Dramatic and Delayed Response to Doxorubicin-Dacarbazine Chemotherapy of a Giant Desmoid Tumor: Case Report and Literature Review

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Key Words

Desmoid tumor · Chemotherapy · Doxorubicin · Dacarbazine

Abstract

Desmoid tumors are benign, slow-growing mesenchymal tumors. Aggressiveness is local with no potential for metastasis or dedifferentiation. The treatment is challenging, particularly in the case of huge intra-abdominal locations. We, herein, report on a 21-year-old patient with a giant intra-abdominal desmoid tumor occupying substantially the entire abdominal cavity. After failure of a first-line combination of celecoxib and tamoxifen, the patient was given doxorubicin-dacarbazine chemotherapy. The treatment was well tolerated, and rapidly, the clinical digestive symptoms improved. After 6 cycles, the computed tomography scan showed a partial response (regression of tumor volume by 55%). During follow-up, the tumor continued to regress: 25 months after the end of chemotherapy, the tumor volume had regressed by 95% when compared to the start of computed tomography and by 90% when compared to the end of chemotherapy. Thirty-three months after the diagnosis, the patient is alive without any symptom. Our case provides further evidence of the remarkable efficacy of a doxorubicin-dacarbazine regimen, especially in function- or life-threatening situations where a rapid response is required. We review the literature and discuss the challenging issue regarding treatment of desmoid tumors.

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Introduction

Desmoid tumors (aggressive fibromatosis) are benign, slow-growing mesenchymal tumors. They represent less than 5% of all soft tissue tumors [1]. Their origin is still controversial, but antecedent trauma including surgery, hormone factors (estrogen levels), and genetic factors seem to be implicated. Tumors may be extra-abdominal or in the abdominal wall, usually sporadic, or intra-abdominal, and often associated with familial adenomatous polyposis (FAP) [2]. Aggressiveness is local with no potential for metastasis or dedifferentiation. Locally, tumors can damage vital structures and threaten life [3], especially in intra-abdominal locations, and have a high rate of recurrence even after complete resection.

The treatment of desmoid tumors is challenging. It includes different strategies such as ‘wait-and-see policy’, surgery and/or radiation therapy [4, 5], and systemic therapies including non-steroidal anti-inflammatory drugs (NSAIDs), hormone therapy such as anti-estrogen drugs [6], cytotoxic chemotherapy and recently investigational targeted therapies such as imatinib or sorafenib. Systemic therapies have been classically reserved to cases not amenable to local treatment because of excessive and unacceptable morbidity or after failure of prior treatment [7]. Nevertheless, these different drugs have been poorly assessed. Data come from case reports or small retrospective studies, and the very rare phase II studies concern chemotherapy and recently targeted therapies. Thus, in absence of comparative trials, their respective role is not clearly established. Situations without any impending threat to life or function are generally treated with less toxic drugs, such as NSAID or hormone therapy. On the contrary, cases with a high risk of life- or function-threatening complications are treated with more toxic approaches such as chemotherapy. This is the case of intra-abdominal mesenteric locations that often infiltrate the intestine and its vasculature, ureters and major vessels, for which surgery is not recommended because of technical difficulties, high risk of serious complications and high incidence of relapses.

Here, we report on a young patient with a giant intra-abdominal desmoid tumor, which showed a dramatic, delayed and durable response to doxorubicin-dacarbazine chemotherapy.

Case Report

In May 2010, a 21-year-old man presented with intractable vomiting associated with abdominal pain, pyrosis, constipation, and increase of abdomen volume. Blood analysis showed an inflammatory syndrome. Hepatic, pancreatic and renal functions were normal. A computed tomography (CT) scan showed a solid and heterogeneous intra-abdominal tumor of 250 mm in its largest diameter. The lesion was close to the stomach, but its origin was difficult to assess. The patient was referred to our institution. His medical history included asthma treated with salmeterol and fluticasone. No history of personal adenomatous polyposis, FAP or desmoid tumor was present. The World Health Organization (WHO) performance status was equal to 2. Physical examination found a hard and huge mass that increased the abdomen volume. Serum levels of HCG, β -HCG, α -FP and LDH were normal.

An endoscopic ultrasound-guided biopsy was performed. Pathological analysis (fig. 1) revealed a poorly cellular proliferation of non-atypical myofibroblastic spindle cells, without histological evidence of malignancy (neither mitosis nor necrosis). Immunohistochemistry showed strong nuclear expression of β -catenin by tumor cells, but no expression of desmin, H-caldesmon, S100 protein, MDM2, CDK4, and AE1/AE3 cytokeratins. Tumor cells did not

express estrogen nor progesterone receptors. The diagnosis of gastrointestinal stromal tumor was ruled out by immunohistochemistry (no expression of CD117, CD34, and DOG1) and molecular biology (no *KIT* and *PDGFRA* mutation). Histology was reviewed within the French Sarcoma Network (*Réseau de Référence en Pathologie des Sarcomes*) and a diagnosis of desmoid tumor was made.

Given the tumor volume and the intra-abdominal location, no surgery was performed. A first-line systemic therapy combining hormone therapy (tamoxifen 60 mg/day) and NSAID (celecoxib 200 mg/day) was decided. After a 3-month treatment, the CT scan showed tumor progression, with a mass measuring 250 × 132 × 322 mm, occupying substantially the entire abdominal cavity (fig. 2a–d).

A second-line treatment based on chemotherapy was started in September 2010. The regimen associated doxorubicin 20 mg/m² daily and dacarbazine 300 mg/m² daily for 3 days, every 21 days, with granulocyte colony-stimulating factor support. The treatment was well tolerated, and rapidly, the clinical digestive symptoms improved. After 3 cycles, the CT scan showed an objective response with decrease in size (245 × 106 × 240 mm). Chemotherapy was continued. After 6 cycles, the CT scan showed further tumor regression (229 × 95 × 217 mm; fig. 2b–e), representing a regression of the tumor volume by 56% when compared to baseline. Chemotherapy was discontinued, and follow-up started.

During all successive visits, the patient did very well with a performance status equal to 0 and no clinical signs, especially digestive ones. On CT scan, the tumor regression continued: the tumor measured 95 × 67 × 73 mm in December 2011 (12 months after the last CT cycle), and 49 × 38 × 30 mm in February 2013 during the last follow-up (25 months after the last cycle; fig. 2c–f), corresponding to a regression of the tumor volume by 95% when compared to the start of CT and by 90% when compared to the end of CT.

Discussion

Although often used as last resort in advanced stages, chemotherapy has been associated with clinical benefit in ~80% of desmoid patients. Objective response rates ranging from 20 to 75% [7] have been reported in the literature. The best chemotherapy regimen remains to be defined. Data are scarce and no randomized clinical trial has been reported comparing different regimens. The weekly methotrexate-vinblastine combination remains the most assessed regimen and represents, especially in younger patients, a less toxic alternative to anthracycline-based regimens.

Anthracyclines, especially doxorubicin, are a standard drug in the treatment of soft tissue sarcomas. In desmoid patients, they have been used either alone or more frequently in combination. The associated response rate is higher than with non-anthracycline-based regimens, but without significant difference in progression-free survival [8, 9]. Different anthracycline-based regimens have been reported. One of the most frequently used is the combination of doxorubicin and dacarbazine, another efficient drug in soft tissue sarcomas. Our literature review [10–15] identified 28 desmoid patients who were informative for the tumor response that had been assessed after administration of the combination either alone (16 cases; group 1) or with another cytotoxic drug, concomitantly (4 cases; group 2) or sequentially (8 cases; group 3). The results presented in table 1 show a high rate of objective responses: 8 complete responses (CR: 29%), 16 partial responses (PR: 57%), 3 stable diseases (SD: 11%), and 1 progressive disease (PD: 4%). In group 1, there were 5 CR (31%), 9 PR (56%) and 2 SD (13%); in group 2, 3 PR (75%) and 1 SD (25%), and in group 3, 3 CR

(38%), 4 PR (50%) and 1 PD (13%). No significant difference could be found between the 3 groups.

We thus treated our patient with the doxorubicin-dacarbazine combination alone. The characteristics of the 17 literature patients (including our present case), with radiological response assessed immediately after doxorubicin-dacarbazine (group 1), are shown in [table 2](#). For the cases with available information, the sex ratio was 5 women for 5 men, and the median age was 33 years (range, 16–66). The most frequent tumor locations were mesentery, all of which, except for our patient, concerned familial forms associated with hereditary digestive polyposis. In our case, there was no personal or familial history evoking FAP. The tumor size was generally large: to our knowledge, our case represents the largest tumor size (332 mm) reported to date in the context of this treatment. The doxorubicin-dacarbazine combination was given after a median number of one line of systemic treatment (range, 0–4). The median number of delivered cycles was 4 (range, 1–10). The rate of objective responses is impressive. Objective responses of desmoid tumors to chemotherapy defy the dogma that benign tumors, without or with very rare mitoses, do not respond to cytotoxic drugs [2]. Clinical responses usually preceded the radiological responses, which interestingly occurred during the treatment, but also after the end of chemotherapy. Typically, the radiological responses are slow to appear, and not infrequently, tumor shrinkage continues months or even years after discontinuation of chemotherapy. This has been observed with chemotherapy, hormone therapy and radiation therapy. The prolonged and continued regression long after discontinuation of treatment suggests that the mechanism of action might be a deprivation of the growth signal or cytokine. In our patient, the tumor volume decreased slowly by 55% during chemotherapy and continued to decrease (–95%) 25 months after the last chemotherapy cycle. Similarly, Patel et al. [10] reported a patient whose desmoid continued to decrease 31 months after the last chemotherapy cycle. The toxicity of the doxorubicin-dacarbazine regimen is well documented [16]. In the most recent series, all 7 patients, like our patient, tolerated the chemotherapy well: 3 patients experienced grade 3 neutropenia, and no treatment-related mortality was reported [13]. However, severe and irreversible long-term toxicity of anthracyclines with the risk of chemotherapy-induced cardiac failure and acute leukemia is more problematic, especially in view of the fact that patients are usually young. In this context, pegylated doxorubicin has been suggested as an alternative to doxorubicin [17].

In conclusion, we reported a case of intra-abdominal desmoid tumor of exceptional size, which provides further evidence of the remarkable efficacy of the doxorubicin-dacarbazine regimen, especially in function- or life-threatening situations. Its long-term morbidity should be discussed with the patient before treatment.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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Monneur et al.: Dramatic and Delayed Response to Doxorubicin-Dacarbazine
Chemotherapy of a Giant Desmoid Tumor: Case Report and Literature Review**Table 1.** Radiological responses of desmoid tumors reported after a combination of doxorubicin and dacarbazine

Ref.	Doxorubicin-dacarbazine alone	Doxorubicin-dacarbazine associated with another drug	Doxorubicin-dacarbazine followed by carboplatin-dacarbazine
[10]	n = 6: 1 CR, 3 PR, 2 SD	n = 3 (CYVADIC): 2 PR, 1 SD	
[11]	n = 1: 1 CR		n = 1: 1 CR
[12]	n = 1: 1 PR		n = 7: 2 CR, 4 PR, 1 PD
[13]	n = 7: 3 CR, 4 PR		
[14]	n = 1: 1 PR		
[15]		n = 1 (MAID): 1 PR	
Total	n = 16: 5 CR, 9 PR, 2 SD	n = 4: 3 PR, 1 SD	n = 8: 3 CR, 4 PR, 1 PD

CYVADIC = Cyclophosphamide, vincristine, doxorubicin, dacarbazine; MAID = mesna, doxorubicin, ifosfamide, dacarbazine.

Table 2. Seventeen cases of desmoid tumors documenting response to a combination of doxorubicin and dacarbazine

Ref.	Sex/age	Tumor location	Max. size (cm)	Previous systemic treatments	Dose/cycle (mg/m ²)	Cycles (n)	Response	Follow-up from diagnosis (months)
[10]	M/16	Head and neck	NR	None	DOX 60–90-DTIC 750–	2	SD	75
	M/22	Pelvis	NR	Chemotherapy	1,000	6	PR	49
	F/32	Mesentery (Gardner ¹)	NR	Tamoxifen		10	PR	120
	M/35	Mesentery (Gardner ¹)	NR	None		9	PR	58
	F/36	Mesentery (Gardner ¹)	NR	None		9	CR	235
	F/66	Neck	NR	None		4	SD	29
[11]	F/42	Mesentery (Gardner ¹)	NR	Tamoxifen	DOX 90-DTIC 900	7	CR	12
[12]	F/48	Mesentery (FAP)	NR	Tamoxifen, NSAID	DOX 60–90-DTIC 1,000	1	PR	47
[13]	NR/NR	Mesentery (FAP)	NR	NR	DOX 80-DTIC 600	4	CR	107
	NR/NR	Mesentery (FAP)	NR	NR		4	CR	106
	NR/NR	Mesentery (FAP)	NR	NR		4	CR	33
	NR/NR	Mesentery (FAP)	NR	NR		4	PR	32
	NR/NR	Mesentery (FAP)	NR	NR		4	PR	57
	NR/NR	Mesentery (FAP)	NR	NR		4	PR	105
	NR/NR	Mesentery (FAP)	NR	NR		5	PR	70
[14]	M/30	Mesentery (FAP)	25	NSAID, tamoxifen, imatinib, statin	DOX 65–95-DTIC 650–950	7	CR	48
Our case	M/21	Mesentery	32	NSAID, tamoxifen	DOX 60-DTIC 900	6	PR	33

¹ Gardner refers to Gardner syndrome. NR = Not reported.

Fig. 1. Histological aspects of a desmoid tumor are shown. Histologic appearance of the core needle biopsy (HE staining, original magnification, $\times 100$): spindle-shaped non-atypical cells in a collagen-rich stroma. Bottom right corner: nuclear β -catenin immunoreactivity by tumor cells ($\times 200$).

Fig. 2. CT scan showing the dramatic tumor response to chemotherapy. Abdomino-pelvic CT scan in transversal (a–c) and coronal (d–f) planes showing the tumor size evolution during and after doxorubicin-dacarbazine chemotherapy: before chemotherapy (a, d), after 6 cycles (b, e), and 25 months after the last cycle (c, f).