

Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG)

D. Garbay¹, A. Le Cesne², N. Penel³, C. Chevreau⁴, P. Marec-Berard⁵, J.-Y. Blay⁶, M. Debled¹, N. Isambert⁷, A. Thyss⁸, E. Bompas⁹, O. Collard¹⁰, S. Salas¹¹, J.-M. Coindre¹², B. Bui¹ & A. Italiano^{1*}

¹Department of Medical Oncology, Institut Bergonie, Bordeaux; ²Department of Medicine, Institut Gustave Roussy, Villejuif; ³Department of Medical Oncology, Centre Oscar Lambret, Lille; ⁴Department of Medical Oncology, Institut Claudius Regaud, Toulouse; ⁵Institut d'hématologie et d'oncologie pédiatrique, Hospices civils de Lyon et Centre Léon Bérard, Lyon; ⁶Department of Medical Oncology, Centre Léon Bérard, Lyon; ⁷Department of Medical Oncology, Centre Georges-François Leclerc, Dijon; ⁸Department of Medical Oncology, Centre Antoine-Lacassagne, Nice; ⁹Department of Medical Oncology, Centre René Gauducheau, Nantes; ¹⁰Department of Medical Oncology, Institut de Cancérologie de la Loire, Saint-Priest-en-Jarez; ¹¹Department of Medical Oncology, Hôpital La Timone, Marseille; ¹²Department of Pathology, Institut Bergonie, Bordeaux, France

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Background: Data regarding the role of chemotherapy (CT) in patients with recurrent and/or unresectable desmoid tumors (DTs) are scarce.

Patients and methods: Records of patients with DT who were treated with CT in centers from the French Sarcoma Group were reviewed.

Results: Sixty-two patients entered the study. The two most common locations were extremities (35.5%) and internal trunk (32.5%). Twelve patients (19.5%) were diagnosed with Gardner syndrome. Thirty-seven patients (54.7%) received previously one or more lines of systemic therapies (nonsteroidal anti-inflammatory drugs: 43.5%, antiestrogens: 43.5% and imatinib: 30.5%). Combination CT was delivered in 44 cases (71%) and single agent in 18 patients (29%), respectively. Thirteen patients (21%) received an anthracycline-containing regimen. The most frequent nonanthracycline regimen was the methotrexate–vinblastine combination ($n = 27$). Complete response, partial response, stable disease and progressive disease were observed in 1 (1.6%), 12 (19.4%), 37 (59.6%) and 12 (19.4%) patients, respectively. The response rate was higher with anthracycline-containing regimens: 54% versus 12%, $P = 0.0011$. Median progression-free survival (PFS) was 40.8 months. The sole factor associated with improved PFS was the nonlimb location: 12.1 months (95% confidence interval 5.6–18.7) versus not reached, $P = 0.03$.

Conclusions: CT has significant activity in DT. Anthracycline-containing regimens appear to be associated with a higher response rate.

Key words: aggressive fibromatosis, chemotherapy, desmoid tumor

introduction

Desmoid tumors (DTs), also known as aggressive fibromatosis, are rare benign neoplasms with unpredictable natural history. Indeed, despite their infiltrative growth pattern and their high propensity for local recurrence, some of these tumors may stop growing or even regress without any intervention. Although surgery has been the standard of treatment of decades, recent studies suggest the benefit of front-line conservative approach in order to avoid mutilating surgical intervention [1] for primary tumor close to critical anatomical structures or for recurrent lesions. Several pharmacological treatments such as hormonal therapy [2] (e.g. tamoxifen), nonsteroidal anti-

inflammatory drugs [2] (NSAIDs) (e.g. celecoxib and sulindac), tyrosine kinase inhibitors such as imatinib [3, 4] or sorafenib [5] and cytotoxic chemotherapy (CT) [6–21] have been associated with clinical benefit in desmoid patients with progressive and/or recurrent disease.

However, data about the role of cytotoxic CT in this setting are scarce and mainly based on small single-center case series [6–21]. In order to address the clinical benefit of CT in patients with DTs, the French Sarcoma Group (FSG) conducted this multi-institutional retrospective study.

patients and methods

patients

From 1993 to 2010, 312 patients with a diagnosis of DT were admitted to one institution of the FSG. Clinical and pathological data were collected by reviewing medical records and were entered in a comprehensive

*Correspondence to: Dr A. Italiano, Department of Medical Oncology, Institut Bergonie, 229 Cours de l'Argonne, 33076 Bordeaux cedex, France. Tel: +33-5-56-33-33-33; Fax: +33-5-56-33-33-85; E-mail: italiano@bergonie.org

database. The histological diagnosis was established according to the World Health Organization Classification of Tumours [22] by an expert pathologist of the FSG. Among these patients, 62 patients received cytotoxic CT for the management of recurrent and/or progressive disease. This study was approved by the local ethics committee.

treatments and evaluation

The choice of CT regimen and duration of treatment were at the discretion of the treating physician. The best response to treatment was evaluated by magnetic resonance imaging or computed tomography according to RECIST [23]. Progression-free survival (PFS) was defined as the time from the start of CT until disease progression, death or last patient contact. National Cancer Institute Common Toxicity Criteria (version 3.0) were used to classify adverse events.

statistical analysis

The statistical analysis of baseline demographics and clinical outcome is based on all data available up to the cut-off date, 30 June 2010. Survival rates were estimated with the use of the Kaplan–Meier method. Descriptive statistics were used to show the distribution of variables in the population. Differences between groups were evaluated by the chi-square test or Fisher's exact test for categorical variables and *t*-test for continuous variables. Prognostic factors were planned to be identified by univariate and multivariate analyses by using Cox regression model. Variables tested in univariate analysis included age, sex, tumor size, tumor location (limb versus extralimb), sporadic case versus Gardner syndrome and type of CT regimen (with or without anthracycline, combination therapy versus single-agent therapy). Variables associated with PFS with a *P*-value < 0.05 in the univariate analysis were planned to be included in the multivariate regression. Analyses were carried out using SPSS 12.0 statistical software (SPSS Inc., Chicago, IL). All statistical tests were two-sided, and *P* < 0.05 indicated statistical significance.

results

patients

The study population included 62 patients with radiologically evaluable disease. Their characteristics are described in Table 1. All the patients had documented recurrent and/or progressive disease at initiation of treatment.

Median age was 30 years (range: 2–66 years). The two most common primary tumor locations were extremities (35.5%), followed by the internal trunk (32.5%). Twelve patients (19.5%) were diagnosed with Gardner syndrome. Thirty-three patients (53%) and eight patients (13%) had previous surgery or radiation therapy, respectively. Thirty-seven (54.7%) patients received one or more previous systemic therapies as follows: NSAIDs (*n* = 27, 43.5%), antiestrogens (*n* = 27, 43.5%) and imatinib (*n* = 19, 30.5%). The median time between diagnosis and initiation of CT was 15 months (range: 0, 4–115 months).

treatments

Combination CT was delivered in 44 cases (71%) and single agent in 18 cases (29%), respectively. Thirteen patients (21%) received an anthracycline-containing regimen (mesna, adriamycin, ifosfamide, dacarbazine: *n* = 9, doxorubicin–dacarbazine: *n* = 3 and doxorubicin: *n* = 1). Others regimens were methotrexate and vinblastine (MTX/VLB): *n* = 27, methotrexate: *n* = 7, metronomic etoposide/cyclophosphamide: *n* = 4, vinorelbine: *n* = 6 and others: *n* = 5. The median duration

Table 1. Patients' characteristics (*N* = 62)

| | No. of patients | % |
|--------------------|-----------------|------|
| Age (years) | | |
| Median | 30 | |
| Range | 2–66 | |
| Children | 13 | 21 |
| Adults | 49 | 79 |
| Sex | | |
| Male | 28 | 45.0 |
| Female | 34 | 55.0 |
| Tumor size (mm) | | |
| Median | 90 | |
| Range | 30–300 | |
| Tumor locations | | |
| Extremities | 22 | 35.5 |
| Internal trunk | 20 | 32.5 |
| Trunk wall | 18 | 29.0 |
| Head and neck | 2 | 3.0 |
| Gardner syndrome | | |
| No | 50 | 80.5 |
| Yes | 12 | 19.5 |
| Previous treatment | | |
| Surgery | 33 | 53.0 |
| Radiotherapy | 8 | 13.0 |
| NSAIDs | 27 | 43.5 |
| Hormonal therapy | 27 | 43.5 |
| Imatinib | 19 | 30.5 |

of treatment was 10 weeks for the anthracycline group and 18 weeks for the nonanthracycline group. CT regimens are described in Table 2.

efficacy

The median follow-up was 71.3 months (range: 6–187 months). Using RECIST, 1 patient (1.6%) had complete response, 12 patients (19.4%) had partial response and 37 patients (59.6%) had stable disease. Progressive disease was observed in 12 (19.4%) patients. Concerning the MTX/VLB combination, the most commonly employed CT regimen in our study (*n* = 27), 4 patients (15%) had partial response and 14 patients (52%) had stable disease. Progressive disease was observed in nine (33%) patients. Concerning the anthracycline-containing regimens, seven patients (54%) had partial response and six patients (46%) had stable disease.

The objective response rate was significantly higher in the anthracycline group than in the nonanthracycline group: 54% versus 12% (*P* = 0.0011).

Median PFS was 40.8 months (Figure 1). On univariate analysis, the sole factor associated with improved PFS was the extralimb location: 12.1 months (95% confidence interval 5.6–18.7) versus not reached, *P* = 0.03 (Figure 1). No multivariate analysis was carried out.

At the time of the analysis, four patients, all with Gardner syndrome died: three from progressive disease and one from peritonitis resulting from tumor necrosis and perforation after CT.

toxicity

Toxicity was manageable and mainly hematological. The proportion of patients with at least one grade 3 or 4 hematological adverse events was higher in the anthracycline group than in the anthracycline-free group: 31% versus 10% $P=0.06$. Four patients (6.5%) experienced one episode of febrile neutropenia. One patient with Gardner syndrome treated with an anthracycline-containing regimen presented a massive necrosis of the tumor with perforation. He died of secondary peritonitis and was considered as treatment failure. No secondary malignancy was observed during the follow-up period.

patient care after CT

After CT completion, 29 patients received at least one new therapeutic intervention for progressive and/or recurrent

Table 2. Chemotherapy regimens in patients with desmoid tumors

| Protocol | Drugs |
|--|---|
| Mesna, adriamycin, ifosfamide, dacarbazine | Doxorubicin 20 mg/m ² (day 1–day 3) Ifosfamide 2.5 g/m ² (day 1–day 3) Dacarbazine 300 mg/m ² (day 1–day 3) 21 days cycle |
| Adriamycin, dacarbazine | Doxorubicin 20 mg/m ² (day 1–day 3) Dacarbazine 300 mg/m ² (day 1–day 3) 21 days cycle |
| Metronomic etoposide | Oral etoposide 75 mg/day for 21 days of 28 days cycle |
| Metronomic cyclophosphamide | Oral cyclophosphamide 50 mg/day for 21 days of 28 days cycle |
| Doxorubicin | Doxorubicin 60–75 mg/m ² 21 days cycle |
| Methotrexate–vinblastine | Vinblastine 6 mg/m ² Methotrexate 30 mg/m ² (J1, J8, 15, 21) 28 days cycle |
| Methotrexate | Methotrexate 30 mg/m ² (J1, J8, 15, 21) 28 days cycle |
| Vinorelbine | Vinorelbine 20 mg/m ² (J1, J8) 21 days cycle |

disease: imatinib in 12 cases, further lines of cytotoxic CT in 11 cases, hormonal therapy in 10 cases, radiotherapy in 8 cases, NSAIDs in 5 cases and surgery in 3 cases. Twenty-nine patients (anthracycline group: $n = 7$, 54% and nonanthracycline group: $n = 22$, 45%) remained free of disease progression without need of new treatment at a mean time of 36 months (range: 0.4–145 months) from the end of CT. Patterns of care after CT completion were not known for four patients (6.5%).

discussion

This study represents the largest series of patients treated with cytotoxic CT for progressive or recurrent DTs. Most of the patients included in this study had aggressive and heavily pretreated disease with a median time of only 15 months between initial diagnosis and indication of CT. Our results showed that cytotoxic CT was associated with a clinical benefit (objective response plus stable disease) in ~80% of patients. This clinical benefit is durable since ~45% of them don't need any other treatment at a mean time of 36 months (range: 0.4–145 months) from the end of CT.

The identification of the best CT regimen remains an important issue. In our series, combination CT of MTX/VBL was the most frequent regimen (43.5% of patients). This combination demonstrated activity against DT with about two-thirds of the patients achieving disease stabilization or objective response. These results are similar to that observed in previous studies [6, 8–11,13,21]. As suggested in previous studies [20], the objective response rate was higher in the group of patients treated with anthracyclines than in the group of patients treated with other drugs. However, no significant difference in terms of PFS was observed. This suggest that PFS, rather than objective tumor response, is a better end point for potential future randomized phase 2 trials assessing the activity of new agents (inhibitors of the Wnt signaling pathway and antiangiogenic drugs) in comparison to existing therapeutic strategies (hormonal therapies, NSAIDs and cytotoxic CT). In our series, toxicity was higher with anthracycline-containing CT but remained manageable. However, given the lack of metastatic potential, many clinicians

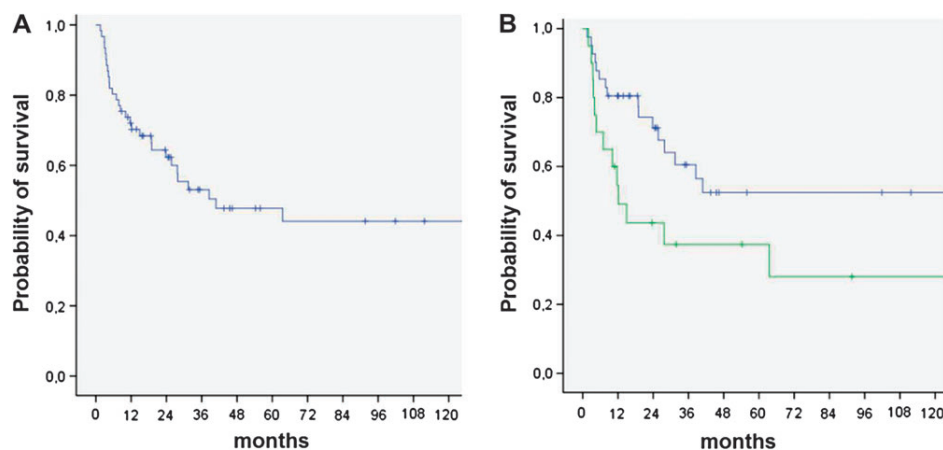


Figure 1. Progression-free survival of the entire cohort of patients (A), and according to tumor location (B) (extralimb: blue line, limb: green line).

remain reluctant about the use of CT in DT, particularly as CT may have severe and irreversible long-term morbidity (including cardiotoxicity for anthracyclines and an increased risk of treatment-induced malignancy) especially in a young population such as DT patients. Pegylated liposomal doxorubicin (PLD) has been recently reported as a potential alternative to doxorubicin in the treatment of patients with aggressive DTs. In a recent retrospective study, PLD was associated with objective response in 4 out of 11 patients and disease stability in the remaining ones [16]. Therefore, this drug which is associated with a lower risk of cardiac and other toxic effects compared with the parent agent has been suggested as reasonable first-line CT option in patient failing previous other systemic agent such as hormonal therapy [20]. We believe that a direct comparison of PLD and of the MTX/VLB combination, the most commonly employed CT regimens in our study, should be useful to define the optimal CT regimen for DT.

In our series, the sole factor associated with PFS was tumor location with patients with extralimb location having better outcome. This adverse prognostic factor was already observed in patients treated by surgery and/or radiotherapy [24]. The difficulty of managing DT in association with Gardner syndrome is also underscored by our results. Indeed, the four patients who died during the study period had all Gardner's syndrome. No death was observed in patients with DT that arise sporadically. However, we did not observe a significant difference in terms of PFS between the two groups of patients confirming the potential clinical benefit of CT even in patients with Gardner syndrome as suggested in previous studies [12].

Besides its retrospective nature, one limitation of our study consists in the fact that it is not possible to affirm that disease stability was related in all the cases to a benefit from CT and not simply to the natural history of the tumor. However, none of the patients included in our study had spontaneous regression before treatment and all of them had progressive disease before starting CT. Recent data suggested that the mutational status of the beta-catenin gene (*CTNNB1*) was predictive of the risk of recurrence in sporadic DT [25]. Future investigations of CT in DT should be conducted in a prospective way and should include a mutation analysis of *CTNNB1*, which could potentially better inform the indication of CT.

Altogether, our study confirms that cytotoxic CT represents an efficient therapeutic option treatment in aggressive and/or unresectable DT and contradicts the classical dogma in oncology that benign tumors without metastatic potential are refractory to CT. The decision to administer CT in this specific setting should be discussed with the patients given its potential morbidity.

disclosure

The authors declare no conflicts of interest.

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