Therapy of aggressive fibromatosis is still an open question: a series of patients treated at a single institution

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Summary

Purpose: This study was an attempt to evaluate the possible role of chemo-hormonotherapy as a possible approach in managing inoperable, deep extra-abdominal aggressive fibromatosis.

Patients and methods: A series of patients with inoperable, deep extra-abdominal aggressive fibromatosis, were treated with combination chemo-hormotherapy. Therapy consisted of 6 cycles standard CVP (cyclophosphamide 750 mg/m² and vincristine 1.2 mg/m², given bolus intravenously (i.v.) on day 1, plus prednisone 40 mg/m²/day, days 1-5, every 3 weeks) and tamoxifen 20 mg daily.

Results: From 1995 to 2004, 9 patients, concomitantly, without selection, were included in this investigation. Their median age was 24 years (range 18-47), with predominantly male sex (6/9). Extremities were the most frequent localization (5/9), followed by chest wall in 3 and abdominal wall in one patient. Tumor size in most patients was 5-10 cm, and 3 patients had bulky disease (over 10 cm). Five patients had undergone previous surgery (3 wide excisions and 2 palliative interventions). Complete remission (CR) was observed in one patient, partial remission (PR) in 4 and stabilization of disease (SD) in 4 patients. In responders, the median duration to the onset of response was 10 months (range 4-14); median response duration was 32+ months (range 14-82). No relapse of disease was observed up until now.

Conclusion: Systemic treatment should be considered in patients with aggressive fibromatosis for whom local treatment approaches are not possible or have failed. All patients should be included in clinical trials.

Key words: aggressive fibromatosis, chemotherapy, hormonal therapy

Introduction

Aggressive fibromatosis is also known as desmoid tumor or musculoaponeurotic fibromatosis [1]. It is a rare benign, monoclonal [2], variable disease with several different clinical entities (abdominal, extra-abdominal, etc.). With an incidence of < 3% of all soft tissue tumors and reported annual incidence of 0.2-0.5 per 100,000 population [3-5] it is rarely investigated in clinical trials.

There are no guidelines concerning its treatment [6]. Although benign, without metastatic potential, aggressive fibromatosis is a locally invasive disease, often with pain, and resulting in deformity, organ dysfunction, and eventually, fortunately rarely, death owing to invasion of vital organs. Surgical approach is generally considered primary treatment, but relapse rates are generally high [7-11]. Some studies have found external beam radiotherapy to be helpful in the management of desmoid tumors [12,13], however, some reports claim that there is little or no benefit from radiation therapy for this disease [14-16]. The potential morbidity with often unsatisfying cosmetic or even
mutilating results of surgery and radiotherapy and the high local recurrence rates have led investigators to assess the role of non-cytotoxic and cytotoxic chemotherapy in settings in which surgery and radiotherapy are either not possible or unsuccessful.

The theory of hormone dependency has been supported by preclinical and clinical investigations [17,18].

This study was an attempt to evaluate the possible role of hormono-chemotherapy as a possible approach in managing inoperable, deep extra-abdominal aggressive fibromatosis. We analyzed the response to therapy, time to response and response duration, and also, the importance of disease stabilization.

**Patients and methods**

Between 1995 and 2005, 9 patients with aggressive fibromatosis were treated at our Institute. The inclusion criteria required histologically confirmed diagnosis and measurable disease. Patients underwent complete physical examination, routine blood tests, and magnetic resonance imaging (MRI) of the tumor area and other radiographic work-up as appropriate and possible. No patient had undergone previous cytotoxic chemotherapy or hormone therapy. No patient had previous family history that suggested predisposition for desmoid tumors or Gardner’s syndrome. The presenting site and symptoms of disease were consistent with those previously reported in the literature. All patients had inoperable, deep extra-abdominal aggressive fibromatosis. Their median age was 24 (range 18-47), with predominantly male sex (6/9) (Table 1). Extremities were the most frequent localization (5/9), followed by chest wall in 3 and abdominal wall in one patient. Tumor size in most patients was 5-10 cm, and 3 patients had bulky disease (over 10 cm) (Table 1). Five patients had undergone previous surgery (3 wide excisions and 2 palliative interventions). The major symptoms on presentation were paresthesia, pain, and limitation in the function of the extremities.

All patients were treated with 6 cycles of CVP (cyclophosphamide 750 mg/m² and vincristine 1.2 mg/m² both given bolus i.v. on day 1, and prednisone 40 mg/m²/daily orally on days 1 to 5, every 21 days), and tamoxifen 20 mg daily. Treatment was mostly given in an outpatients setting. Follow up was performed every 3 months by clinical examination, MRI and/or computed tomographic (CT) scans.

CR was defined as the complete disease disappearance for at least 1 month. PR was defined as reduction of 50% or more in the sum of the products of the two greatest perpendicular diameters of measurable lesions. SD was defined as no significant change in tumor size on physical examination or less than 50% reduction of tumor size on MRI. All other treatment outcomes were considered treatment failure.

**Results**

**Response to therapy**

Five patients who were treated with CVP+ tamoxifen responded. CR was observed in one (aggressive fibromatosis of extremity), PR in 4 (3 extremities and one thoracic wall), and SD in 4 patients (one extremity, one abdominal and 2 thoracic wall) (Table 2). In responding patients, the median time to the onset of response was 10 months (range 4-14) and the median response duration was 32+ months (range 14-82) (Figure 1). No relapse of disease was observed thus far.

<table>
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**Table 1. Patient characteristics**

<table>
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<td>PR</td>
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**Table 2. Treatment results**

Median response duration 32+ months
CR: complete response, PR: partial response, SD: stable disease
In general CVP + tamoxifen therapy was tolerated reasonably well. No severe toxicity requiring erythrocyte or platelet transfusion or G-CSF support was noted. No febrile neutropenia occurred. No patient required inpatient management. Moderate nausea was the main side effect. There were no treatment delays due to toxicity.

### Discussion

With all possible approaches in the treatment of aggressive fibromatosis, any therapeutic decision should always be a result of multidisciplinary team with experience in sarcomas [19], especially in the cases in which surgery is clearly unfeasible. Surgery remains the mainstay of treatment, and as it seems, it represents the only procedure with curative potential. Patients having tumors less than 5 cm in diameter had a significantly better outcome, with a 5- and 10-year disease-free survival rate of 94%, whereas patients with tumors ≥ 5 cm in diameter had a 72% 5-year disease-free survival rate [20]. However, the lesions tend to be bulky at presentation. Data shows that wide surgical margins did not lower the relatively high recurrence rate reported in several series, that range from 24 to 77% at 10 years [7-11], suggesting that optimal surgical treatment still remains the primary goal in the therapy of this disease [22]. Reoperation and post-operative radiation are associated with a high risk of local recurrence [21]. Although microscopic surgical margins may not make a difference in primary lesions, adjuvant radiotherapy may have a role in patients with positive margins. If the margins of resection are negative, there is no evidence that adjuvant treatment improves the outcome and such patients should only be followed [21].

The role of radiotherapy remains controversial because local control is often achieved at a considerable cost, due to significant treatment-related morbidity from the high doses of external radiation therapy (>50 Gy) [22,23].

Available data shows that aggressive fibromatosis can occur at any age, yet the low median age (24 years) of our group of patients suggests that surgery and radiotherapy should be planned carefully, with maximum preservation of the involved organs and limb function with good final cosmetic and functional result. Unsatisfactory cosmetic or even mutilating result of surgery and radiotherapy should be avoided, especially in recurrent disease.

Our report indicates that local control of disease can be safely achieved by CVP + tamoxifen chemohormonotherapy for extended periods of time. However, as previously noted by Weiss and Lackman [24], response to therapy might be slow, suggesting a delayed introduction of second- or third-line therapy. Duration of therapy remains controversial, yet our results suggest that extended therapy can control disease for a long time.

The implication of achieving stabilization of disease in terms of disease control also remains controversial. Recent reports suggest that vitamin D3 may also have a potential role in the control of this disease [25]. As long as the number of patient treated with systemic agents remains low, no matter how promising response rates are, systemic treatment with cytotoxic agents will be experimental or applicable to situations in which more conventional modalities have already been tried [17]. However, more studies like ours, most probably multicenter for greater accrual of patients, would explore more accurately the potential role of cytotoxic agents in the treatment of aggressive fibromatosis.

### References