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Clinical Outcome of Tamoxifen and Sulindac for Desmoid Tumors in Adults: A Phase II Single Institution Experience

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Abstract

Background: Desmoid tumors are rare soft tissue neoplasms that have a variable and often unpredictable clinical course. We have conducted a phase II study to evaluate the efficacy and safety of tamoxifen and sulindac in treatment of primary unresectable and recurrent desmoid tumors.

Methods: Eligible patients were ≥18 years of age who had measurable histologically confirmed recurrent or newly diagnosed tumors not amenable to R0 resection, or those who underwent tumor excision with gross residual desmoid tumor. The primary objective was to estimate progression-free survival. Patients received 20 mg tamoxifen and 300 mg sulindac daily for up to 12 months according to absence of disease progression or unacceptable drug toxicity.

Results: 25 patients, 12 males and 13 females, whose ages ranged from 18-60 years. Most (88%) had a good performance status (ECOG 1). A total of 6 of 15 patients with recurrent desmoid tumors had histories of prior local radiotherapy for their primary tumors. There were 10 newly diagnosed patients, 15 (60%) had recurrent disease and only one patient had a diagnosis of familial adenomatous polyposis. Only 22 patients completed the treatment protocol and were evaluated for clinical response and time to progression. All patients were evaluated for safety profile. The overall response rate was 60%, with complete response observed in 8% and partial response in 52%. At two years, the estimated progression-free survival rate was 55% with a median progression-free survival of 25 months.

Conclusion: According to the results of this study, systemic treatment with tamoxifen and nonsteroidal anti-inflammatory drugs is safe and effective in patients with desmoid tumors.

Keywords: Desmoid tumor, Sulindac, Tamoxifen

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Introduction

Desmoid tumors (DTs) are considered benign, deeply seated monoclonal myofibroblastic neoplasms that grow slowly and are infiltrative.[1,2] They are also known as

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aggressive fibromatosis.[3]

Desmoid tumors mainly occur as 2 groups, either as part of familial adenomatous polyposis (FAP) that result from APC inactivating mutations or sporadically as a result of a somatic B-catenin activating mutation.[4,5] These tumors can be present at any soft tissue site, but preferentially locate in the abdominal wall, extremities, shoulders, neck, and chest wall. Familial adenomatous polyposis mostly presents with intra-abdominal tumors,[6,7] whereas sporadic cases occur more on the extremities and limb girdles.[8]

Females who develop DTs during or after pregnancy have a predilection for tumor development in the abdominal wall; thus, the effects of estrogen appear to be important.[9]

Desmoid tumors do not metastasize, but they have high potential for local recurrence.[10-12] Although there is a high rate of local recurrence, DT can regress spontaneously.[13] This regression is reported more often in cases of local recurrence than primary disease.

For decades, surgery with complete resection has been considered the standard treatment for DT; however, surgery is difficult and possibly associated with morbidity, particularly since completely resected DTs can recur.[11,14] Hence, a conservative approach in order to avoid surgical complications is used for primary tumors and recurrent lesions.[4]

Numerous systemic treatments for DTs such as hormonal therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), tyrosine kinase inhibitors, and cytotoxic chemotherapy have shown clinical benefit in the treatment of progressive and recurrent DTs.[15,16] According to some studies, AF were negative for estrogen receptor (ER) alpha but positive for ER-beta.[17-19] Tamoxifen is the most commonly used medication; it may be given at doses equivalent to that given in breast cancer (20 mg daily) or may be used at higher doses.[20,21]

The goal of this prospective phase II study was to evaluate the efficacy and safety of tamoxifen and sulindac in treatment of primary unresectable and recurrent DTs.

Patients and Methods

Patient eligibility

Eligible patients had evidence of histologically confirmed recurrent or newly diagnosed DT not amenable to R0 resection or underwent tumor excision with gross residual DT. Further criteria were age ≥18 years at initial diagnosis; measurable disease present on MRI or CT; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; no concurrent uncontrolled medical diseases; good hepatic, renal, and hematologic functions; and no other current or previous malignancies.

Exclusion criteria consisted of prior treatment with nonsteroidal anti-inflammatory agents (NSAIDs), tamoxifen or estrogen antagonists; females who did not agree to use non-hormonal methods of contraception; pregnancy or breast feeding; treated with other cytotoxic chemotherapy or radiation for the current recurrence; history of deep venous thrombosis; or advanced liver disease. All patients gave written or informed consent before treatment. The trial protocol was approved by Mansoura faculty of medicine Institutional Research Board (IRB); code number/17.04.130.

Pre-treatment evaluation

Initially, patients underwent thorough history and clinical examinations that included blood chemistries, CBC, and recent imaging of either computed tomography (CT) scans or MRI prior to administration of the current study medications.

Treatment

Patients received tamoxifen (20 mg/day) and sulindac in the form of 3, 100 mg doses (300 mg/day). Medications were given for up to 12 months based upon the absence of disease progression or unacceptable drug toxicity. Patients who achieved a complete response (CR) received one additional month of treatment after the CR.

Protocol therapy continued according to the original plan. Dose modifications or interruptions of sulindac and tamoxifen were allowed for life-threatening grades 3 or 4 toxicities (NCI-CTC

version 3). Adjuvant RT was not allowed during protocol therapy or the follow-up period. Surgery was allowed if the tumor could be excised without residual (R0) during therapy.

Toxicity assessment

We used National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3 to assess the adverse events in this study.

Response assessment and follow-up

All patients underwent regular follow-up visits that included history and physical examinations. During the first 2 years of treatment, patients underwent either CT or MRI scans at least every 4-6 months, then annually until documented sustained stable disease (SD) or the patient expired. In addition, each female had an annual pelvic ultrasound.

In this study, our clinical definition for SD was response and therapeutic success. Based on a comparison to the initial imaging (CT or MRI), we based the degree of response according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Complete response was no evidence of any residual tumor; partial response (PR) indicated a decrease by >30% with no new lesions; SD was considered to be neither PR nor PD; and progressive disease (PD) indicated an increase by >20% or the appearance of one or more new disease sites. The outcome was categorized using a cross-sectional area in a patient who suffered from multiple desmoids or diffuse growths. In mesenteric desmoids, complications such as bowel obstruction were always regarded as PD.

We followed all patients for recurrence and survival, including those who choose to discontinue treatment.

Statistical analysis

The primary end points of the study were an estimation of PFS rate and response rate for patients under treatment with sulindac and tamoxifen. The Kaplan-Meier method was used to estimate PFS. The secondary end point was toxicity as assessed by the NCI-CTCAE version 3.0. Age was expressed as median values. We used the unpaired t-test, two-sided Fisher's exact test, and SPSS version 23 (SPSS, Inc., Chicago, IL, USA) for data analyses.

Table 1. Patient characteristics (n=25).

Patient characteristics	Patients (n=25)	
	Number	%
Age (years)		
Median	32	
Range	18-60	
Sex		
Male	12	48
Female	13	52
Performance status (ECOG)		
0	2	8
1	22	88
2	1	4
Size (cm)		
≤5	6	24
>5	19	76
Disease status		
Newly diagnosed	10	40
Recurrent	15	60
History of FAP		
Yes	1	4
No	24	96
Prior radiation therapy		
Yes	6	24
No	19	76
Site of disease		
Mesentery	5	20
Pelvis	1	4
Abdominal wall	4	16
Shoulder	5	20
Axilla	3	12
Arm	2	8
Chest wall	3	12
Foot	1	4
Calf	1	4

ECOG: Eastern Cooperative Oncology Group; FAP: Familial adenomatous polyposis

Results

Patients' characteristics

We conducted this prospective phase II study

in the Clinical Oncology and Nuclear Medicine Department at Mansoura University Hospital. There were 25 patients with measurable recurrent or primary unresectable DT seen between June 2013 and December 2016 who enrolled in this study.

Table 1 shows the patients' characteristics. There were 12 male and 13 female patients with a median age of 32 years (range: 18-60 years). Of the 25 patients, 19 had tumors greater than 5 cm (76%) and 6 (24%) had tumors less than or equal to 5 cm.

Most patients (88%) had a good performance status of ECOG 1. There were 6 out of 15 patients with recurrent DT who had histories of prior local radiotherapy for primary disease. The most common disease sites were the mesentery, shoulders, and abdominal wall followed by the axilla and chest wall. A total of 10 patients had newly diagnosed DT, 15 (60%) had recurrent disease, and only one patient had a diagnosis of FAP.

Table 2. Response rates for treated patients

Response	Patients (n=25)	%
Overall response rate (ORR)	15	60
Complete response (CR)	2	8
Partial response (PR)	13	52
Stable disease (SD)	7	28
Progressive disease (PD)	3	12

Three (12%) patients discontinued treatment due to disease progression. No patient stopped treatment due to intolerable toxicity. Only 22 patients completed the treatment protocol and were evaluated for clinical response and time to progression. We evaluated all patients for safety profile.

Assessment of response and survival

Table 2 lists the overall response rates (ORR). The ORR for all of the patients was 60%, with 8% that had CR and PR in 52%. We observed SD in 7 (28%) and PD in 3 (12%) patients. The majority of the objective responses were achieved within

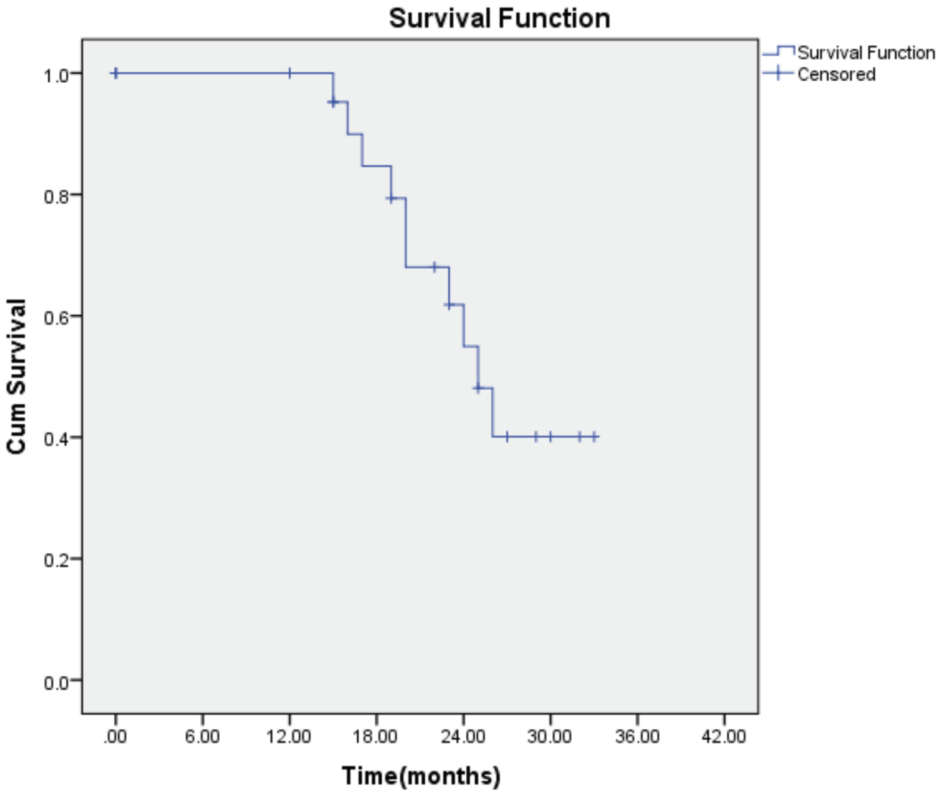

Figure 1. Progression-free survival (PFS) curve for 25 patients with primary unresectable or recurrent desmoid tumors (DTs) treated with tamoxifen and sulindac.

6 months after initiation of therapy. Time to tumor progression (TTP) was measured from the day of assignment to the protocol to the first evidence of progression, death from any cause, or the last date of follow-up if the patient did not experience any event with a median follow-up period of 15 months (range: 3-36 months). No patients died due to disease progression or from any unrelated cause. At two years, the estimated PFS rate was 55% (Figure 1) with a median PFS of 25 months (95% CI: 21.6-28.3).

Toxicity

The treatment was well-tolerated. Table 3 lists the treatment related toxicities. There were no grade 3 or 4 toxicities reported. The adverse effects of NSAID use (gastritis or emesis) or that related to tamoxifen (ocular problems or thromboembolism) were very rare.

Ovarian cysts

During the course of therapy, 2 out of 13 females Developed from 1-4 ovarian cysts. The two patients were asymptomatic and diagnosed by a routine required pelvic ultrasound.

Discussion

Desmoid tumors are rare, aggressive tumors.[22-23] Surgery has been the main line of treatment for many years; however, complete resections are difficult and DTs are prone to recurrence even after complete surgical resection.[11]

Positive margins of resected DTs are reportedly not adverse prognostic factors.[24,25] Conservative treatments for primary unresectable and recurrent disease have become respectable lines of treatment and show a better response rate with an anthracycline-containing regimen and hormonal treatment.[26]

In our study, we focused on the safety and efficacy of systemic treatment with tamoxifen and sulindac for unresectable primary and recurrent DTs. We found that DTs were more common in females with a median age of 32 years. Assessment of performance status showed that 90% of patients were ECOG 1. Tumor size ≤5 cm was observed in 24% of patients. The most common site of involvement was the mesentery and shoulders in five patients each, followed by the abdominal wall. These data coincided with previously reported patient and tumor characteristics.[18,27]

Table 3. Adverse effects according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3 (NCI-CTCAE).

Adverse effect	Grades 1/2		Grades 3/4
	Number	%	Number
Gastritis	2	8	0
Vomiting	3	12	0
Ocular	1	4	0
Abdominal pain	1	4	0
Headache	3	12	0

Patients treated with 20 mg of tamoxifen per day and 300 mg of sulindac per day had their medication response assessed. We observed that 52% achieved PR and 8% had CR. There was 55% of cases with PFS at 2 years and a median of 25 months.

The results of the current study are similar to a response achieved by Hansmann et al. who used high dose tamoxifen and sulindac as the first-line treatment for DT.[28] On the other hand, these results differed from those reported by Skapek et al., who reported an ORR of 8% (PR and CR) and 2 years PFS of 36%. This might be attributed to the study population of children <19 years of age and those with a poor prognosis.[29]

Treatment of DTs with chemotherapy associated with long lasting response for years ranged from 50%-80%; however treatment is also associated with cumulative toxicity which may limit the use of cytotoxic drugs.[30] Our results are similar to results reported by Garbay et al. who assessed different chemotherapy regimens in patients with recurrent and/or unresectable DT. In their study, one patient had a CR, 12 patients had PR and 37 patients had SD. Progression-free survival at 2 years was 60%.[27]

The treatment was well-tolerated with no reports of any grade 3 or 4 toxicities. Grade 1 and 2 toxicities of vomiting and gastritis were the most common toxicities. This has proven that

NSAIDs are well-tolerated with minimal adverse effects.[7]

The study by Garbay et al. used chemotherapy in patients with primary unresectable and/or recurrent DTs. They reported grades 3 or 4 hematological adverse events, especially in the anthracycline regimen (31%) compared to the anthracycline-free regimen (10%).[27]

This result might support the use of tamoxifen and NSAIDs in recurrent and/or unresectable primary DT instead of chemotherapy as they achieved similar results in terms of efficacy with less toxicity.

In the current study, 2 out of 13 (15%) females developed ovarian cysts during treatment, which were less than 4 in numbers. All were asymptomatic. This finding was less than reported by Skepak et al. who diagnosed ovarian cysts in 40% of patients; however, their results resembled the current study results in that all were asymptomatic.[29]

Although our study reported the safety and efficacy of systemic treatment with tamoxifen and NSAIDs in DTs, the small number of cases was one of the study limitations. Additional studies should be performed on larger numbers of patients. In the current study, we did not classify patients according to risk factors, which was another limitation. Patients should be divided into subgroups that consider risk factors that affect progression and disease recurrence in order to select the most appropriate treatment for each patient, whether surgery, chemotherapy, NSAIDs, or hormones.

Conflict of Interest

None declared.

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