Anti-Cancer Drugs 2002, 13 (suppl 1):S7–S9

ET-743: The US experience in sarcomas of soft tissues

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Ecteinascidin-743 (ET-743) has shown promise as a new and effective treatment for soft-tissue sarcomas. Two independent, multicenter, Phase II studies have been performed in the USA for patients with unresectable soft-tissue sarcomas (either chemotherapy-naïve or pretreated patients). The patients received ET-743 at a dose of 1500 μg/m² as a 24 h continuous intravenous infusion every 3 weeks on an outpatient basis. Assessments were conducted every 6 weeks until documented progressive disease, unacceptable toxicity, or withdrawal. Responses were assessed in accordance with conventional oncological criteria and toxicities were graded using the National Cancer Institute common toxicity criteria. A total of 72 patients were enrolled: 36 patients to each study. Confirmed objective response rates were 14% (95% confidence interval (CI) 5 to 30%) and 8% (95% CI 2 to 23%) in chemotherapy-naïve and pretreated patients, respectively. In chemotherapy-naïve patients, 12-month progression-free and overall survival rates were 18% (95% CI 4 to 32%) and 49% (95% CI 20 to 78%), respectively. For patients with progressive disease despite prior conventional chemotherapy, 12-month progression-free and overall survival rates were 11% (95% CI 2 to 24%) and 55% (95% CI 35 to 75%), respectively. The median duration of response was 11 months. The durability of major responses in a subset of patients was impressive, as was the number of patients who achieved disease stabilization without showing objective response. Overall, ET-743 had a favorable safety profile. The most common grade 3–4 toxicities included neutropenia and transiently increased transaminase concentrations. ET-743 did not cause alopecia, mucositis, cardiotoxicity or neurotoxicity. The side effects were reversible, non-cumulative and manageable. There were no treatment-associated deaths. In conclusion, ET-743 is an active chemotherapeutic agent that can induce objective responses and clinical benefit in a subset of patients with metastatic or advanced soft-tissue sarcoma. [© 2002 Lippincott Williams & Wilkins.]

Key words: Ecteinascidin-743, soft-tissue sarcoma, chemotherapy.

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Introduction

Soft-tissue sarcomas (STS) are rare, heterogeneous mesenchymal neoplasms, accounting for approximately 1% of adult malignancies. Chemotherapy is currently used for the treatment of advanced or metastatic STS, but relatively low objective response rates have been noted with the few standard cytotoxic agents available for this disease, especially in adults. Doxorubicin is currently the agent of choice for first-line treatment of STS, despite having a reported objective response rate of only 9% in a recent series.[1] Ifosfamide monotherapy has been associated with variable response rates, but in general its activity has been judged to be similar to that of doxorubicin.[2] Combination chemotherapy with doxorubicin and ifosfamide has been reported to improve the response rate, but not the overall survival rate of patients with advanced sarcomas.[3] It is also clear that combination therapy may be associated with increased toxicities, including myelotoxicity.[4] Few other chemotherapeutic agents have shown any anti-tumor activity in STS, and when activity is present, as with dacarbazine, it is generally minor. There is therefore a pressing medical need to identify novel anti-tumor agents for STS, given the limited activity of available chemotherapeutic options for these patients.

Ecteinascidin-743 (ET-743) is active *in vitro* at nanomolar concentrations against a variety of human solid-tumor types, including STS cell lines and xenografts.[5–7] Early Phase I studies have shown that ET-743 has anti-tumor activity against advanced, heavily pretreated STS and osteosarcomas.[8,9] Further studies to establish the extent of ET-743 anti-tumor activity in patients with STS are being actively pursued.

ISSN 0959-4973

Clinical evaluation of ET-743

Patients with unresectable metastatic or advanced STS were recruited to two multicenter, Phase II studies in the USA, on the basis of their previous treatment: chemotherapy-naïve patients were enrolled in one study, and patients with disease progression despite prior conventional chemotherapy ('pretreated') were enrolled in a second study. Patients received ET-743 at a dose of 1500 $\mu g/m^2$ as a 24 h continuous intravenous infusion every 3 weeks on an outpatient basis. Assessments were performed every 6 weeks until documented progressive disease, unacceptable toxicity or withdrawal of the patient from the study. Disease response was assessed in accordance with conventional oncological criteria for objective response. Toxicities were graded using the National Cancer Institute common toxicity criteria.

Clinical efficacy of ET-743

In the two studies, a total of 72 patients with metastatic or advanced STS were recruited; 36 were chemotherapy-naïve. The patients' clinical characteristics are summarized in Table 1. Four patients (11%) in the chemotherapy-naïve group had received adjuvant chemotherapy more than 12 months previously (these patients were nevertheless considered chemotherapy-naïve). All the pretreated patients had received doxorubicin and 31 (87%) had received ifosfamide, either as monotherapy or as part of a combination regimen within the 12-month period preceding study entry; 25 (70%) patients had received a combination of doxorubicin and ifosfamide as first-line chemotherapy. The median number of previous chemotherapeutic agents used was three (range one to six). It should be noted that all patients had clinically worsening disease at the time of entry to the study.

The clinical responses to ET-743 treatment over a median follow-up period of approximately 9 months are summarized in Table 2. In chemotherapy-naïve patients, the response rate was 14% (five of 35 evaluable patients; 95% confidence interval (CI) 5 to 30%) and in chemotherapy-pretreated patients the response rate was 8% (three of 36; 95% CI 2 to 23%). At 12 months, progression-free and overall survival rates for first-line treatment with ET-743 (chemotherapy-naïve patients) were 18% (95% CI 4 to 32%) and 49% (95% CI 20 to 78%), respectively. For second- or third-line treatment with ET-743 (pretreated patients), 12-month progression-free and overall survival rates were 11% (95% CI 2 to 24%) and 55% (95% CI 35 to 75%), respectively. The median duration of response was 11 (range 1–20) months. Eight of the 36 pretreated patients (22%) received more than six cycles of ET-743 according to the study procedure. The impact of this disease stabilization is important to recognize, and might potentially be overlooked if response rates alone were reported.

Table 1. Patients' demographic and clinical characteristics at study entry

Characteristic	Chemotherapy-naïve ($n = 36$)	Pretreated ($n = 36$)
Male	16 (44)	14 (39)
Age (years)	47 (21–74)	48 (19–68)
STS subtype		
Leiomyosarcoma	15 (42)	13 (36)
Liposarcoma	9 (25)	10 (28)
Synovial sarcoma	1 (3)	6 (17)
Other	11 (30)	7 (19)

Values are number (%) or median (range). STS = soft-tissue sarcomas.

Table 2. Summary of objective clinical response rates

Variable	Chemotherapy-naïve ($n = 35$)	Pretreated ($n = 36$)
Complete response	1 (3)	1 (3)
Partial response	4 (11)	2 (6)
Stable disease	5 (14)	13 (35)
Progressive disease	25 (69)	20 (56)

Values are number (%).

Table 3. Summary of the incidences of grade 3–4 hematological and non-hematological toxicities†

Variable	Chemotherapy-naïve ($n = 35$)	Pretreated ($n = 36$)
Hematological toxicity		
Anemia	1 (3)	6 (17)
Thrombocytopenia	0	6 (17)
Neutropenia	12 (33)	14 (39)
Febrile neutropenia	0	2 (6)
Non-hematological toxicity		
Aspartate aminotransferase	12 (33)	8 (22)
Alanine aminotransferase	13 (36)	9 (25)
Creatine phosphokinase	1 (3)	1 (3)

Values are number (%).
†Graded using the National Cancer Institute common toxicity criteria. Toxicity grades shown represent the greatest experienced for that toxicity.

Clinical safety of ET-743

The main grade 3–4 toxicities are summarised in Table 3. Overall, the main grade 3–4 toxicities were neutropenia and increased concentrations of aminotransferases, which occurred in 26 patients (37%) and 46 patients (59%), respectively. The overall rate of febrile neutropenia with ET-743 treatment was low (6%), even though no hematopoietic growth factors were used in the supportive care of these patients. There were no reports of grade 3–4 increases in serum bilirubin, alkaline phosphatase or creatinine concentrations. Nausea, vomiting and fatigue reached grade 2–3 severity in 17%, 11% and 32% of patients, respectively. There were no reports of mucositis, alopecia, cardiotoxicity

or neurotoxicity. No cumulative toxicity occurred in either study, and there were no treatment-associated deaths.

Conclusions

The preliminary results with ET-743 for the treatment of metastatic or advanced STS are encouraging, with disease stabilization occurring in a significant proportion of patients, and objective responses occurring in 14% of chemotherapy-naïve patients and 8% of pretreated patients. These results are noteworthy because they show that clinical responses can be obtained with ET-743 in patients with clinical resistance to doxorubicin and ifosfamide. The 12-month progression-free survival rates in chemotherapy-naïve and pretreated patients were 18% and 11%, respectively. These latter rates are encouraging, because all the pretreated patients and the majority of chemotherapy-naïve patients had worsening disease on entry to the study. In addition, the median duration of response with ET-743 was 11 months, and was clearly associated with clinical benefit from control of bulky symptomatic disease in certain patients.

Overall, ET-743 treatment given as a 24 h intravenous infusion every 3 weeks has a favorable toxicity profile. Neutropenia occurred with similar frequency in both chemotherapy-naïve and pretreated patients. The incidences of grade 3–4 hematological toxicities were generally lower when ET-743 was used as first-line rather than second- or third-line chemotherapy. This observation is consistent with the fact that pretreated patients are likely to have had reduced hematopoietic reserve as a result of previous myelotoxic chemotherapy.

Summary

Experience in the USA supports the assertion that ET-743 is effective treatment for a subset of patients with STS, either as first-line treatment or to control disease after failure of conventional chemotherapeutic agents. Clinical studies are in progress to investigate the potential activity of this agent in sarcomas of bone and to explore more fully its activity in patients with metastatic or advanced STS, as well as breast and ovarian cancers.

Postscript: After recent modification of the ET-743 treatment schedule, the next generation studies in the USA administer ET-743 at a dose of 1300 $\mu g/m^2$ via 3 hour iv infusion in conjunction with dexamethasone premedication. Results from this more convenient infusion schedule are pending from these active studies.

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