

The Role of Imatinib Mesylate in Adjuvant Therapy of Extra-abdominal Desmoid Tumors

MARKOS IOANNOU, NIKOLAOS DEMERTZIS, IOANNA IAKOVIDOU and STAMATIOS KOTTAKIS

Department of Orthopaedic Surgery, "METAXA" Cancer Hospital, Piraeus, Greece

Abstract. *Background: Extra-abdominal desmoid tumors are rare neoplasms with variable biological behavior. The mainstay of treatment is surgery. Complementary treatment with tyrosine-kinase receptor inhibitor drugs, particularly imatinib mesylate, has been reported in the literature. The purpose of this study was to determine the possible presence of tyrosine-kinase receptors in extra-abdominal desmoid tumors as a marker for imatinib mesylate therapy. Patients and Methods: From 1999 to 2004, immunohistochemical methods were carried-out in 14 patients with histologically confirmed extra-abdominal desmoid tumors to determine c-KIT positivity (existence of tyrosine-kinase receptors and PDGFRA and PDGFRB). Results: All desmoid tumors were c-KIT negative, which demonstrates absence of tyrosine-kinase receptors. Conclusion: The histological c-KIT markup is an easy and reliable method that can detect whether a desmoid tumor is sensitive to additional treatment with a tyrosine-kinase receptor inhibitor. Molecular biological analysis for the identification of KIT and PDGFR mutation should be performed before imatinib mesylate is included in any treatment protocol.*

Extra-abdominal desmoid tumors are rare, slow-growing, histologically benign tumors with variable biological behaviour (1-3).

Despite its benign microscopic features, it has an aggressive local behavior and, if not excised adequately, has a tendency to recur locally and invade neighboring structures with potential for morbidity, deformity, or even death. The term desmoid, coined by Muller in 1838, is derived from the Greek word "desmos", which means tendon-like. The synonym aggressive fibromatosis describes the marked cellularity and aggressive local behavior. This course and the

tendency for recurrence make the treatment of these relatively rare fibrous tumors challenging. Desmoid tumors are often classified as low-grade fibrosarcomas (4-6).

Although desmoid tumors are more common in persons aged 10-40 years than in others, they do occur in young children and older adults (7). Desmoid tumors most commonly appear in young women during or after pregnancy, especially second pregnancy. The tumors regress during menopause (Lotfi, 1989) and after tamoxifen treatment (Wilcken, 1991). Desmoid tumors may regress after exposure to oral contraceptives (Waddell, 1975) and have been associated with hereditary syndromes (Gardner's syndrome), and endogenous/exogenous female sex hormones in adults. However in children, these associations are difficult to establish (8-13).

A connective tissue growth disorder has been suggested as a bases for the disease (14-16). Based on X-chromosome molecular biological analysis, fibromatosis appears to be a monoclonal disorder, suggesting a neoplastic rather than an inflammatory fibrous reactive process (17). An abnormal expression of c-sis and platelet-derived growth factor (PDGF), which can be mitogenic for fibrocytes has been previously reported (13, 15).

A somatic APC gene mutation (adenomatous polyposis gene mutation) in patients with increased levels of [beta]-catenin has been established, which may explain the proliferative advantage of these cells in sporadic aggressive fibromatosis (14). In addition, the tumor-suppressor gene Rb1 has shown decreased expression and may also play a role in the pathophysiology of the disease.

The clinical behavior of extra-abdominal desmoid tumors remains unpredictable. They are usually slow-growing, locally aggressive and invasive to surrounding tissues. Although both spontaneous regression and disappearance, as well as spontaneous regression after biopsy, have been reported (14, 18), most lesions are refractory to multiple surgical procedures and adjuvant therapy. They often recur after surgery, particularly after marginal or intralesional excision. Distant hematogenous or lymph node metastases have not been observed, however multicentric disease and recurrence or reactivation at sites other than the primary location have

Correspondence to: Markos Ioannou, MD, Rodou Street 37, Marousi 15122, Athens, Greece. Tel: +30 6977872865, e-mail: markosioannou@yahoo.gr

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been reported (19, 20). Mortality is rare among patients with extra-abdominal desmoid tumors; however, the disfigurement and loss of function that result from tumor progression or its treatment is significant (21-23).

The delineation of optimal therapy for desmoid tumor has been confounded by the rarity of the diagnosis, as well as a lack of randomized and prospective direct comparisons of treatment approaches.

Current management of desmoid tumors involves a multidisciplinary approach, with surgical and adjuvant treatment modalities. Radiation therapy and sometimes chemotherapy have been used for inoperable or recurrent disease. Cytotoxic chemotherapeutic agents, antiestrogens, goserelin, progesterone, testolactone, non-steroidal anti-inflammatory drugs, interferon and iridium 192 implantation have been used in the management of desmoids, as well as isolated limb perfusion with tumor necrosis factor alpha-1a (1, 5, 8, 10, 30-38).

Wide margin surgical resection remains the main treatment option for local control of the tumor in all age groups (3, 25, 39-42). Although often difficult to achieve because of the tumor's extent and invasiveness, wide margin surgical resection offers the best chance to limit local recurrence (3, 25, 41, 42). Generally accepted rates of local recurrence after surgical excision are approximately 30-50% (23, 27-29), reflecting the impact of tumor location and the ability of the surgeon to achieve negative surgical margins. At doses of 50-60 Gy, radiotherapy has demonstrated local control rates of 75% in cases for which surgery is not feasible (43). Adjuvant radiotherapy has been shown to reduce recurrence rates by as much as 50%, and may offset the negative prognostic impact of positive surgical margins, allowing for a surgical approach combined with radiotherapy that balances local control with a significant impact on long-term function and morbidity (23).

Despite having a relatively high local failure rate, surgical resection of extra-abdominal desmoid tumors, with adjuvant radiotherapy for a positive surgical margin remains the standard approach. However, since a significant proportion of patients will experience local recurrences that are not amenable to surgical resection or radiotherapy, a variety of systemic therapy approaches have been investigated.

Imatinib mesylate is a selective tyrosine kinase inhibitor, designed for the treatment of chronic myelogenous leukaemia (44, 45). Imatinib mesylate also possesses inhibitory activity against multiple class 3 receptor tyrosine kinases (RTKs), including PDGFRA and PDGFRB, as well as the c-KIT subtype (44). This agent blocks ligand activated receptor phosphorylation, mitogen-activated kinase activation and proliferation, resulting in inhibition of cellular growth and proliferation (46).

Inhibition of c-KIT RTK activity is hypothesized to account for the dramatic responses observed in the majority

of patients with gastrointestinal stromal tumors (GISTs) treated with imatinib mesylate (47).

In this aspect, immunohistochemical staining for KIT in other stromal tumors might be of certain interest since treatment eligibility for selective tyrosine kinase inhibitors hinges on positive immunostaining (48).

Data from previous studies on c-KIT immunoreactivity in extra-abdominal desmoid tumors are contradictory with positive reports (49-53), negative reports (54, 55) and reports with weak focal staining (48).

Whether the reported effects of imatinib mesylate in extra abdominal tumors by some authors (49, 50, 52, 53, 56, 57) are encouraging, this data remains confusing, because the rarity of the diagnosis, the limited number of subjects in the literature, the absence of statistical studies and the inclusion in a majority of studies of varied anatomical presentation are limiting the ability to draw definitive conclusions.

Patients and Methods

Fourteen patients with extra-abdominal desmoid tumors were treated at "METAXA" Cancer Hospital, Greece, between 1999 and 2004. Nine patients underwent initial treatment at the institution, whereas five were referred from other hospitals for additional treatment of recurrent disease. Nine patients were female and six were male. The mean age at the time of diagnosis was 48 years (range 18-75 years) (Table I).

In all patients we performed routine laboratory tests, plain radiographs of the lesion and chest, computed tomography (CT), and magnetic resonance imaging (MRI) in addition to arteriography (when appropriate). Histologic specimens were available for all patients, and were reviewed by one pathologist. Distribution of anatomic tumour sites were paravertebral, the thigh, the popliteal area, the leg, the buttock, the pelvis, the quadriceps, the scapula and the hip as described in Table I.

Nine patients presented at our institution with primary lesions whereas five presented after one (three patients) or more (two patients) local recurrences after surgical treatment outside our institution. At our department all patients were initially treated with surgical excision obtaining a wide margin. Six of the 14 patients had a wide local excision. Nine patients had a marginal excision whereas one had positive margins at surgery. These nine patients received post-operative adjuvant radiation therapy in our institution (Table I). We used a total radiation dose between 50 and 60 Gy to a field encompassing the tumor bed and providing optimal sparing of radiosensitive adjacent structures.

After internal review board approval, we performed immunohistochemical (IHC) and qualitative real-time polymerase chain reaction analysis of the fourteen desmoid tumor specimens.

Results

All desmoid tumors were c-KIT and PDGFR negative, which suggests a lack of tyrosine-kinase receptors. Based upon these data, none of the above patients would have been eligible for treatment with a tyrosine-kinase receptor inhibitor, such as Imatinib mesylate.

Table I. Presentation, therapy and outcome of 14 extra-abdominal desmoid tumors.

Gender	Age	Site	Status at initial treatment	Therapy	Current status (duration)
F	53	Right thigh	Primary	Surgical+ adjuvant radiotherapy	Disease-free (30 months)
F	26	Right leg	Primary	Surgical+ adjuvant radiotherapy	Disease-free (28 months)
M	28	Right buttock	Primary	Surgical+ adjuvant radiotherapy	Disease-free (40 months)
M	58	Left thigh	Primary	Surgical (wide excision)	Disease-free (36 months)
M	75	Right popliteal area	Primary	Surgical+ adjuvant radiotherapy	Disease-free (46 months)
F	54	Pelvic	Primary	Surgical (wide excision)	Disease-free (36 months)
F	72	Para vertebral (TL area)	Primary	Surgical+ adjuvant radiotherapy	Disease-free (6 years)
M	18	Right popliteal area	Primary	Surgical (marginal resection)	Recurrence at 12 months p.op.-amputation
F	70	Para vertebral (T12)	Primary	Surgical+ adjuvant radiotherapy	Disease-free (6 years)
F	25	Right quadri-ceps	2nd Recurrence	Surgical (wide excision)	Disease-free (61/2 years)
F	65	Para vertebral (cervical spine)	Recurrent	Surgical+ adjuvant radiotherapy	First rib resection – Brachial plexus paralysis after radio therapy
M	57	Right scapula	2nd Recurrence	Surgical+ adjuvant radiotherapy	Disease-free (27 months)
M	32	Right hip	Recurrent	Surgical+ adjuvant radiotherapy	Recurrence after 8 months
F	40	Left thigh and buttock	Recurrent	Surgical+ adjuvant radiotherapy	Reccurence after 10 months

Discussion

Despite the initial optimism for the adjuvant treatment of desmoid tumors with tyrosine-kinase receptor inhibitors, not all lesions contain these receptors as demonstrated by this series. The histological c-KIT mark-up is an easy and reliable method that can determine whether a desmoid tumor would be sensitive to additional treatment with a tyrosine-kinase receptor inhibitor. Because of the limited number of subjects in the literature and in this study no credible statistical conclusions can be drawn except that molecular biological identification of KIT and PDGFR mutation should be performed prior to considering imatinib mesylate in any treatment protocol.

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