen mutation in gastrointestinal stromal tumours.[12] Mutations in exon 11 seem to be more sensitive to imatinib than other mutations.[12] Perhaps further studies of KIT gene mutations in melanoma will give more consistently promising results than have been obtained from investigation of c-kit protein expression.

- **There are few reports of successful imatinib therapy for melanoma**
- **Such therapy is successful for gastrointestinal stromal tumours with KIT gene mutation or c-kit protein expression**
- **In the reported case of nasopharyngeal metastatic melanoma with KIT exon 11 mutation and c-kit expression, such therapy was successful**
- **Oncologists should consider biological therapies for melanoma patients with these biological characteristics**

Our melanoma patient had a good outcome following imatinib therapy. Therefore, oncologists should be encouraged to explore such treatment in patients with melanomas expressing c-kit protein or containing a KIT gene mutation. With further research, it may be possible to identify which is the better prognostic predictor for imatinib therapy: KIT gene mutation or c-kit protein expression.

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