Adherence to treatment guidelines for primary sarcomas affects patient survival: a side study of the European CONnnective TIssue CAncer NETwork (CONTICANET)


1Melanoma and Sarcomas Unit, Veneto Institute of Oncology-IRCCS, Padova; Departments of 2Surgery, Oncology and Gastroenterology; 3Molecular Medicine, University of Padova, Padova; 4Pathology Unit; 5Radiotherapy Unit and; 6Medical Oncology, Veneto Institute of Oncology-IRCCS, Padova, Italy; 7Department of Medical Oncology, Leon Berard Cancer Center, University of Lyon, Lyon, France

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Background: The impact of adherence to clinical practice guidelines (CPGs) for loco-regional treatment (i.e. surgery and radiotherapy) and chemotherapy on local disease control and survival in sarcoma patients was investigated in a European study conducted in an Italian region (Veneto).


Patients and methods: The completeness of the adherence to the Italian CPGs for sarcomas treatment was assessed by comparing the patient’s charts and the CPGs. Propensity score-adjusted multivariate survival analysis was used to assess the impact of CPGs adherence on patient clinical outcomes.

Results: A total of 151 patients were included. Adherence to CPGs for loco-regional therapy and chemotherapy was observed in 106 out of 147 (70.2%) and 129 out of 139 (85.4%) patients, respectively. Non-adherence to CPGs for loco-regional treatment was independently associated with AJCC stage III disease [odds ratio (OR) 1.77, \( P = 0.011 \)] and tumor-positive excision margin (OR 3.55, \( P = 0.003 \)). Patients not treated according to the CPGs were at a higher risk of local recurrence [hazard ratio (HR) 5.4, \( P < 0.001 \)] and had a shorter sarcoma-specific survival (HR 4.05, \( P < 0.001 \)), independently of tumor stage.

Conclusions: Incomplete adherence to CPGs for loco-regional treatment of sarcomas was associated with worse prognosis in patients with non-metastatic tumors.

Key words: clinical practice guidelines, prognosis, sarcomas

Introduction

Sarcomas are a rare form of malignancy that may arise in soft tissues, bones and viscera [1–3]. According to several clinical practice guidelines (CPGs) for the diagnosis and the treatment of sarcomas, surgery is the mainstay of treatment and the achievement of microscopically negative resection margins is still the main objective for surgical oncologists [1, 4–12]. After surgery, radiotherapy represents the standard adjuvant approach, particularly for patients who have microscopically positive tumor resection margins as well as larger, deeper and high-grade tumors [13–15]. Although radiation therapy has been shown to improve tumor local control but not overall survival (OS), these two treatment modalities are considered the gold standard for the loco-regional treatment of sarcomas, especially for patients at higher risk of disease progression [4–8].

Within the frame of the CONnective TIissues CAncers NETwork (CONTICANET) project funded by the European Commission [3, 16–19], which aimed at improving the outcomes of sarcoma patients by increasing the level of standardization of the diagnostic and therapeutic procedures, a population-based series of sarcoma cases was collected in different regions of the EU. Patients were enrolled for 2 years and then followed for 3 years in order to: (i) build up the population-based incidence of sarcoma and (ii) to investigate the effect of the adherence to the CPGs on patient survival [18].

This side study, conducted in the Veneto region (Northeast of Italy), investigated the association between the adherence to treatment guidelines (regarding both loco-regional treatments such as surgery and radiotherapy and systemic chemotherapy) and local disease control and disease-specific survival of 151 prospectively enrolled and followed patients with primary non-metastatic sarcomas (i.e. AJCC TNM stages I–III).

Methods

The details regarding the process of data gathering and analysis have been already published elsewhere [18].

This side study considered patients (age \( \geq 18 \) years) who were enrolled during a period of 2 years, followed-up for 3 years and underwent diagnosis, treatment and follow-up in public hospitals of the Veneto region. The following groups of patients were excluded from the data analysis:

- patients presenting with metastatic sarcomas since prognosis of these patients is dismal no matter what kind of treatment they undergo [20, 21];
- patients with gastrointestinal stromal tumor (GIST) as this tumor type is considered a different disease with its proper guidelines [22];
- patients with dermatofibrosarcoma protuberans because this tumor histotype shows a very high likelihood of cure after wide excision alone (even in the case of locally recurrent disease) [23].

Clinical practice guidelines

The CPGs for diagnosis and treatment of visceral and soft tissue sarcomas from the Italian National Research Council [8] were compared with the data extracted from the medical records. The Italian guidelines for sarcomas treatment were based on those from the European Society of Medical Oncology (ESMO): the only major difference from this international CPGs is the tumor size cutoff used to discriminate between small and large tumors (3 cm in the Italian CPGs versus 5 cm in the ESMO CPGs).

A single surgeon (CRR) assessed the adherence to the treatment guidelines retrospectively (i.e. when the patients completed the planned treatments and all hospital charts were available) to ensure the homogeneity of the data analysis.

Completeness of the adherence to the guidelines in surgery

Head and neck, superficial trunk and extremity sarcomas. Whenever possible, primary surgery should involve a wide excision with a 1–2 cm margin. For high-grade, large (>3 cm) or deep-seated tumors, surgery alone is acceptable only in the case of amputation or compartmental resection with negative histological margins (R0). Wide excision alone, with no adjuvant treatment, is acceptable only for superficial, small (<3 cm) and low-grade lesions. Histologically positive margins (R1) or incomplete excisions (R2) have to be considered inadequate, and should be followed by further appropriate treatment.

Retropertitoneal and visceral sarcomas. Complete resection, which has to include the adjacent organs when they are macroscopically involved by the tumor, is the standard treatment whenever feasible. Neo-adjuvant/adjuvant...
chemotherapy and/or radiotherapy may be advised after a multidisciplinary team meeting, preferably within a clinical trial.

**Completeness of the adherence to the guidelines in radiotherapy**

The combination of a wide surgical excision and adjuvant radiation therapy should be considered the standard treatment of the head and neck, superficial trunk and extremity sarcomas.

The absence of adjuvant radiotherapy is acceptable for superficial, small (<3 cm) and low-grade tumors, and for limb sarcomas when amputation is carried out. For non-operative sarcomas, primary radiation therapy could be an option. The optimal treatment strategy involves a 50 Gy delivered dose with an additional boost of 10 Gy in the case of microscopic residual tumor (R1), with a target volume encompassing the tumor bed and the surgical scars, including draining orifices, with adapted security margins. Furthermore along this line, the interval between surgery and radiation therapy must not exceed 12 weeks.

**Completeness of the adherence to the guidelines in loco-regional treatments**

Surgical and radiological loco-regional treatments have to be planned in a multidisciplinary fashion, as appropriate for the above-listed criteria, before and after surgery.

**Completeness of the adherence to the guidelines in chemotherapy**

For non-readily operable sarcomas, primary chemotherapy or radiation therapy can be an option. For readily operable sarcomas, neo-adjuvant chemotherapy should be carried out only as part of a clinical research protocol. In the adjuvant setting, systemic chemotherapy should be carried out only within the context of a prospective clinical trial or in patients with histologically positive margins after wide surgical excision.

**Statistical analysis**

The following variables were considered for the analyses: clinical center where the patient was treated (university, non-university hospital) patient’s age and sex, primary tumor site (visceral/retroperitoneal, superficial), primary tumor diameter (millimeters), tumor location (deep, superficial), tumor grading (G1, G2, G3), tumor histotype (liposarcoma, leiomyosarcoma and any other type) and AJCC TNM stage (I, II, III).

Fisher’s exact test, Mann–Whitney test (univariate analysis) and logistic regression (multivariate analysis) were fitted to the data to assess predictors of non-adherence to CPGs.

Local disease-free survival (LDFS) and sarcoma-specific OS were the end points of this study.

The influence of conformity to treatment guidelines on patients survival independently of other known prognostic factors was assessed by using the Cox regression model. The proportional hazard assumption was verified by using the Therneau and Grambsch test based on Schoenfeld’s residuals [24], and the variables were selected using the Akaike information criterion (AIC) [24, 25].

We used a propensity score weighting method to balance the observed covariates between treatment and observation groups [26, 27]. Propensity scores reflect the probability that a patient will receive a given therapy (adherent or not to guidelines) based on the observed covariates: by incorporating these criteria into the construction of the prognostic model, the selection bias, which is intrinsic to non-randomized studies, can be reduced. A propensity score was calculated for each patient by means of logistic regression; afterwards, the quartiles of the score were employed to categorize patients into relatively homogeneous groups, which were ultimately used to run a shared frailty Cox model that takes into account the non-independence of patients belonging to the same score category.

As a measure of prognostic model accuracy, the C-index was calculated according to Harrell et al. [25]: this parameter (which ranges from 0.5 in the case of no prognostic value of the model to 1 in the case of perfect prognostic prediction) corresponds to the proportion of all pairs of patients whose survival time can be ordered such that the subject with the higher predicted survival is the one who actually survived longer.

The different prognostic outcome of patients undergoing treatment adherent or not to the guidelines was graphically illustrated through the Kaplan–Meier survival curves, whose estimates were formally compared using a log-rank test.

For all analyses, which were carried out with STATA 11.0/SE [Stata Corp., College Station, TX], the α-level of significance was set at 5%.

**Results**

There were 267 potentially eligible patients in our database. Out of these, 116 were excluded because they were affected with dermatofibrosarcoma protuberans (n = 20), GIST (n = 81) and AJCC TNM stage IV tumor at presentation (n = 15). Overall, 151 patients who were eligible represent the cohort of cases analyzed in this study (Table 1). Overall, 71 patients had tumor-free excision margins after surgery (R0, 48%). Radiotherapy was administered to 36 patients (24%): 20 had an R0 resection after surgery (of these patients, 18 had deep located tumors and 12 high-grade tumors) and 16 had microscopically tumor-positive excision margin (of these patients, 14 had deep located tumors and 16 high-grade tumors).

**Adherence to guidelines for treatment of sarcomas**

Adherence to guidelines for loco-regional therapy (which represents the standard treatment) and systemic chemotherapy (which is not considered a standard treatment but can be recommended on the basis of a shared decision-making process) was achieved in 106 out of 147 (70.2%) and 129 out of 139 (85.4%) patients, respectively. Patients having a tumor with a diameter of >5 cm (P = 0.049), a deep location (P = 0.016), a high grade (P = 0.003), an AJCC TNM stage III (P < 0.001) and tumor-positive resection margins (P = 0.005) were at risk of non-adherence to guidelines for loco-regional treatment. Adherence to guidelines for loco-regional treatment was not influenced by center (P = 0.522), patient age (P = 0.196), sex (P = 0.853), tumor site (P = 0.446) and histotype (P = 0.501).

Upon multivariate logistic regression analysis (stepwise procedure), AJCC TNM stage III [odds ratio (OR) 1.77, 95% confidence interval (CI) 1.14–2.76; P = 0.011] and tumor-positive excision margins (OR 3.55, 95% CI 1.55–8.10; P = 0.003) independently predicted incomplete adherence to CPGs for loco-regional treatment.

Of note, despite the non-significance of tumor site, visceral/retroperitoneal tumors were larger (P = 0.027) and deeply located (P < 0.001).

After implementing the propensity score weighting method, all covariates were balanced and no longer had statistically significant differences.
Table 1. Clinical and pathological features of 151 soft tissue sarcomas diagnosed in the Veneto Region between 2007 and 2008

<table>
<thead>
<tr>
<th>Variables</th>
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<tr>
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<tr>
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<td>University hospital</td>
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<tr>
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<tr>
<td>Male</td>
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<tr>
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local disease-free survival

High tumor grade [hazard ratio (HR) 4.46; 95% CI 1.92–10.36; P = 0.001], deep tumor location (HR 3.48; 95% CI 1.06–17.42; P = 0.040), larger tumor size (HR 1.01; 95% CI 1.001–1.008; P = 0.024), AJCC TNM stage III (HR 2.36; 95% CI 1.51–3.68; P < 0.001), non-adherence to loco-regional treatment (HR 6.27; 95% CI 3.03–12.99; P < 0.001) and to chemotherapy (HR 6.21; 95% CI 2.61–14.78; P < 0.001) predicted local relapse at univariate analysis.

Upon multivariate survival analysis, the best predictive model (C-index 77.44, AIC 254.62) retained only TNM staging (HR 1.85; 95% CI 1.07–3.23; P = 0.028) and adherence to loco-regional treatment (HR 5.47; 95% CI 2.50–11.99; P < 0.001), even after an adjustment for the propensity score. The Kaplan–Meier survival curves for loco-regional treatment adherence to guidelines are reported in Figure 1A (log-rank test, P < 0.001). Overall, these findings suggest that patients not treated according to the guidelines present a fivefold higher risk of loco-regional disease relapse when compared with those treated following the guidelines, independently of the disease stage.

disease-specific survival

High tumor grade (HR 7.05; 95% CI 2.44–20.35; P < 0.001), deep tumor location (HR 9.90; 95% CI 1.35–72.74; P = 0.024), AJCC TNM stage III (HR 4.66; 95% CI 2.06–10.52; P < 0.001) and non-adherence to loco-regional treatment (HR 5.53; 95% CI 2.53–12.10; P < 0.001) predicted LDFS at univariate analysis. Adherence to guidelines for chemotherapy was not a predictor of survival (HR 2.26; 95% CI 0.66–7.67; P = 0.192).

Upon multivariate survival analysis, the best predictive model (C-index 79.68, AIC 224.53) retained only TNM staging (HR 1.99; 95% CI 1.03–3.84; P = 0.039) and adherence to guidelines for loco-regional treatment (HR 4.05; 95% CI 1.73–9.47; P < 0.001), even after adjustment for the predictive score. The Kaplan–Meier survival curves for adherence to the guidelines for loco-regional treatment are reported in Figure 1B (log-rank test, P < 0.001). Overall, these findings suggest that patients not treated according to the guidelines present a fourfold higher risk of loco-regional disease relapse when compared with those treated following the guidelines, independently of the disease stage.

discussion

In this study, which was conducted on 151 sarcoma patients prospectively enrolled for 2 years and followed-up for 3 years within the frame of a European study in an Italian region (Veneto), the completeness of the adherence to guidelines for loco-regional treatment was associated with LDFS and disease-specific survival.

Patients with more advanced tumors and tumor-positive excision margin were less likely to be treated in adherence to the guidelines, probably reflecting a relatively higher degree of treatment complexity for locally advanced sarcomas with more aggressive histopathological patterns. Although visceral and retropertoneal tumors were larger and deeply located when compared with non-visceral tumors, adherence to CPGs did not differ between these subgroups.

Considering that these differences may affect results of the study, the data analysis was conducted by using the propensity score [26, 27], which is a methodology applied in trials where a randomized design cannot be pursued: this is the case of a study investigating the impact of the adherence to the guidelines on patients’ outcomes. The propensity score can balance the features of patients receiving two treatments, thus reducing the confounding effect of the differences that may influence the results. Combining the propensity scores and the
multivariate analysis, as carried out here, allows an adjustment of the known confounding factors. These methodologies do not consider unknown confounding factors, as in the case of a randomized study, but offer a reliable solution to reduce differences between treatment groups.

The completeness of the adherence to the loco-regional treatment guidelines was judged upon considering surgery and radiotherapy together, as these two approaches are complementary to each other in the treatment of primary sarcomas [13–15]. In fact, the appropriateness of the loco-regional treatment may be achieved even in the case of adequate surgery alone, as non-adherence to guidelines for surgery (due to anatomical reasons), followed by a properly conducted radiotherapy, may however result in an appropriate loco-regional outcome. Such is the case of a patient with microscopically positive deep tumor margin after a wide excision of a large sarcoma laying over the thighbone who underwent adjuvant radiotherapy, which had been properly planned after a pre-operative multidisciplinary evaluation. Surgery alone should be considered inadequate as no free-of-tumor margins were achieved; however, radiotherapy was delivered as suggested by the guidelines in the case of inadequate surgery. Considering surgery and radiotherapy together leads to judge the whole loco-regional treatment as properly conducted according to treatment guidelines. Patients mistreated in terms of loco-regional therapies had a fivefold increase of local recurrence (HR 5.47; \(P < 0.001\)) and a fourfold increase of risk of death for sarcoma (HR 4.05; \(P < 0.001\)). These effects occurred independently of the AJCC TNM tumor stage.

Unlike adherence to guidelines for loco-regional treatment, adherence to guidelines for systemic chemotherapy (which is not considered the standard treatment of sarcomas, but can be still recommended on the basis of a shared decision-making process) had no independent prognostic value for LDFS and OS. These findings pinpoint the importance of properly planned and conducted loco-regional therapies for the adequate treatment of non-metastatic sarcomas.

Previously conducted research focused on differences in treatment patterns and patient outcomes between specialized centers and district hospitals, concluding that patients affected by sarcomas and treated in referral centers were more likely of being treated according to the guidelines, thus leading to better survival rates [28, 29].

In the UK, optimal diagnostic management and treatment were achieved in 23 and 60% of patients, respectively [29]. A study conducted in the Netherlands shows how these rates varied significantly between referral centers and district hospitals, where patient volume had no significant influence on compliance with the guidelines [30]. On this basis, the national guidelines were established and circulated in 2004 in the Netherlands, and resulted in an optimization of diagnosis and treatment in patients with sarcomas, mainly due to an increased centralization [31].

According to studies conducted in France [28] and Finland [32], patients treated in referral centers have a better outcome than those treated in district hospitals, where the expertise of the operators (i.e. greater number of procedures carried out), along with the multidisciplinary team meetings, ensure the adherence to the guidelines.

While some of these studies move from the evidence of a greater compliance to guidelines in referral centers, our study was conducted in a geographical area where no referral center is designated by the healthcare system, and compared guidelines and patient charts irrespectively from their origin, leading to a quantitative evaluation of the compliance with the guidelines.

A cost analysis conducted within the CONTICANET reports that the costs for sarcoma patients treated according to the guidelines are lower than those for patients who received inadequate treatments [19]. The primary aim of this study was to determine an association between disease-free survival and health costs. The incremental cost-effectiveness ratio was expressed as cost per relapse-free year gained according to adherence or non-adherence to guidelines. Treatment adherent to guidelines and undertreatment had an average cost of 23 571 and 27 313 euro, respectively; this suggests that the adherence to the guidelines is both less expensive and more effective.

Our findings combined with the above economic considerations underline that the adherence to the guidelines should be considered almost mandatorily for the treatment of sarcomas as it offers the advantages from both a patient and a...
healthcare system perspective. However, the findings of our study will have to be confirmed in larger series, as analyses were conducted on a relatively small sample size and in a particular geographical area.

Policies to improve the referral of sarcoma patients to specialized units with high expertise in this field have been introduced in several countries, such as in the UK, where sarcoma-suspicous lesions are centralized into sarcoma-dedicated units [33, 34]. This could not remain the only way to improve the adherence to the guidelines for the diagnosis and the treatment of sarcomas: the compliance to the guidelines may also be increased by multidisciplinary team meetings [35, 36], which are usually conducted in ultra-specialized environments. The participation of physicians from the geographical area surrounding a cancer center to the multidisciplinary meetings in order to evaluate suspicious/new cases may be considered a reliable policy to ensure adherence to guidelines. Web-based technology may be of great help in pursuing this attempt. For instance, the Veneto Institute of Oncology institutional website offers restricted access to surgical, medical and radiation oncologists of the Veneto Region in order to refer patients affected by sarcomas for a multidisciplinary evaluation.

Taken together, our findings strongly suggested that a complete adherence to treatment guidelines in patients with sarcomas should be achieved for all cases, as non-conform therapeutic management is associated with a significantly higher risk of local relapse (fivefold) and death from disease (fourfold), independently of tumor stage.

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disclosure

The authors have declared no conflicts of interest.

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Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients

L. Boussemart¹,², E. Routier¹, C. Mateus¹, K. Opletalova¹, G. Sebile¹, N. Kamsu-Kom², M. Thomas¹, S. Vagner², M. Favre³, G. Tomasic⁴, J. Wechsler¹, L. Lacroix² & C. Robert¹,²

¹Department of Medical Oncology; ²Inserm, U981, Institut Gustave Roussy, Villejuif; ³Papillomavirus Unit, Inserm, U190, Institut Pasteur, Paris; ⁴Department of Pathology, Institut Gustave Roussy, Villejuif, France

Background: BRAF inhibitors are being developed for the treatment of metastatic melanoma harboring a V600E mutation. The use of vemurafenib significantly increases progression-free survival (PFS) and overall survival (OS) in this population of patients, but is associated with numerous adverse skin reactions.

Patients and methods: We carried out a systematic dermatologic study of 42 patients treated with vemurafenib. We collected detailed dermatologic symptoms, photos and biopsy specimens of the skin lesions which enabled us to classify the side-effects. The management and evolution of the skin symptoms are also reported.

Results: All patients presented with at least one adverse skin reaction. The most common cutaneous side-effects consisted in verrucous papillomas (79%) and hand–foot skin reaction (60%). Other common cutaneous toxic effects were a diffuse hyperkeratotic perifollicular rash (55%), photosensitivity (52%) and alopecia (45%). Epidermoid cysts (33%) and eruptive nevi (10%) were also observed. Keratoacanthomas (KA) and squamous cell carcinoma (SCC) occurred in 14% and 26% of the patients, respectively.

Conclusions: These cutaneous side-effects are cause of concern due to their intrinsic potential for malignancy or because of their impact on patients’ quality of life. Management of this skin toxicity relies on symptomatic measures and sun photoprotection.

Key words: BRAF inhibitor, melanoma, side-effects, squamous cell carcinoma-targeted therapy, vemurafenib

Introduction

New anticancer therapies targeting various kinases implicated in cancer onset or progression are now commonly used and they improve the prognosis of several cancers.

Activating B-RAF (V600E) (also known as BRAF) kinase mutations occur in ~7% of human malignancies and ~60% of melanomas [1]. A novel class I RAF-selective inhibitor, vemurafenib, demonstrated an unprecedented 60% antitumor response rate among patients with BRAF(V600E)-positive melanomas, but vemurafenib is not devoid of side-effects. Among the most intriguing of these side-effects are skin neoplasms originating from keratinocytes that occur following treatment with BRAF inhibitors (vemurafenib and dabrafenib), as previously observed with sorafenib, a multikinase inhibitor and a pan-RAF inhibitor [2].

In this study, we prospectively followed up 42 patients undergoing vemurafenib treatment either in the context of...