Efficacy of First-Line Chemotherapy in Patients with Advanced Lung Sarcomatoid Carcinoma

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Background: Sarcomatoid carcinomas (SCs) are rare tumors that may arise in the lung, accounting for 0.4% of non–small-cell lung cancers; the prognosis is poor. Only few retrospective small-size series have studied the efficacy of chemotherapy (CT) for metastatic SC.

Methods: Multicenter study of patients with advanced or metastatic SC who received first-line CT. Clinical characteristics at baseline, response to first-line CT (Response Evaluation Criteria in Solid Tumors version 1.1), progression-free survival (PFS), and overall survival (OS) were retrospectively collected.

Results: Ninety-seven patients were included. Median age was 62 (54–72) years. The majority of patients were men (70%), white (84%), and smokers (84%). Overall, 73% of patients received first-line platinum-based CT. At first tumor evaluation, 69% of patients experienced progression, 31% had disease control, and 16.5% had partial response. Partial response was observed in 20% of patients receiving platinum-based CT, and in none of those receiving non–platinum-based CT (p = 0.018). Median PFS was 2.0 months (confidence interval [CI] 95%: 1.8–2.3). PFS was not statistically different between patients receiving or not receiving a platinum-based CT. Median OS was 6.3 months (CI 95%: 4.7–7.8). There was a trend toward better OS for patients treated with platinum-based CT (7.0 months [CI 95%: 4.9–9.0] versus 5.3 months [CI 95%: 2.8–7.6]; p = 0.096). In multivariate analysis, disease control at first evaluation (hazard ratio = 0.38 [CI 95%: 0.21–0.59]) and at platinum-based CT (hazard ratio = 0.92 [CI 95%: 0.85–0.99]) was associated with better OS.

Conclusion: SC is associated with poor prognosis and high rate of resistance to conventional first-line CT. New therapeutic strategies are needed, based on better knowledge of the carcinogenesis of SC.

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Sarcomatoid carcinomas (SCs) are rare tumors that may arise in the lung, where they account for approximately 0.4% of non–small-cell lung cancers (NSCLC).[1] SCs have been reported to be associated with a poor prognosis, as compared with other NSCLCs. In the Surveillance Epidemiology Endpoints Results database, SC histology was associated with significantly shorter overall survival (OS) (hazard ratio [HR] = 1.60; confidence interval [CI] 95%: 1.35–3.06; p = 0.004) in early-stage NSCLC.[1] For metastatic disease, median OS was 3 months in the Surveillance Epidemiology Endpoints Results database,[1] and 5 to 8.5 months in five retrospective series collectively including less than 50 patients.[2–6] Limited information is available about the efficacy of chemotherapy (CT) for SC. We have recently shown that SC histological type was independently associated with a 7.5 risk of progression during a first-line treatment by platinum-based CT in a retrospective cohort of 178 NSCLCs.[2] Finally, a 58% to 85% disease progression rate after first-line CT was also reported in two small-size retrospective series.[3,4] In this article, we conducted a multicentric retrospective study to focus on types of CT and outcome in a large cohort of patients with histologically proven advanced or metastatic SC.

PATIENTS AND METHODS

Patients were screened in the archive of chest and pathology departments from nine medical centers and from a French National Cancer Institute–sponsored network for rare thoracic tumors. From January 1999 to September 2012, all consecutive patients with pathologically proven SC presenting at an advanced or metastatic stage, who received a first-line CT, were included in this analysis. All the pathological specimens were locally reviewed according to the World Health Organization's classification 2004. After reviewing, 18 cases were overruled out by the pathologists. At the time of diagnosis, baseline clinical data were collected. Response to CT was evaluated every two to three cycles and classified as recommended by Response Evaluation Criteria in Solid Tumors criteria.[7] Computed tomography scans were retrospectively

analyzed for 84 patients. Data were collected from medical records for the remaining 13 cases. Best response was reported. End point was defined as September 1, 2012. According to national guidelines, each patient signed a research approval form.

RESULTS

Clinical and Anatomic Characteristics

From 1999 to 2012, 97 consecutive patients with pathologically confirmed SC, treated with first-line CT, were included in this study. Most frequent subtypes were pleomorphic (61%), spindle-cell (13.5%), and giant-cell carinoma (9.5%) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A477). Median age was 62 (54–72) years. The majority of patients were men (70%), white (84%), and smokers (84%). Patients were often symptomatic (84%). Most frequent symptoms were cough (35%), chest pain (31%), and weight loss (30%). Performance status (PS) was 0 to 1 in 72% of cases. At baseline assessment, all patients had an advanced or metastatic disease. Among them, 42 presented with metastatic had relapse after previous surgery. Sixteen percent of patients had stage III disease and were not eligible for chemoradiotherapy because of tumor volume. Eighty-four percent had stage IV disease. Metastatic locations were similar to that observed in NSCLCs overall, that is the adrenal glands, the lung, the pleura, the brain, the bone, or the liver but also included unusual anatomic sites, such as the subdiaphragmatic nodes, the peritoneum, the kidney, and the pancreas. Sixty-two percent of patients had more than two metastatic locations (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A477).

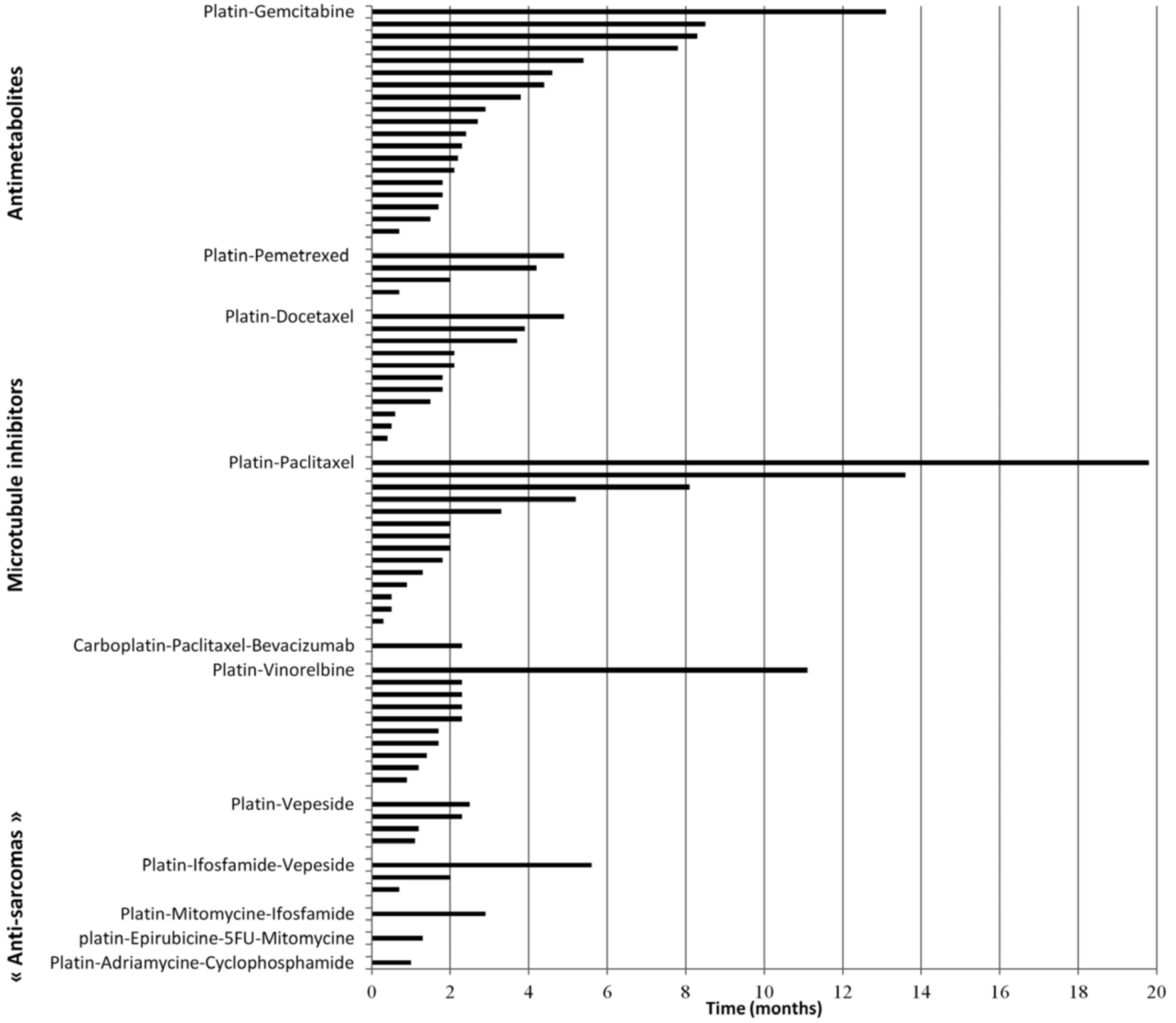

FIGURE 1. Waterfall plot of individual progression-free survival according to chemotherapy regimen. 5FU, fluorouracil.

First-Line CT

First-line treatment was platinum-based CT regimen for 71 patients (73%) and a non–platinum-based CT for 26 patients (27%). Third-generation drug was associated with platinum in 61 patients (63%). Main regimens for monotherapy were gemcitabine, erlotinib, pemetrexed, docetaxel, paclitaxel, and vinorelbine. Patients who received platinum-based CT had a better PS (0–1) than those who did not received platinum-based CT (93% versus 23%; $p < 0.0001$).

Outcome

Patients received a median number of three cycles of CT (interquartile range, 2–4). First assessment of response was performed after a median of two cycles of CT (interquartile range, 1–3). At first evaluation, 69% of patients showed progressive disease and 31% disease control (DC), with 16.5% of partial responses (PRs) and 14.5% of stable disease. PR was observed in 20% of patients receiving a platinum-based versus none of those receiving non–platinum-based regimen ($p = 0.018$). Response rates did not differ between treatment regimens. The best response was always that observed at the first evaluation. Age, sex, ethnicity, tobacco status, symptoms, PS, histological subtypes, stage, and previous surgery did not significantly correlate with response rate.

Median progression-free survival (PFS) was 2.0 months (CI 95%: 1.8–2.3). At univariate analysis, no factor including age, sex, ethnicity, tobacco status, symptoms, PS, histological subtypes, stage, and previous surgery significantly influenced PFS. PFS was not statistically different in patients treated with or without platinum-based CT. According to individual PFS (Fig. 1), some patients had a better PFS with platinum plus gemcitabine or platinum plus paclitaxel regimen than other combinations. At multivariate analysis, no factor was associated with better PFS.

Median OS was 6.3 months (CI 95%: 4.7–7.8). There was a trend toward a better OS for patients treated with platinum-based CT (7.0 months; CI 95%: 4.9–9.0) versus others (5.3 months; CI 95%: 2.8–7.6; $p = 0.096$). At univariate analysis, DC was the only factor associated with a significantly better OS (Table 1). At multivariate analysis, DC at first evaluation (HR = 0.38; CI 95%: 0.21–0.59) and platinum-based CT (HR = 0.92; CI 95%: 0.85–0.99) and nonsmoking status (HR = 0.92; CI 95%: 0.85–0.99) were associated with prolonged OS.

DISCUSSION

This study is the first to report on a large cohort of patients (n = 97) with advanced or metastatic lung SC. Our findings indicate that these tumors were associated with a poor outcome and resistance to conventional first-line CT. Progression rate was 69% at first evaluation. Median PFS and OS were 2.0 months (CI 95%: 1.8–2.3) and 6.3 months (CI 95%: 4.7–7.6), respectively. Similar results with high rates of progression ranging from 58% to 85% under first-line CT have been previously reported in smaller retrospective studies.[3,4] These rates are higher and the survival is shorter than those usually observed for other NSCLC histological subtypes: progression rate to first-line CT was 38%, median PFS was 4.3 months, and median OS was 8.9 months in the analysis of three randomized studies including 984 patients with NSCLC of other histological subtypes than SC.[8]

In our analysis, progression rates were not different among patients treated with or without platinum-based CT and among patients treated with different platinum-based CT regimens. The drugs used were heterogeneous because of the time of patient recruitment, inherent to the rarity of SC. Nevertheles, almost 90% of patients treated with platinum-based CT received a third-generation drug. Interestingly, PR was observed only in patients who received platinum-based CT. This could suggest that platinum-based CT might have a higher efficacy even if this observation did not translate into a longer PFS ($p = 0.301$). Nevertheles, PFS may be not precise enough when evaluated retrospectively. At univariate analysis, there was a trend toward a longer OS for patients treated with platinum-based CT; at multivariate analysis, platinum-based CT was associated with a slight but significantly decreased risk of death of 8% ($p = 0.027$). A trend was also observed for better OS in patients with good PS but with no influence at multivariate analysis. Although our study is likely to lack of statistical power, one possible

TABLE 1. Univariate and Multivariate Analyses of Factors Associated with Overall Survival

	Univariate		Multivariate	
	HR (CI 95%)	**p^a**	**HR (CI 95%)**	**p^a**
Age (<62 vs. ≥62 yr)	1.23 (0.81–0.88)	0.350		
Ethnicity (white vs. other)	0.96 (0.89–1.03)	0.249		
Sex (men vs. women)	1.33 (0.83–2.14)	0.234		
Tobacco-smoking status (current/former vs. never smoker)	0.95 (0.88–1.02)	0.179	0.92 (0.85–0.99)	0.040
Performance status (0−1 vs. 2−3)	1.04 (0.99–1.11)	0.149		
Clinical stage (III vs. IV)	0.94 (0.88–1.01)	0.112	0.93(0.86–1.02)	0.057
Previous radical surgery (yes vs. no)	1.04 (0.99–1.10)	0.120	1.04 (0.98–1.11)	0.211
Chemotherapy (with vs. without platinum)	0.95 (0.90–1.00)	0.099	0.92 (0.85–0.99)	0.027
Control vs. progression at first-line CT	0.35 (0.22–0.57)	<0.001	0.38 (0.21–0.59)	<0.001

Data were obtained from 96 patients, with one missing datum.
[a]Cox's model, for multivariate analyses a backward procedure was used.
HR, hazard ratio; CI, confidence interval; CT, chemotherapy.

explanation may be that factor "PS" is confounded by factor "cisplatin," that is that cisplatin-based CT was delivered to patients with higher PS.

To conclude, our study indicates that SC is associated with poor prognosis, with a high rate of resistance to conventional first-line CT. New therapeutic strategies are needed, possibly based on a better knowledge of the carcinogenesis of this rare tumor.

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