Low-dose chemotherapy for extra-abdominal desmoid tumor

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ABSTRACT

الأهداف: لتحديد نسبة النتائج في المرضى المصابين بالورم الرباطي البطني، والمعالجين بجرعات مخففة من العلاج الكيميائي (ميثوتريكسيت وفينبلاستين) من حيث إستجابة الورم والتسمم.

الطريقة: تمت مراجعة نتائج 12 مريضاً إستعادياً من الذين تلقوا جرعة مخففة من العلاج الكيميائي للورم الرباطي البطني الزائد. أجريت هذه الدراسة خلال الفترة مابين عام 1996م وحتى عام 2003م، بجامعة ومركز ماكجيل الصحية (MUHC) – مونتريال – كندا. تم تقييم المرضى لمعرفة شكواهم، استجابة الورم للعلاج، الآثار الجانبية للعلاج، وأثر المعالجة على الأعراض. كان هناك 7 إناث و5 ذكور بمتوسط عمر 46 عاماً.

النتائج: كان المرض ذو الصلة بالحالة المرضية بما في ذلك الألم لدى سبعة مرضى، محدودية الوظيفة لدى سبعة مرضى، والآثار الشكلية لدى ثلاثة مرضى. بلغ متوسط حجم الورم 11cm (3–20cm)، كان متوسط فترة المتابعة 43 شهراً (15–71 شهر). تم إعطاء العلاج الكيميائي على بشكل أسبوعي. كانت المضاعفات الرئيسية ملحوظة. فقط مريضين لم يتعرضا للتسمم. وفقًا للفئة المعيارية (RECIST) ستة أورام أظهرت استجابة جزئية، وستة أورام بقيت مستقرة. لم يحدث تقدم للأورام. حقق ستة مرضى من بين سبعة الذين تعرضوا لأورام مؤلمة زوال ملحوظ للأعراض. تحسنت الوظيفة لدى ثلاثة مرضى واستعادها أربعة منهم. تحسنت الشكلية لمريضين من بين ثلاثة مرضى. على الأقل بقيت الأورام التي تمت متابعتها مستقرة لدى ثمانية مرضى، أحدها تراجع بشكل ملحوظ بينما تعرض ثلاثة للتقدم على متوسط 54 شهراً. احتاج مريض واحد فقط للخضوع لعملية جراحية. كان الأثر الجانبي الوحيد على المدى الطويل اعتلال عصبي حسي محيطي.

خاتمة: تبين أن الجرعة المخففة من العلاج الكيميائي علاج مساعد قيم لمنع التقدم المحلي للورم وتحسين الأعراض.

Objective: To assess the outcome of patients with extra-abdominal desmoid tumor treated with low dose chemotherapy (methotrexate and vinblastine) both for tumor response and treatment related toxicity.

Methods: We retrospectively reviewed the outcome of 12 patients who underwent low dose chemotherapy for extra abdominal desmoid of different locations. The study took place in the McGill University Health Center, Montreal, Canada between 1996 and 2003. We evaluated the patients for their compliance, tumor response, complications of treatment, and impact of treatment on symptoms. There were 7 females and 5 males with a mean age of 46 years.

Results: Disease related morbidity included pain in 7 patients, functional limitation in 7 and cosmetic defects in 3. The mean tumor size was 11 cm (3-20 cm). The mean follow-up was 43 months (15-71 months). Chemotherapy was administered weekly. Complications were significant. Only 2 patients did not experience the toxicity. According to Response Evaluation Criteria in Solid Tumors, 6 tumors showed a partial response and 6 remained stable. None showed progression. Of the 7 patients who had painful tumors, 6 achieved significant symptom relief. Function was improved in 3 and restored to normal in 4. Cosmesis was improved in 2 of the 3. At latest follow-up, tumors remained stable in 8, one has markedly regressed and 3 exhibited progression at an average of 54 months. Only one patient required surgery. The only long term side effect was a sensory peripheral neuropathy.

Conclusion: Low dose chemotherapy was found to be a valuable adjunct to prevent local progression and improve symptoms.

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Aggressive deep fibromatosis is a benign lesions of fibroblast and of mesenchymal origin.[1] Extra-abdominal lesions most commonly involve shoulder girdle, pelvic girdle, chest wall and neck.[2,3] Epidemiologically, desmoid tumors represent 3% of all soft tissue tumors.[4] The estimated incidence in the general population is approximately 2-4 per million per year.[5] Young adults ranging from 10-40 years are the most commonly affected.[5] Histology shows normal looking fibroblastic cells with low to moderate cellularity and abundant collagen production. Mitoses are scarce and necrosis is rare. Differential diagnosis includes fibrosarcoma, reactive fibroblastic proliferations, desmoplastic fibroma, myxoma, and nodular fasciitis.[6] The mechanisms of the development and regulation of growth of desmoid tumors are unknown. There is an evidence that hormones, especially estrogen, may play some sort of regulatory role. This is supported by the higher incidence of desmoid tumors in women during their reproductive years, the apparent tendency of tumors to develop during pregnancy or soon after, their occasional disappearance after menopause, the production of similar lesions in laboratory animals by estrogen administration and the potential benefit of antiestrogen drugs.[7,8,14] A connective tissue growth disorder has been implicated in the pathogenetic process leading to the development of desmoid tumor.[9] More than 97% of desmoid tumors occur sporadically, without identifiable hereditary component. No genetic mutations have been recognized.[10] The clinical behavior and natural history of desmoid tumors remain unpredictable and enigmatic. In some patients, the disease progress rapidly and aggressively despite treatments, whereas in others it is more indolent and may remain stable without any subsequent problem.[11] Typically, however, most desmoids are slow-growing tumors that infiltrate tissues and organs and can sometimes lead to compression of vital structures and even death on occasion.[12] Spontaneous regression has been reported even in a case of multicentric tumors.[13] Multicentric disease and recurrence or reactivation at sites other than the primary location has been reported.[15] Therefore, despite their benign nature histologic appearance, their biologic behavior can be seen as locally "malignant" necessitating resection with wide margins similar to that required in cancer surgery. Behavior of a desmoid tumor both determines the treatment approach and provides a mean of evaluating treatment efficacy. Rapidly growing tumors are managed more aggressively and persistence of rapid growth is an indication of ineffective treatment.[7] A desmoid exhibiting reduction of size suggests either effective treatment or favorable natural history. The aims of systemic therapy for desmoid tumors are to induce remission, minimize complications and prevent disease recurrence, but mostly to avoid morbidity and functional impairment associated with extensive surgery and/or radiotherapy. In the past, non-cytotoxic systemic therapy such as non-steroidal anti-inflammatory drugs together with anti-estrogens was considered the first-line treatment.[16,17] Cytotoxic chemotherapy has been tried after failure of non-cytotoxic treatment and in patients with unresectable tumors or with residual disease.[18] Doxorubicin has been used, usually in combination with other agents, such as dacarbazine or cyclophosphamide and vincristine. Response rates as high as 50% have been reported, but at the expense of severe toxicity both acute (especially nausea and vomiting) as well as delayed; myocardial toxicity being of particular concern.[19] The use of interferon-alpha[20,21] and imatinib[22] have also been reported with some success. In view of the "benign: nature of desmoids, Weiss and Lackman[23] suggested the use of non-alkylating agents to minimize the health hazards of chemotherapy, the so called "low dose chemotherapy' regimen. This consists of methotrexate (50 mg weekly) combined with vinblastine (10 mg weekly). In a series of 12 patients with short follow-up, 3 had a complete response and 7 had a partial response.[25] All had a significant symptomatic relief. In an earlier report from this group, acute toxicity consisted of nausea in 7 of 8 patients as well as mild to moderate hematology toxicity in almost all patients. Although it was sometimes necessary to reduce the chemotherapy doses there was no need to discontinue the treatment.[26] Peripheral neuropathy was noted in 3 of 7 patients and reported as non-severe. Another study using a similar regimen in 30 patients noted partial responses in 12 and stable disease in 18, but no complete tumor response was recorded.[24] Of the 19 patients 2 experienced grade 3 leukopenia (**Table 1**). Neither anemia nor thrombocytopenia superior to grade 1 was recorded. Treatments had to be delayed in some patients. Half of the patients stopped treatments on their own, most often after 6 months. No persistent peripheral neuropathy was noted. Grade 1 elevation of liver transaminases was noted in 4 and grade 1 alopecia in 5. Of much interest was the reported overall actuarial progression free interval of 67% at 10 year. Following these reports low dose chemotherapy has been suggested as an excellent first round of treatment for any patient in whom contemplated local treatment has significant morbidity.[27]

We favored an interdisciplinary approach to desmoid management. Newly diagnosed tumors that are small and easy to widely excise are usually dealt with surgically, but this represents an infrequent scenario. When tumors are asymptomatic or progression is not

Table 1 - Tumor study base in chemo toxicity criteria.

Chemo toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asthenia	Mild	Moderate Affects adls	Severe Impacts adls	Disabling	Death
Neutropenia	<Lln – 1500/mm³ <Lln – 1.5 x 10^9/l	<1500 – 1000/Mm³ <1.5 – 1.0 X 10^9/l	<1000 – 500/Mm³ <1.0 – 0.5 X 10^9/l	<500/Mm³ <0.5 X 10^9/l	Death
White blood cells	<Lln – 3000/mm³ <Lln – 3.0 x 10^9/l	<3000 – 2000/Mm³ <3.0 – 2.0 X 10^9/l	<2000 – 1000/Mm³ <2.0 – 1.0 X 10^9/l	<1000/Mm³ <1.0 X 10^9/l	Death
Platelets	<Lln – 75,000/mm³ <Lln – 7.5 x 10^9/l	<75,000– 50,000/Mm³ 75.0-50.0 X 10^9/l	<50,000-25,000/Mm³ <50.0-25.0 X 10^9/l	<25,000/Mm³ <25.0 X 10^9/l	Death
Stomatitis	Erythema	Patchy ulcerations Pseudomembranes	Bleeding with minor trauma	Tissue necrosis Spontaneous bleeding	Death
Neuropathy-motor	Weakness on testing only	Symptomatic on function, adls normal	Weakness affects adls - cane, brace	Disabling Paralysis	Death
Neuropathy-sensory	Loss of dtrs Paresthesias, normal function	Sensory alteration, paresthesia/tingling Adls normal	Sensory alteration or paresthesia interfere with adls	Disabling	Death
Cardiac	Ekg abnormal Asymptomatic	Non-urgent medical intervention indicated	Incomplete control with meds Pacemaker	Life threatening Chf, syncope, hypotension, shock	Death
Hepato-biliary liver dysfunction		Jaundice	Asterixis	Encephalopathy Coma	Death
Infection febrile neutropenia			Present	Life threatening Septic shock, acidosis	Death

adls - activity of daily livings, dtrs - deep tendon reflex, Lln - low limit of normal

Table 2 - Response Evaluation Criteria in Solid Tumors (RECIST).[28]

Complete response	Disappearance of all lesions
Partial response	At least 30% decrease in longest diameter of single tumor or sum of LDs of multiple
Stable disease	Neither PR nor PD criteria met
Progressive disease	Greater than 20% increase in LD of single tumor or the sum of LDs in multiple masses, or appearance of new lesions

CR - Complete response, PR - Partial response, SD - Stable disease, PD - Progressive disease, LD - longest diameter

Table 3 - Magnetic resonance imaging documented size and Response Evaluation Criteria in Solid Tumours (RECIST) Criteria.[28]

Patient no.	Tumor site	Pre-treatment tumor size	End of treatment tumor size	Percentage of change in longest diameter	RECIST
1	Axilla	10 x 6 cm	6.5 x 6 x 6.5 cm	-40	Partial response
2	Post. thigh	10 cm	10 cm	0	Stable disease
3	Deltoid	5 x 12 cm	3.5 x 3.5 x 8 cm	-33.3	Partial response
4	Post. thigh	15 x 10 cm	12 x 2 x 4 cm	-20	Stable disease
5	Axilla	6 x 5.5 x 4 cm	6.5 x 4.5 x 5 cm	+8.3	Stable disease
6	Thigh	3 x 4.5 x 20 cm	3 x 4.5 x 20 cm	0	Stable disease
7	Thorax post	11 x 10 x 4 cm	11 x 10 x 4 cm	0	Stable disease
8	Thigh	10 x 8.5 x 6.5 cm	6.8 x 4.5 x 2.8 cm	-32	Partial response
9	Clavicular	17 x 16 x 10.5 cm	6 x 6.8 x 4.5 cm	-60	Partial response
10	Post. thigh	20 x 40 cm	17 x 4.3 x 6.4 cm	-57.5	Partial response
11	Clavicular	10 x 6.5 x 5.5 cm	9 x 6.5 cm	-10	Stable disease
12	Scapular	6 x 5 x 8 cm	4.4 x 5.2 cm	-35	Partial response

PR - Partial response, SD - Stable disease, post - posterior

clinically demonstrated we favored observation with repeated imaging and close follow-up. For tumors that were symptomatic, growing and where surgery would have extensive we favored low dose chemotherapy regimen. The purpose of this study was to assess the outcome of patients with extra-abdominal desmoid tumor treated with low dose chemotherapy both for tumor response and treatment related toxicity.

Methods. We obtained the ethics committee approval not for the treatments, but for the retrospective review of charts. Patients were identified using our prospective musculoskeletal tumor database. This was a review of outcome following treatment, patients consented to treatment, but did not consent for a study and did not have to. The study took place in the McGill University Health Center, Montreal, Canada between 1996 and 2003. The ethics board of the hospitals gave consent for the research and charts review. The medical records of all patients with histologically proven extra-abdominal desmoid tumor who were given low dose chemotherapy were reviewed retrospectively. Selection criteria included proper MRI imaging pre- and post- treatment and a minimal follow-up of one year after completion of chemotherapy, discussed with the reviewing radiologist. Patients seen but treated or followed outside our institutions were excluded. Appropriate ethic approvals were obtained. Toxicity criteria from the National Cancer Institute common terminology criteria for adverse events version 3.0 (CTCAE) were used (**Table 1**). Tumor response was assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) (**Table 2**).[28] Statistical analysis was carried out using SPSS version12.0

Results. We recorded 12 patients, 5 men and 7 women. Their mean age was 46 years ranging from 26-69 years. Significant symptoms included pain in 7 patients, functional limitation in 7 and cosmesis in 3. Desmoids involved the shoulder girdle in 7, proximal thigh in 4 and popliteal fossae in one. The mean tumor size was 11 cm, ranging from 3-20 cm. All tumors underwent histological confirmation with open or core needle biopsies. The mean follow-up after completion of chemotherapy was 43 months, ranging from 15-71 months. Chemotherapy consisted of Methotrexate and Vinblastine administered weekly. Number of cycles varied from 16-50 depending on tumor response, patient tolerance and compliance. Only 3 patients could tolerate the recommended dosage and schedule of chemotherapeutic agents. Complications were significant and included sensory neuropathy in 5 (grade II), asthenia in 3 (grade II: one and grade III: 2), and neutropenia in 2 (one grade II and one grade III). Filgrastim was occasionally given to avoid treatment delay or dose reduction. One treated patient had an elevation of bilirubin, and found to have Gilbert's disease. Only 2 patients did not experience toxicity (**Table 1**). Of 12 one patient (retired) were working prior to chemotherapy treatments. During chemotherapy the work status was as follows: 6 patients kept their full-time employment, 2 were unable to work and 3 necessitated temporary work arrest during course of treatments. Job descriptions were not available and prevented further analysis. According to RECIST criteria after completion of chemotherapy, 6 tumors exhibited partial response and 6 remained stable. None progressed, including one where treatments were stopped at only 16 weeks, but no tumor regressed completely (**Table 3**). Symptoms improved as follow: Of the 7 patients who had painful tumors 6 of them achieved symptom relief. Of the 7 patients with impaired function, partial improvement was noted in 3 and normal function was restored in 4. Cosmetic outcome was improved in 2 out of 3. At latest follow-up, tumor size remained stable in 8, one exhibited marked shrinkage over the years and 3 showed some progression. Progression occurred after an average of 54 months. Only one patient ultimately required surgery. We did not observe any long term side effects of the low dose chemotherapy regimen other than sensory peripheral neuropathy, which occurred in 42% of patients.

Discussion. Only a few reports of small series have addressed the risks and benefits of the low dose chemotherapy regimen. The limitations of the present study include its small sample, its retrospective nature and the loss to follow-up of other cases were this treatment regimen was provided, but outside our direct supervision. We found this regimen to be of value as most tumors remained stable or regressed somewhat during treatment (**Table 3**). Symptoms reduction was also observed, but may be the result of the anti-inflammatory effect of the chemotherapy as tumor volume reduction was infrequent. In many cases, this relief was maintained long after treatments stopped. Interestingly, only one patient among the 12 underwent surgery after his tumor grew again one year after cessation of treatments. He refused a second course of low dose chemotherapy. We have found that low dose chemotherapy treatments were not as well tolerated as previously reported.[23,26] All treatments were given on an outpatient basis, but only 50% of patients were able to keep their regular work without interruption. Additionally, significant side effects, including permanent peripheral neuropathy, were found frequent

and lasting. Patients were able to resume their normal activities following completion of chemotherapy. Of interest there were no long term sequelae other than the sensory neuropathy already noted. This is consistent with the results reported in other series. We therefore support the use of low dose chemotherapy regimen as an effective means to avoid extensive surgical resection, but encountered significant difficulty with tolerance and observance of the proposed regimen. Dose reduction of vinblastine may lessen this risk. Non cytotoxic drug therapy should probably be considered as first line of treatment in non-urgent cases. Other chemotherapy regimens should be considered only following failure of the low dose regimen. Management of desmoid tumors deserves better attention with the initiation of large prospective multicentric studies.

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