Neoadjuvant Chemotherapy for Ewing's Sarcoma of Bone

No Benefit Observed after Adding Ifosfamide and Etoposide to Vincristine, Actinomycin, Cyclophosphamide, and Doxorubicin in the Maintenance Phase—Results of Two Sequential Studies

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BACKGROUND. Ifosfamide (IF) alone or combined with etoposide (ET) was reported to be effective in the treatment of patients with Ewing's sarcoma who relapsed after treatment with the VACA regimen, which consisted of vincristine (VC), actinomycin (AC), cyclophosphamide (CP), and doxorubicin (AD). The purpose of this article is to report the results achieved in a new neoadjuvant protocol in which IF and ET were added to the conventional VACA regimen and administered to patients with localized disease.

METHODS. In this study, eighty-two patients were treated between May 1988 and October 1991. Chemotherapy consisted of two induction cycles of VC/CP/AD followed by alternating cycles of VC/AD/CP, VC/IF/AC, IF/ET, and VC/CP/AC after local treatment. Twenty-two patients (27%) were treated with surgery only, 22 (27%) underwent surgery followed by radiation therapy, and 38 (46%) received radiotherapy only.

RESULTS. At a median follow-up of 6.7 years (range, 4–9 years), 43 patients (52%) remained continuously disease free, and 39 relapsed (34 with metastases, 4 with local recurrence and metastases, and 1 with a local recurrence). These results were similar to those obtained at the same institute in a previous neoadjuvant study (March 1983 and April 1988) that included 108 patients treated with the conventional 4-drug regimen. The 5-year disease free and overall survival in the current study were 54% and 59%, respectively, and in the first study were 50% and 56%, respectively.

CONCLUSIONS. The comparison of these two sequential studies, although not randomized, referred to homogeneous groups of patients observed at the same institution who were treated by the same medical team. No advantage was observed when IF and ET were added to the VACA regimen. ***Cancer*** **1998;82:1174–83.**
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During the past 25 years, the prognosis for patients with Ewing's sarcoma of bone that is nonmetastatic at presentation has dramatically improved, from a long term survival of less than 15% to a 50% cure rate. This improvement is due the multimodal approach combining surgery and/or radiotherapy with systemic adjuvant or neoadjuvant chemotherapy.[1–11]

At the authors' institutions, adjuvant chemotherapy in the treatment of nonmetastatic Ewing's sarcoma of bone was started in 1972. In the first adjuvant study (REA-1), carried out between 1972 and

1978, 85 patients were treated with a 3-drug regimen (vincristine [VC], cyclophosphamide [CP], and doxorubicin [AD]). With a minimum follow-up of more than 15 years, the event free survival (EFS) was 32%.[4] A second adjuvant study (REA-2), performed between 1979 and 1982, used a 4-drug chemotherapy regimen with the 3 drugs cited plus actinomycin D (AC). For the 59 patients who entered the study, the EFS with a minimum follow-up of 13 years was 57%.[4]

This longer and higher rate of survival observed in the above-mentioned studies as well as studies by other authors[2,3,5,11] emphasized the problem of local failure when radiation alone was used for local control. For this reason, the following study (REN-1), performed between March 1983 and April 1988, increased the use of surgery for local control. To make surgery feasible by reducing the soft tissue mass in otherwise unresectable lesions, chemotherapy was changed from adjuvant to neoadjuvant, using the same four drugs as in the previous REA-2 adjuvant study. Three cycles were delivered before local therapy. With a follow-up ranging from 8 to 12 years, 44% (48 of 108) of patients remained continuously free of disease.[12]

At the end of the 1980s, ifosfamide (IF) alone or in combination with etoposide (ET) was also reported to induce a high response in those patients with metastatic Ewing's sarcoma in whom chemotherapy with the traditional 4-drug VACA regimen (VC, AC, CP, AD) had failed.[13–17] Based on these data, in May 1988 we started a new neoadjuvant protocol (REN-2), adding IF and ET to the VACA regimen.

The purpose of this article is to report and compare the results for the 82 patients treated with this new protocol with those from the previous REN-1 neoadjuvant study,[12] in which only the four conventional drugs were used.

MATERIALS AND METHODS

Patient Selection

Eligibility criteria were the same as those of the previous studies and included histologic diagnosis of Ewing's sarcoma of bone, age ≤40 years, no distant metastases at diagnosis, no previous treatments, and an interval no longer than 4 weeks between the biopsy and the beginning of therapy. Of the 112 newly diagnosed cases of Ewing's sarcoma of bone observed between May 1988 and October 1991, 86 were eligible for the study. Twenty-six were excluded for metastatic disease at presentation (20), previous treatments elsewhere (4), and age >40 years (2). After diagnosis, 4 of the 86 eligible patients preferred to move elsewhere for treatment; therefore, 82 patients entered the study. Table 1 describes the characteristics of these 82 patients and those of the 108 patients treated in the previous REN-1 neoadjuvant study.

TABLE 1
Patient Characteristics in the Current Study (REN-2) and in the Previous Neoadjuvant Study (REN-1)

Characteristics	No. (%) of patients: REN-1 (3/83–4/88) n = 108	No. (%) of patients: REN-2 (5/88–10/91) n = 82	*P* value
Gender			
Male	68 (63%)	50 (61%)	NS
Female	40 (37%)	32 (39%)	
Age (yrs)			
<14	58 (54%)	39 (48%)	NS
≥14	50 (46%)	43 (52%)	
Site			
Extremities	68 (63%)	58 (71%)	NS
Central	40 (37%)	24 (29%)	
Volume			
<100 mL	42 (39%)	22 (27%)	NS
>100 mL	66 (61%)	60 (73%)	
LDH			
Normal	62 (57%)	52 (63%)	NS
Elevated	46 (43%)	30 (37%)	

LDH: lactate dehydrogenase; NS: not specified.

Preoperative Evaluation

All patients had a complete history, a thorough physical examination, and several chemical laboratory tests. The diagnosis of Ewing's sarcoma was based on representative specimens obtained from an open biopsy and evaluated by light and electron microscopy. Pathologic criteria for diagnosis was a small, round-cell tumor occurring in the bone with no histologic, cytologic, or ultrastructural evidence of lymphoma, rhabdomyosarcoma, or neuroblastoma. No attempt was made to differentiate Ewing's sarcoma from peripheral neuroectodermal tumors.

The primary tumor was staged by standard radiographs, technetium-99 bone scintigram, computed tomography (CT) scan, and in some cases magnetic resonance imaging. Following the method reported by Gobel et al.,[18] tumor volume was estimated by measuring, on CT scan, the three diameters of the lesion, including the soft tissues. The formulas varied depending on whether the mass was elliptical or spherical: volume $= A \times B \times C \times 0.78$ (for elliptical tumors) or $\times 0.52$ (for spherical tumors).

Metastatic disease was excluded based on the results of bone scintigram and CT scan of the chest.

Induction Chemotherapy and Evaluation of Radiologic Response to Chemotherapy

Before local treatment, two cycles of VC, AD, and CP were given (Fig. 1). During induction chemotherapy

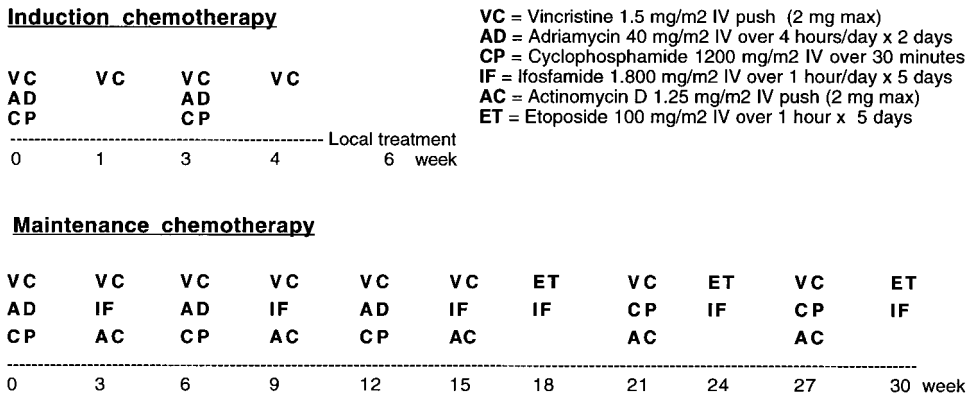

FIGURE 1. The REN-2 chemotherapy protocol is shown.

and before local treatment, patients were evaluated for regression of the primary tumor with physical examinations, conventional radiographs, and CT scans. The radiologic response to chemotherapy was classified as 1) good (complete resolution of the soft tissue mass, if present, and delineation of the bone lesion); 2) fair (reduction of at least 50% of the soft tissue mass, if present); 3) poor (less than 50% regression of the soft tissue mass, regardless the change in the bone lesion); and 4) radiologic progression of the bone and/or soft tissue component.

Local Treatment

Local treatment was scheduled 2 weeks after the last cycle of chemotherapy. The type of local treatment was decided on an individual basis. After being advised of the possible postsurgical functional sequelae, all patients were offered surgery as local treatment; those with tumors located in the sacrum or spine were the only exceptions. In tumors of the extremities, amputation was recommended for pathologic fractures that otherwise could not be treated as well as for lesions of the distal femur, leg, or foot in young, growing children. In these patients, radiation therapy would have caused an unacceptable limb-length discrepancy with worse functional impairment than would result from amputation. Patients with tumors located in the sacrum or spine, as well as those who refused surgery, were treated locally by radiation therapy (cobalt-60, 55–60 gray [Gy]) according to a previously reported procedure.[8]

Postoperative radiotherapy was given to all patients with inadequate surgical margins at full dose. In patients with adequate margins, a reduced dose (40–45 Gy) was given if the type of surgical reconstruction allowed it.

Pathologic Evaluation of Patients Who Underwent Surgery

After surgery, all macroscopic specimens were carefully observed, and surface labeled histologic sections were taken. Surgical margins were evaluated according to Enneking et al.,[19] where reduced and wide margins were considered adequate and marginal and intralesional margins were considered inadequate. The response to chemotherapy was determined by a thorough histologic examination of an entire coronal section of the tumor[20] and classified as Grade 1 (evidence of macroscopic foci of viable tumor cells), Grade 2 (only isolated microscopic nodules of viable tumor cells), and Grade 3 (no nodules of viable cells).

Postoperative Chemotherapy and Follow-Up

After local treatment, maintenance chemotherapy was delivered in alternating cycles of VC/AD/CP, VC/IF/AC, IF/ET, and VC/CP/AC, according to the schedule reported in Figure 1.

After treatment, patients were followed with a physical check-up and standard radiographs of the chest and the involved bone every 3 months for 4 years, and then twice a year. Additional studies, including biopsies, were done if indicated by the cited clinical and radiologic examinations.

Comparison with the REN-1 Study

Our first neoadjuvant study (REN-1), carried out between June 1983 and April 1988, used 3 cycles of VC/CP/AD as induction chemotherapy, whereas the maintenance treatment alternated cycles of VC/CP, VC/AD, and VC/AC.[12] Table 2 compares the scheduled doses and dose intensities in the two studies.

As reported in Table 1, the patient characteristics were similar in the two studies. The choice of local treatment followed the same criteria as for the REN-

TABLE 2
Comparison between the Projected Cumulative Doses and the Dose Intensities in the REN-2 and REN-1 Chemotherapy Regimens

	REN-1		REN-2	
	Total dose (mg/m^2)	Dose intensity ($mg/m^2/wk$)	Total dose (mg/m^2)	Dose intensity ($mg/m^2/wk$)
Vincristine	40.5	0.65	18	0.46
Cyclophosphamide	15.600	252	8.400	215
Doxorubicin	480	7.74	400	10.26
Actinomycin D	9	0.15	7.5	0.19
Ifosfamide	—	—	54.000	1384
Etoposide	—	—	1.500	38.4
Duration of chemotherapy	60 wks		39 wks	

1 study, and surgery was proposed whenever possible. The REN-2 study always employed postoperative radiotherapy in all surgically treated patients, except when irradiation was contraindicated by the type of reconstruction, whereas the REN-1 study prescribed postoperative radiotherapy only when surgical margins were inadequate (marginal or intralesional).

Statistical Analysis

Results were evaluated according to disease free survival, type and time of recurrence, chemotherapy-related toxicity, and local complications. The Kaplan-Meier product limit estimate[21] was used to calculate event free survival (EFS) and disease free survival (DFS) from diagnosis to the onset of local recurrence, distant metastasis, second malignancy, death from toxicity, or last follow-up. Postrelapse outcome and overall survival (OS) were also evaluated, but this data must be considered with some caution. After relapse no homogeneous treatments were given, as most patients moved to other institutions, where they were treated with different therapies. The log rank test was used to calculate the differences between the groups.[22]

No patients were lost to follow-up, and there were no events other than relapse or second malignancies. All deaths were related to these two factors.

RESULTS

Clinical, Radiologic, and Histologic Response to Induction Chemotherapy

As a clinical response to induction chemotherapy, 94% of the 70 clinically evaluable patients had a reduction or complete remission of pain and functional symptoms associated with a resolution or reduction of the soft tissue mass.

The radiologic response was good in 32 patients, fair in 39, and poor in 7. Response to chemotherapy could not be evaluated in four patients, as the soft tissue mass was not measurable. Of the seven patients who did not respond, all but two had a partial recovery from pain, but clinically and on CT scan the soft tissue mass remained unaltered. During induction chemotherapy, the tumor mass showed a clinical and radiologic increase in only two patients.

In patients who responded, pain usually disappeared after the first cycle of induction chemotherapy. Measurable tumor regression, evaluated clinically and radiologically, occurred predominantly during the first cycle, with only a slight additional regression after the following cycle.

TABLE 3
Comparison between the Results of the REN-2 and REN-1 Studies

	REN-1	REN-2
No. of patients	108	82
Mean yrs of follow-up (range)	10.7 (9–13)	6.7 (4–9)
Disease free survival	48 (44%)	43 (52%)
Relapses	57 (53%)	39[a] (48%)
Second malignancies	1 (1%)	1[a] (1%)
Deaths from toxicity	2[b] (2%)	0

[a] One patient who relapsed with local recurrence also developed acute leukemia.
[b] Doxorubicin cardiotoxicity in both cases.

Local Treatment

The primary tumor was treated with surgery alone in 22 patients (27%), surgery followed by radiotherapy in 22 (27%), and radiotherapy alone in the remaining 38 (46%).

Of the patients who were treated surgically, 5 were amputated, 2 had a rotationplasty, and 37 had a limb-salvage procedure. The reasons for the amputations were as follows: 2 patients had pathologic fractures and a poor radiologic response in very large lesions located in the humerus and the tibia, and 3 were very

young patients (ages 5 and 7 years) with tumors located in the femur (2) and tibia (1).

In 25 of the 37 patients treated with resection it was necessary to reconstruct the bone continuity. This reconstruction was done with prosthesis in 12 cases, allograft in 7, and autograft in 6.

Surgical Margins and Histologic Response to Chemotherapy

The 44 patients who had surgery for local control, whether with or without postoperative irradiation, were evaluable for surgical margins and histologic response to primary chemotherapy. Surgical margins were radical or wide in 35 cases and marginal or intralesional in 9. The histologic response was Grade 1 in 23 patients (52%), Grade 2 in 11 (25%), and Grade 3 in 10 (23%). No relationship was found between histologic response, site, and tumor volume.

Disease Free Survival

On March 1, 1997, the median length of follow-up for the disease free patients was 86 months (range, 65–115 months).

As shown in Table 3, 43 patients (52%) remained continuously disease free and 39 (48%) relapsed, 2 during maintenance chemotherapy and the others 3–43 months (median, 19 months) after the treatment ended. The actuarial 5-year disease free survival was 54% (Fig. 2) and the overall survival 59% (Fig. 3). One of the relapsed patients developed a second neoplasm. This patient, a girl age 14 years with a Ewing's sarcoma of the tibia locally treated by radiotherapy, had a local recurrence that required amputation 24 months after the beginning of chemotherapy. Six months after the amputation, she developed an acute myeloid leukemia and died of this disease 3 months later.

As illustrated in Table 4, no relation was found between disease free survival, age, gender, and tumor volume. Patients with normal levels of serum lactate dehydrogenase (LDH) at presentation had a significantly higher rate of disease free survival than patients with high levels of the enzyme (71% vs. 23%, $P = 0.0001$). Regarding the site of the lesion, patients with the tumor located in the extremities had better disease free survival than those with the tumor located in the central bones (59% vs. 42%). This difference, however, was not statistically significant. Regarding local therapy, no difference in prognosis was noted.

Histologic response to chemotherapy was assessed only in the 44 patients locally treated by surgery. The rate of disease free survival was significantly higher in Grade 2 or 3 responses than in Grade 1 responses (Table 4). Nine of 10 patients (90%) with Grade 3 responses and 10 of 11 patients (91%) with Grade 2 responses were continuously free of disease, as opposed to 6 of 23 patients (26%) who had a Grade 1 histologic response.

Pattern of Relapse

Relapse consisted of metastases alone in 34 cases (87%), metastases and local recurrence in 4 (10%), and in local recurrence alone in 1 (3%) (Table 5). This occurred in the above-mentioned patient, who also had a second tumor. The first metastases were located in other bones (20), lungs (15), the central nervous system (1), and skin (1). In one patient, lung and bone metastases were contemporary. The median time to bone metastases was 18.6 months (range, 4–61 months) and to lung metastases 26.2 months (range, 6–84 months).

Of the 4 patients who had both metastases and local recurrence, the 2 events were contemporary in 3, whereas the remaining patient had the local recurrence 49 months after the beginning of treatment and metastases diagnosed 11 months later.

The 5 patients with a histologically confirmed local recurrence had the tumor in the extremities: the femur (2), tibia (2), and humerus (1). For these patients, the local treatment had been radiotherapy in 4 and surgery in 1. This last patient, who had a Ewing's sarcoma of the distal tibia, had wide surgical margins with a Grade 2 histologic response. The mean time to the appearance of local recurrence was 23.4 months (range, 6–49 months).

Postrelapse Outcome

The 39 patients who relapsed received further different therapies in different institutions. Of these, 32 died 3–19 months after relapse (mean, 12.7 months), 5 are alive with uncontrolled disease 8–14 months after relapse (mean, 10.8 months), and 1 is alive and apparently disease free 16 months after relapse. This patient relapsed 38 months after the beginning of treatment with a solitary lung metastasis, which was surgically removed.

Compliance with the Protocol and Systemic Toxicity

Only 50 of the 1140 chemotherapy cycles (4%) had to be delayed more than 1 week (mean, 1.9; range, 1–3 weeks) for persistent myelosuppression or complications related to the treatment of the primary lesion. Seventy-two patients (88%) had 90% or more of the scheduled chemotherapy dose intensity.

In all the chemotherapy cycles, a Grade 4 hematologic toxicity was observed in 15% of cases (188 patients), and hospitalization was necessary 23 times to treat febrile episodes during myelodepression (20) or

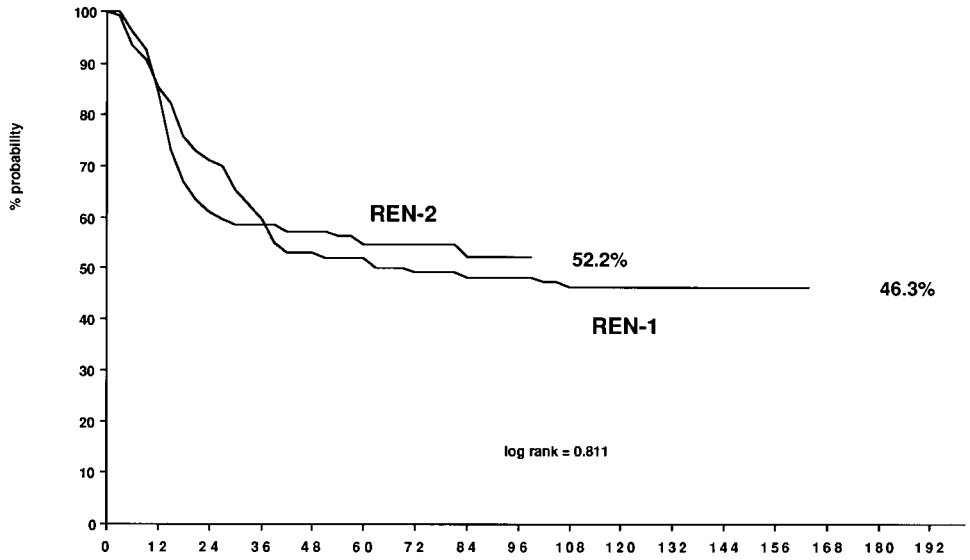

FIGURE 2. Disease free survival is shown.

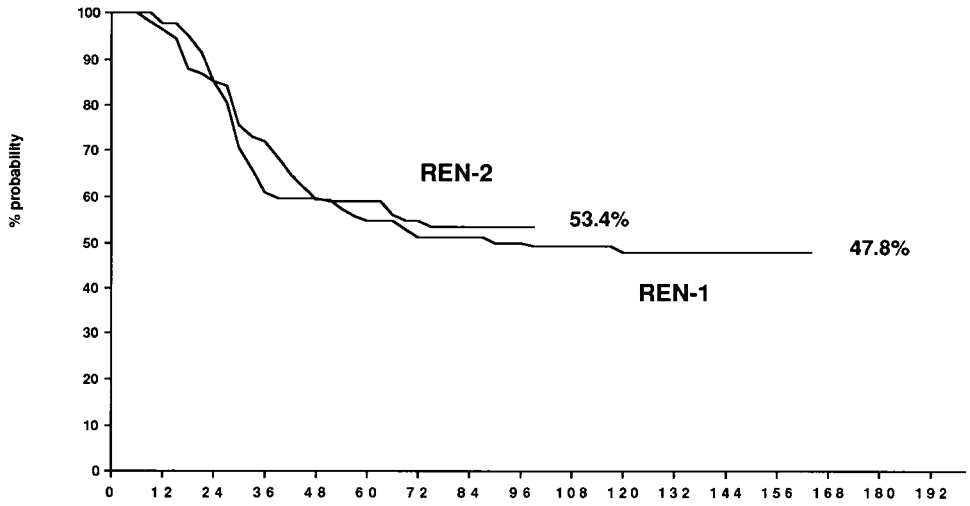

FIGURE 3. Overall survival is shown.

bleeding (3). Only one case of life-threatening bacterial sepsis (*Pseudomonas aeruginosa*) was observed.

Although the cumulative dose of AD was 400 mg/m^2, there were no clinical cases of AD cardiotoxicity. It must be stressed, however, that patients were not systematically checked by echocardiography. Only one patient had a transient macroscopic hematuria after IF administration.

Local Complications

Local complications after treatment of the primary lesion were classified as early when they occurred within 3 months after the local treatment and late if they occurred after that period of time.

Early complications were observed in 16 patients, all with tumors located in the extremities. Twelve occurred in patients who had surgery alone and three in patients who had radiotherapy after surgery. Local complications consisted of five infections, nine nerve palsies, and one postoperative detachment of the extensor apparatus after prosthetic reconstruction. The last early complication, skin necrosis, required plastic surgery and was observed in a patient locally treated with radiotherapy alone.

TABLE 4
Comparison between the 5-Year Disease Free Survival in REN-1 and REN-2 Studies, according to Several Variables

	REN-1		*P* value	REN-2		*P* value
Gender						
Male	30/68	44%	NS	27/50	54%	NS
Female	24/40	60%		17/32	53%	
Age (yrs)						
<14	32/58	55%	NS	24/39	61%	NS
≥14	22/50	44%		20/43	46%	
Volume						
<100 mL	22/42	52%	NS	14/22	64%	NS
≥100 mL	32/66	48%		30/60	50%	
Site						
Extremities	43/68	63%	0.001	34/58	59%	NS
Central	11/40	27%		10/24	42%	
LDH						
Normal	36/62	58%	NS	37/52	71%	0.0001
Elevated	18/46	39%		7/30	23%	
Local treatment						
Surgery	26/42	62%		12/22	55%	
Radiotherapy	24/51	47%	NS	19/38	50%	NS
Surg. + radiotherapy	4/15	27%		13/22	59%	
Histologic response						
Grade 1	6/23	28%		6/23	26%	
Grade 2	8/16	50%	0.001	10/11	91%	0.001
Grade 3	16/18	89%		9/10	90%	
High low risk[a]						
Low risk	23/31	74%	NS	12/18	67%	NS
High risk	31/77	40%		32/64	50%	

LDH: lactate dehydrogenase; NS: not specified.

[a] According to the German Cooperative Ewing's Sarcoma Study 86 criteria.

TABLE 5
Comparison between the Pattern of Relapse in the REN-1 and REN-2 Studies

	No. (%) of patients	
	REN-1	REN-2
Relapses	57	39
Only metastases	35 (61%)	34 (87%)
Only local recurrence	0	1 (3%)
Local recurrences and metastases	22 (39%)	4 (10%)
Local recurrences	22/108 (20%)	5/82 (6%)
Mean mos to local recurrence (range)	26.8 (10–82)	23.4 (6–49)
Metastases	57/108 (53%)	38/82 (46%)
Site of the first metastases		
Lung	28 (49%)	15 (39%)
Bone	21 (37%)	20 (53%)
Lung and bone	8 (14%)	1 (3%)
Other sites	0	2 (5%)
Mean mos to metastases (range)	27.6 (3–108)	19.3 (4–84)

Late complications were observed in 11 patients, all surgically treated. These complications included 4 cases of delayed union that required a new autograft, 4 cases of mechanical failure of the implant that required revision, and 2 cases of late deformities (deviation of the ankle axis in one and talipes equinus in the other).

Comparison with the Previous REN-1 Study

Of the 108 patients treated with the first neoadjuvant study, local treatment with surgery alone was performed in 42 (39%), with radiotherapy alone in 51 (47%) and with surgery followed by radiotherapy in 15 (14%). Therefore, the percentage of patients treated surgically was almost the same (57 of 108, 53%, vs. 44 of 82, 54%) in the two studies. In the second study, however, the percentage of resected patients who received postoperative radiotherapy was significantly higher (22 of 37, 59%, vs. 15 of 55, 27%; $P = 0.004$). The clinical and radiologic response to preoperative chemotherapy was the same in the two studies, as was, in the evaluable patients, the histologic response to

chemotherapy (Grade 1 response, 52% vs. 40%; Grade 2, 25% vs. 28%; Grade 3, 23% vs. 31%; $P = 0.45$).

In the first neoadjuvant study, at a median follow-up of 112 months (range, 106–124 months), 48 patients (44.4%) remained continuously free of disease; 2 died of AD cardiotoxicity; 1 developed an osteosarcoma in the irradiated field; and 57 relapsed, 35 with metastases and 22 with local recurrence and metastases (Table 3). The mean time to local recurrence was 26.8 months (range, 10–82 months) and to metastases 27.6 months (range, 3–108 months).

Comparing these results with those obtained in the REN-2 study, in which a 6-drug regimen was used, the two studies showed no differences in terms of DFS (Fig. 2). This was despite the fact that the rate of local recurrences in the REN-1 study (Table 5) was significantly higher (22 of 108, 20%, vs. 5 of 82, 6%; $P = 0.009$).

In the REN-1 study, the rate of disease free survival was not related to patient gender, age, tumor volume, or, in contrast with the second study, the type of local treatment or the serum level of LDH. As in the first study, the DFS rates of the patients treated surgically correlated with the histologic responses to chemotherapy (Table 4). Eighteen and 16 patients with Grade 3 and 2 response, respectively, had a disease free survival rate of 89% and 50% versus 26% for the 23 patients with a Grade 1 response ($P = 0.001$). In contrast with the REN-2 trial, the DFS rate in REN-1 correlated with tumor site (43 of 68, 63%, for tumors of the extremities vs. 11 of 40, 27%, for axial tumors; $P = 0.001$).

The time to relapse and the sites of first metastases were comparable in the two studies.

Using the German Cooperative Ewing's Sarcoma Study 86 (CESS-86) protocol criteria[23] to classify patients at higher risk (central tumor site, tumor volume >100 mL), the rate of DFS was found to be slightly higher in the 6-drug regimen than in the VACA regimen (32 of 64, 50%, vs. 31 of 77, 40%). This difference, however, was not statistically significant.

DISCUSSION

For years, the VACA regimen has been the standard chemotherapy for nonmetastatic Ewing's sarcoma.[2–4,6,9]

When, at the end of the 1980s, IF alone[13,16] or in combination with ET[14,15,17] was reported to be very effective in treating patients with metastatic Ewing's sarcoma, three multicenter neoadjuvant studies[11,23,24] replaced CP in the VACA regimen with IF (to form the VAIA regimen).

Two of these studies, the IVA Study by the French Society of Pediatric Oncology[11] and the ET-2 Study by the United Kingdom's Children Cancer Study Group,[24] used the VAIA regimen as adjuvant treatment for all patients with Ewing's sarcoma. The other study, CESS-86,[8,23] administered it only to patients considered to be at high risk of relapse (tumor volume >100 mL or central location of tumor). The results of these three new trials were contradictory when compared with those obtained by the same groups using the standard VACA regimen. Whereas in the French study no advantages were found with the VAIA regimen, the German and English studies found significant benefits when CP was replaced with IF.

In the REN-2 study, CP was not replaced with IF, but after local treatment in the maintenance chemotherapy IF and ET were added to the four drugs of the conventional VACA regimen. It must be stressed, however, that in this 6-drug protocol the cumulative doses and the dose per week of VC and CP were reduced; the cumulative doses of AC and AD were also reduced, but, due to the different schedule, the dose per week of these last two drugs was higher than in the VACA regimen (Table 2).

At a median follow-up of about 7 years (range, 4–9 years), 43 of 82 patients (52%) who entered the study remained continuously event free, and the actuarial 5-year overall and event free survival were 59% and 54%, respectively.

In contrast with our previous adjuvant and neoadjuvant trials,[12] in the current study the DFS was not related to tumor site as opposed to LDH serum levels at presentation, to the type of local treatment, or, in patients treated with surgery, to the histologic response to chemotherapy. As previously reported by the authors[20,25] and others,[3,11,26,27] in Ewing's sarcoma both the level of serum LDH at presentation and the histologic response to induction chemotherapy had prognostic significance.

When the results of the current study were compared with those obtained with the REN-1 study, in which 108 patients were treated with the conventional VACA regimen, it was observed that the addition of IF and ET to the standard 4-drug regimen did not improve survival. The 5-year EFS (50% vs. 54%) and the overall survival (61% vs. 59%) were the same in the two studies. It is important to stress that the distribution of patient characteristics (and in detail site and tumor volume and serum LDH values) were similar in the two studies.

Smith et al.[28] published a meta-analysis that showed the importance of doxorubicin in the treatment of Ewing's sarcoma. Because the 6-drug REN-2 regimen reduced the cumulative doses of AD (as well as VC, CP, and AC) compared with the 4-drug REN-1 regimen, it cannot be ruled out that the theoretic advantage of adding IF and ET might have been hid-

den by the disadvantages brought about by these reductions. On the other hand, it must be stressed that the different schedule used in REN-2 resulted in an increased dose intensity of AD and AC (Table 2). In other words, in the REN-2 regimen, the addition of two new drugs could not compensate for the reduction of the cumulative dose of the conventional four drugs of the VACA regimen.

The only difference observed when the results of the two studies were compared was the rate of local recurrence, which in the 6-drug regimen was significantly lower than in the 4-drug regimen (6% vs. 20%; $P = 0.009$). A possible explanation of this difference could be that although the percentage of patients surgically treated was the same in the two studies, the first trial had a higher percentage of patients who did not undergo radiotherapy after resection. Postoperative radiotherapy was given only when the resection margins were inadequate, whereas in the REN-2 study, radiation therapy was given to all patients regardless of the surgical margins, unless contraindicated for the type of surgical reconstruction performed. The failure of the strategy adopted in the REN-1 study of reserving radiotherapy only for resected patients with inadequate margins seems to be confirmed by one patient in the REN-2 study. This patient developed a local recurrence despite a wide resection of an almost totally necrotic Ewing's sarcoma of the tibia, and did not receive radiotherapy.

The REN-1 and REN-2 patients were classified as high and low risk according to the criteria adopted in the CESS studies.[23] The high risk patients treated with a 6-drug regimen, including IF, had a higher rate of DFS than the high risk patients treated with the VACA regimen. This difference, however, was not statistically significant.

In the REN-2 study, the use of IF and ET was probably not innocuous. None of patients developed renal Fanconi's syndrome or chronic cystitis, as reported by other authors who used IF or the combination IF and ET.[29] However, the acute leukemia that developed in one patient had cytogenetic, morphologic, and clinical findings characteristic of leukemia associated with ET-containing regimens.[30,31]

In the current study, the addition of IF and ET to the VACA regimen in the neoadjuvant treatment of Ewing's sarcoma of bone seemed to confer no advantages. These results were in contrast with the preliminary results of the randomized Intergroup Ewing's Sarcoma Study (IESS-III),[32] in which patients were randomized to receive a 4-drug regimen with VC, AC, CP, and AD (VACA arm) or a 6-drug regimen consisting of VACA plus IF and ET (VACA + IF/ET arm). At a median follow-up of 18 months, the 3-year EFS was 50% for the 200 patients of the VACA arm and 80% for the 198 patients of the VACA + IF/ET arm ($P = 0.0007$). In this study, the addition of IF and ET to the VACA regimen improved the outcome of nonmetastatic Ewing's sarcoma.

When compared with our REN-2 study, the VACA + IF/ET regimen had important differences: the cycles of IF/ET were delivered since the induction phase, whereas in our study IF and ET were delivered only in the maintenance phase of chemotherapy; the IESS-III study provided 10 cycles of the combination IF/ET, whereas in our study only 3 cycles were delivered. Therefore, the different outcomes obtained in the two studies might have been due to the differences in schedule and number of cycles of IF/ET. On the other hand, it must be stressed that the IESS-III study involved a study population with a median follow-up of 18 months only, and the possibility of late relapse in Ewing's sarcoma is well known. So it is possible that the early use and the increased number of cycles of IF and ET only delay the time to recurrence.

This is why the final results of the randomized Intergroup Ewing's Sarcoma Study (IESS-III) will be of major importance in assessing whether the addition of IF and ET to the standard VACA regimen with the four conventional drugs improves relapse free and overall survival. However, this controlled multicenter study, although not fraught with all the methodologic problems that sequential studies involve, could not guarantee homogeneous local treatment, which is proven to be very important for the outcome of patients. For this reason, this report of two sequential studies involving a homogeneous group of patients observed at a single institution and treated by the same medical team could contribute to solving the problem.

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