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ORIGINAL REPORT

Successful Chemotherapeutic Modality of Doxorubicin Plus Dacarbazine for the Treatment of Desmoid Tumors in Association With Familial Adenomatous Polyposis

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ABSTRACT

Purpose
Desmoid tumors are locally aggressive and can be fatal in familial adenomatous polyposis (FAP) patients if they are not suitable for surgery or radiation therapy. Here, we prospectively investigated the efficacy of a chemotherapeutic regimen involving doxorubicin (DOX) and dacarbazine (DTIC) for inoperable FAP-associated desmoid tumors.

Patients and Methods
From an initial group of 120 FAP patients, seven of the 11 individuals with symptomatic unresectable desmoid tumors that were unresponsive to conventional hormone therapy were enrolled onto this study. The general chemotherapy regimen comprised four or five cycles of DOX (20 mg/m^2 daily) plus DTIC (150 mg/m^2 daily) throughout 4 days of drip intravenous infusion (day 1 through 4) every 28 days, followed by the cyclooxygenase–2 inhibitor meloxicam (10 mg/m^2). The primary end point was relapse-free survival. The secondary end points included toxicity, clinical improvement, and tumor regression according to computed tomography.

Results
Significant tumor regression was observed clinically and radiologically in all seven patients. Three patients showed a complete response. The average progression-free survival period was 74.0 months (range, 32.5 to 107.5 months). Three patients showed grade 3 adverse events with no treatment-related mortality. All seven patients survived and remained without tumor progression. An adenomatous polyposis coli germline–mutation analysis revealed no mutations in the specified regions.

Conclusion
A chemotherapeutic regimen of DOX plus DTIC followed by meloxicam is an effective and safe treatment for FAP-associated desmoid tumors. This modality should be considered for use as first-line chemotherapy in symptomatic desmoid tumors that are unresponsive to conventional medical therapy, due to the absence of useful presymptomatic markers.

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INTRODUCTION

Familial adenomatous polyposis (FAP) is a well-known model for colorectal tumorigenesis.[1] This dominantly inherited genetic disorder is caused by mutations of the adenomatous polyposis coli (*APC*) gene on chromosome 5q21q22,[1] and germline *MYH* mutations.[2] Patients with FAP develop hundreds of colorectal polyps that eventually lead to cancer and have an approximately 1,000-fold higher risk of developing desmoid tumors (desmoids) compared with the general population.[3] Sporadic desmoids are rare, accounting for fewer than 0.1% of all tumors, and are generally nonaggressive benign fibromatoses.[4] There are notable differences in the characteristics of FAP-associated and sporadic desmoids. The former are found in 3.6% to 13% of all FAP patients[5] and are locally invasive. Desmoids are a frequent cause of death in patients with FAP (10.9%), second only to colorectal carcinoma (58.2%), and are the most common single cause of death after prophylactic colectomy.[6]

Surgery is the widely accepted first-line treatment for extra-abdominal and abdominal-wall desmoids, but it is not recommended for mesenteric desmoids because of the high risk of recurrence and the difficulties involved in the operation.[7-10] Palliative surgery for intra-abdominal desmoids is hazardous, with a perioperative mortality rate of 10% to 60% (usually from blood loss), and can result in

further tumor progression.[9,11-14] Alternative treatment options are therefore required for patients with tumors that are not amenable to surgery. Nonoperative therapies, such as radiotherapy, antiestrogen therapy using tamoxifen, and nonsteroidal anti-inflammatory drugs (NSAIDs), have shown limited success in such cases.[10,15] Thus, there is a need to establish an optimal chemotherapeutic protocol. Several retrospective reports have suggested that the use of combination therapy involving doxorubicin (DOX) and dacarbazine (DTIC) was effective in a FAP patient with an intra-abdominal desmoid.[16,17] Here we report our experience of the prospective study using this combination therapy followed by the cyclooxygenase–2 (COX-2) inhibitor meloxicam in patients with intra-abdominal FAP-associated desmoid tumors.

PATIENTS AND METHODS

Patients

A total of 120 FAP patients underwent prophylactic surgery, involving total colectomy, mucosal proctectomy, or ileal J-pouch anal anastomosis (IAA), at the Hyogo College of Medicine, Japan, between January 1993, and December 2004. Eleven of these patients had intra-abdominal desmoids. Seven of the 11 patients with intra-abdominal desmoids who were treated at the Hyogo College of Medicine between April 1993 and March 2005 were enrolled onto the present study. All seven patients gave their written informed consent. The study group included four women and three men with a mean age of 32.2 years (range, 28.1 to 37.1 year). The DOX plus DTIC protocol comprised DOX (20 mg/m^2 daily) plus DTIC (150 mg/m^2 daily) over 4 days of drip intravenous infusions (d.IV; day 1 through 4; Fig 1). This cycle was repeated every 28 days, and patients were advised to stay on this regimen for at least four cycles. All patients were administered meloxicam (10 mg/m^2), which is a selective COX-2 inhibitor that offers an alternative to coxib, after the DOX/DTIC treatment. Three of the seven patients had formerly been prescribed other NSAIDS, such as sulindac, etodolac, and mofezolac. Complete follow-up was achieved for all seven patients. The ethics committee of Hyogo College of Medicine approved the study protocol.

Analysis of Germline Mutations of the APC Gene

mRNA and genomic DNA were extracted from lymphocytes in the peripheral blood of four FAP patients with desmoid tumors, all of whom gave their informed consent for the procedure. For the screening step of the germline-mutation search in the *APC* gene, we used an in vitro–synthesized protein (IVSP) assay using six overlapping primer pairs (systems A to F), which covered the entire coding region. Systems A to F corresponded to codons 1 to 479, 348 to 758, 658 to 1,283, 1,099 to 1,700, 1,547 to 2,246, and 2,123 to 2,844, respectively. The IVSP assay was carried out as described previously.[18] Direct polymerase chain reaction DNA sequencing was carried out for all samples that showed an aberrant band.

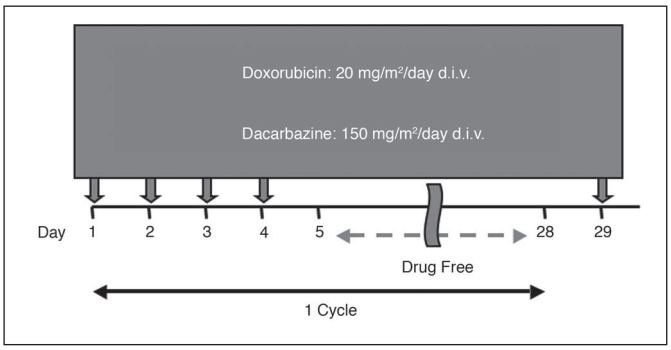

Fig 1. Regimen of doxorubicin plus dacarbazine. d.IV, drip intravenous infusion.

Outcome

The primary end point was relapse-free survival. The secondary end points included toxicity, clinical improvement and tumor regression according to computed tomography (CT). Complete response (CR) was defined as the disappearance of the tumor on a CT scan. Partial response (PR) was defined as a reduction in the sum of the products of the perpendicular axes of the tumor of more than 50% that persisted for at least one month after treatment. Minimal response (MR) was defined as any response that was less than 50%. Toxicity to chemotherapy was assessed according to the criteria for adverse events published by the National Cancer Institute (version 3.0).

RESULTS

Six patients received four cycles of DOX/DTIC chemotherapy and the remaining patient received five cycles. The patient characteristics and treatments are listed in Table 1. The four patients who gave informed consent for the *APC* germline–mutation analysis showed no apparent mutations in the relevant regions. In all seven cases, significant tumor regression was detected both clinically and radiologically. Three patients showed CR (Fig 2). The average progression-free survival period was 74.0 months (range, 32.5 to 107.5 months). All of the patients seemed to tolerate the chemotherapy well, and no treatment-related mortality was reported. Three patients showed grade 3 adverse events. All seven patients are currently alive with no evidence of tumor progression.

DISCUSSION

Recent advances in surgical procedures—such as IAA, which allows both radical removal of the rectal mucosa and the preservation of natural anal function—have drastically improved the quality of life and prognosis of FAP patients.[19] However, desmoid tumors remain a life-threatening complication and an important prognosis-determining factor of FAP. Many investigators have failed to demonstrate the influence of genetic factors independent of the *APC* gene in susceptibility to FAP-associated desmoid tumors, and there are no other reliable indicators of desmoid growth.[20] The clinical management of FAP patients in order to reduce the risk of serious desmoid tumors could be achieved through early detection by frequent imaging diagnoses, the application of effective treatments other than surgery, or feasible chemoprevention. However, no methods have been demonstrated to prevent desmoid tumors. Our study confirmed that the DOX/DTIC regimen achieved significant objective tumor shrinkage in all seven patients, with tolerable toxicities and no increase of tumor size. The main implications of these results are discussed below.

First, this is a prospective study giving confirmable evidence of the value of the regimen initially described by Patel et al both in terms of efficacy and safety. DOX interferes with the function of topoisomerase II,[21] and DTIC is an *N*-methyl-type compound that produces alkylating species.[22] The DOX/DTIC combination therapy is used for soft tissue sarcoma as well as for Hodgkin's lymphoma.[22] The evidence seems to strongly point to the success of the evident tumor regressions and the ongoing relapse-free survivals in FAP-associated desmoids. The toxicity profile of the DOX/DTIC regimen is well reported in the literature.[22,23] In our experience,

Table 1. Patient Characteristics and Treatment

Patient No.	Time Since Colectomy months	Cycle of DOX/DTIC Treatment	Response	Progression-Free Survival Time (months)	Neutropenia Grade	*APC* Germline Mutation and Consequence
1	39	4	CR	107.5	0	4660-4668 insA, Premature stop at codon 1558
2	20	4	CR	106.2	2	637C > T, R213X
3	17	4	CR	33.2	3	Not done
4	9	4	PR	32.5	3	Not done
5	12	4	PR	56.7	2	No mutation in the coding region
6	15	4	PR	104.7	0	Mutation in system A
7	18	5	PR	76.9	3	Not done

Abbreviations: DOX, doxorubicin; DTIC, dacarbazine; CR, complete response; PR, partial response.

DOX administered as a d.IV for 4 days showed no cardiotoxicity and no grade 4 neutropenia, while DTIC administered as a d.IV caused no serious nausea, an adverse effect commonly associated with its bolus injection.

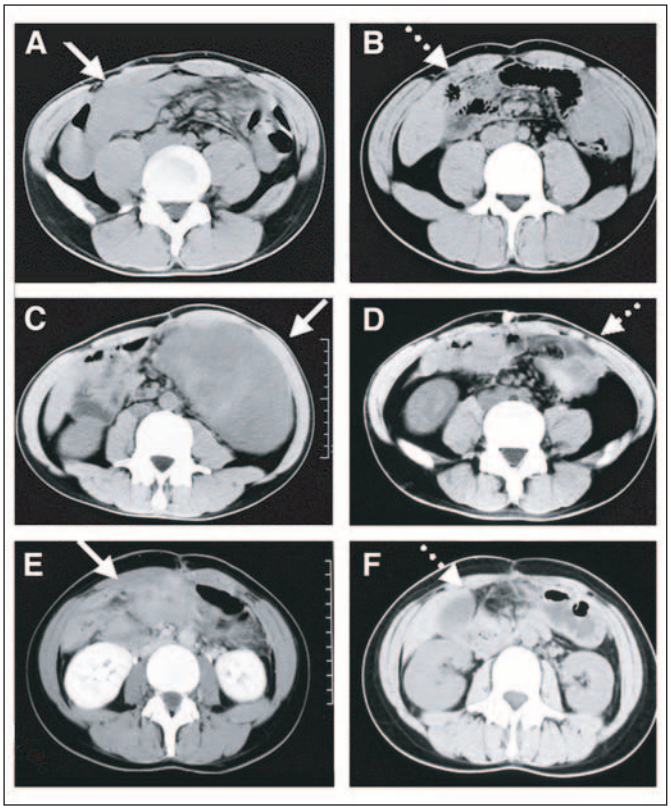

Fig 2. Patient 1: An intra-abdominal desmoid was found 39 months after IAA. (A) CT scan before DOX/DTIC therapy showing a large mass the in abdomen. (B) CT scan of the same patient after DOX/DTIC therapy, showing CR with no residual tumor. Patient 2: A pelvic desmoid was found 20 months after IAA. (C) CT scan before DOX/DTIC therapy showing a large mass in the pelvis. (D) CT scan of the same patient after DOX/DTIC therapy, showing only scarring and fibrosis of CR with no residual tumor. Patient 3: An intra-abdominal desmoid was found 17 months after IAA. (E) CT scan before DOX/DTIC therapy showing a large mass in the abdomen. (F) CT scan of the same patient after DOX/DTIC therapy, showing CR with no residual tumor. IAA, ileal J-pouch anal anastomosis; DOX, doxorubicin; DTIC, dacarbazine; CT, computed tomography; CR, complete remission.

Second, meloxicam might hold promise for the management of FAP. NSAIDs are believed to have the potential to restore normal apoptosis, inhibit angiogenesis and tumor invasiveness, and attenuate tumor-mediated immune suppression.[25] DOX is known to induce the overexpression of multidrug resistance-1 (MDR-1), which is frequently associated with decreased drug accumulation in cancer cells and poor prognosis. A recent report revealed that meloxicam, particularly at low concentrations, inhibits MDR-1 overexpression via COX-2 activity and prostaglandin E2 release in acute myeloid leukemic cells.[26] Meloxicam might therefore be an effective first-line chemopreventive agent, as the popular alternative COX-2 inhibitor, coxib, carries a high risk of adverse cardiovascular events.

Third, our data do not reveal a significant relationship between the incidence of desmoid tumors as an extracolonic manifestation in FAP and *APC* mutations. Nugent et al reported that desmoid tumors and extracolonic cancers are commonly associated with mutations in the *APC* gene at codon 1,309.[27] Caspari et al reported that FAP patients with mutations in codons 463 to 1,387 frequently developed congenital hypertrophy of the retinal pigment epithelium, while all individuals with mutations in codons 1,445 to 1,578 developed desmoid tumors.[28] Taken together, these results suggest that desmoids are a phenotypic variant of FAP due to an abnormal fibroblastic response caused by the effects of a specific germline mutation. However, our data reveal no significant correlation between the manifestation of desmoids and a specific *APC* mutation site. It remains to be clarified whether the known genotype-phenotype relationships can be utilized for individual therapeutic decisions in presymptomatic or symptomatic mutation carriers. Our current findings are partly compatible with the report by Friedl et al,[29] who describe a higher incidence of desmoids in patients with mutations in codons 1,445 to 1,580 compared with those with mutations 5′ of this codon. Therefore, this modality should be considered early on in cases of symptomatic desmoid tumors that are unresponsive to conventional medical therapy, because of the lack of useful specific screening markers.

Our current study provides evidence of the usefulness of the DOX/DTIC regimen in the treatment of unresectable desmoid tumors, though it does not present a direct comparison with other chemotherapeutic regimens. The DOX/DTIC regimen should be considered as first-line chemotherapy for FAP-associated desmoid tumors because of its safety and efficacy.

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Authors' Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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