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Results of API–AI based regimen in osteosarcoma adult patients included in the French OS2006/Sarcome-09 study

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In the OS2006 study, patients younger than 18 years were treated with a methotrexate-based regimen (MTX), patients older than 25 years with a doxorubicin–cisplatin–ifosfamide-based regimen (API–AI), whereas patients aged 18–25 years received either API–AI or MTX. We herein report the prespecified subgroup analysis of the outcome of 106 patients treated with API–AI. Preoperative chemotherapy combined three doxorubicin–ifosfamide–cisplatin (API) and two doxorubicin–ifosfamide (AI) courses. Postoperative chemotherapy was assigned by risk group: localised patients with a good histological response (<10% viable cells) received two AI and two cisplatin–ifosfamide (PI) courses; patients with synchronous metastases, poor histological response or unresectable primary received five cycles of etoposide–ifosfamide (EI). Of the 106 patients, 61 were randomised to receive or not zoledronate. Median age was 30 years (range 18–67), 66 (62%) patients were >25 years. The primary tumours were axial in 28 patients (26%), and 28 (26%) presented with metastases. Ninety-six patients (91%) had

Key words: osteosarcoma, adult patients, doxorubicin–cisplatin–ifosfamide regimen

Abbreviations: AI: doxorubicin–ifosfamide; AP: doxorubicin–cisplatin; API: doxorubicin–cisplatin–ifosfamide; CI: confidence interval; CT: computed tomography; CTCAE: common terminology criteria for adverse events; EFS: event-free survival; EI: etoposide–ifosfamide; HDTMX: high-dose methotrexate; IQR: interquartile range; MRI: magnetic resonance imaging; MTX: methotrexate; OS: overall survival; PI: cisplatin–ifosfamide

Additional Supporting Information may be found in the online version of this article.

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surgery, conservative in 82 (85%); 36 patients (38%, 95% CI 28–48%) were good responders. Toxicity was manageable, with no significant difference in severe acute toxicity between patients aged >25 years and those younger. With a median follow-up of 4.8 years, the 5-year event-free survival and overall survival rates were 46% (95% CI 36–56) and 57% (95% CI 47–67), respectively. The primary tumour size and initial metastases correlated with a higher risk of event. In these 106 osteosarcoma adult patients, API–AI proved feasible with no excess of toxicity, and favourable activity despite poor-prognosis factors.

What's new?

Osteosarcoma paediatric patients are commonly treated with high-dose methotrexate combined to other active agents. Methotrexate pharmacokinetics varies considerably with age, however, with few prospective studies dedicated to adult patients and currently no consensus concerning the optimal chemotherapy regimen in these patients. This paper describes the population of 106 adult osteosarcoma patients enrolled in the OS 2006 phase III study, their treatment and their outcomes using a chemotherapy backbone without methotrexate that combines doxorubicin, cisplatin, and ifosfamide. This study confirms prior findings that the API-AI regimen has acceptable toxicity and yields favourable activity in adult osteosarcoma patients with poor prognosis factors.

Introduction

Two pivotal randomised studies carried out in the 1980s,[1,2] and several controlled and uncontrolled trials conducted afterwards, demonstrated that neoadjuvant and adjuvant chemotherapy markedly improves event-free survival (EFS) and overall survival (OS) in patients with nonmetastatic high-grade resectable osteosarcoma. There is a consensus among paediatricians to combine high-dose methotrexate (HDTMX) to other active agents including doxorubicin, cisplatin or ifosfamide for treating paediatric patients.[3–5]

However, it is not clear which is the best chemotherapy regimen in nonpaediatric osteosarcoma patients, Only a few prospective studies were dedicated to adult osteosarcoma patients. In the retrospective EMSOS review, the 5-year OS was 46% in the 238 patients older than 40 years with nonmetastatic high-grade osteosarcoma,[6] and 22% in the 43 patients older than 65 years in the Rizzoli series.[7]

HDMTX pharmacokinetics varies considerably with age, and a dose of 8 g/m^2 routinely administered in adults, is lower than the recommended dose of 12 g/m^2 per cycle in children.[8,9] HDMTX induces hepatic dysfunction and neurological toxicity and may impair renal clearance despite standardised monitoring and preventive use of leucovorin rescue.[10] HDMTX renal toxicity is significantly more frequent in adults than in children,[11] and often combines delayed HDMTX clearance and renal dysfunction, avoiding patients to resume HDMTX therapy after normalisation of renal function. Consequently, combination of HDTMX with cisplatin, doxorubicin or ifosfamide may lead to dose reductions illustrating the limitations of HDTMX-containing multidrug regimen in adult patients.

The European Osteosarcoma Intergroup phase III study EOI2 showed a similar efficacy and a better tolerance of preoperative doxorubicin and cisplatin combination (AP) compared to HDTMX-based chemotherapy.[12] Based on these results, in France, two phase II studies were successively conducted with the doxorubicin–cisplatin–ifosfamide (API–AI) regimen. First, a monocentric study enrolled 32 patients, aged 15–49 years (median age: 21 years) assessing a dose-dense schedule. The authors reported a 5-year EFS rate of 65% and a 5-year OS rate of 69%.[13] Secondly, a multicentre study conducted by the French Sarcoma Group in 47 patients aged 17–50 years (median age: 23 years) assessed the API–AI regimen. The 5-year EFS rate was 65% and the 5-year OS rate was 74%, similar to those obtained in the first study.[14] Using a 3-week interval, toxicity was mainly haematological. The API–AI regimen's tolerance compared favourably with that of the MTX-based regimen used to treat adult osteosarcoma patients.

As of 2007, all newly diagnosed French osteosarcoma patients younger than 50 years old were proposed the prospective randomised OS2006 trial, with the API–AI regimen as one of the backbone chemotherapy regimen.[15] This trial was designed to evaluate the effect of adding zoledronate to chemotherapy; patients could decline the randomisation and only accept the registration of clinical data and participation to ancillary studies.

Here, we described the safety and efficacy of the doxorubicin–cisplatin–ifosfamide (API–AI) chemotherapy regimen in the cohort of randomised and registered but non-randomised adult patients prospectively enrolled in the French OS2006 trial before March 2014.

Materials and Methods

Study design and participants

The French OS2006 study enrolled patients with localised or metastatic high-grade osteosarcoma. The OS2006 study included a phase III randomised trial evaluating zoledronate in combination with chemotherapy (NCT00470223; http://www.unicancer.fr/protocole-sarcome-09). Patients who accepted to participate in the study but were not randomised were treated with the same chemotherapy, without zoledronate and prospectively registered in the OS2006-database. The protocol was approved by an independent ethics committee and the institutional review boards.

Key eligibility criteria for study registration were patients with newly diagnosed, biopsy-proven, high-grade osteosarcoma,

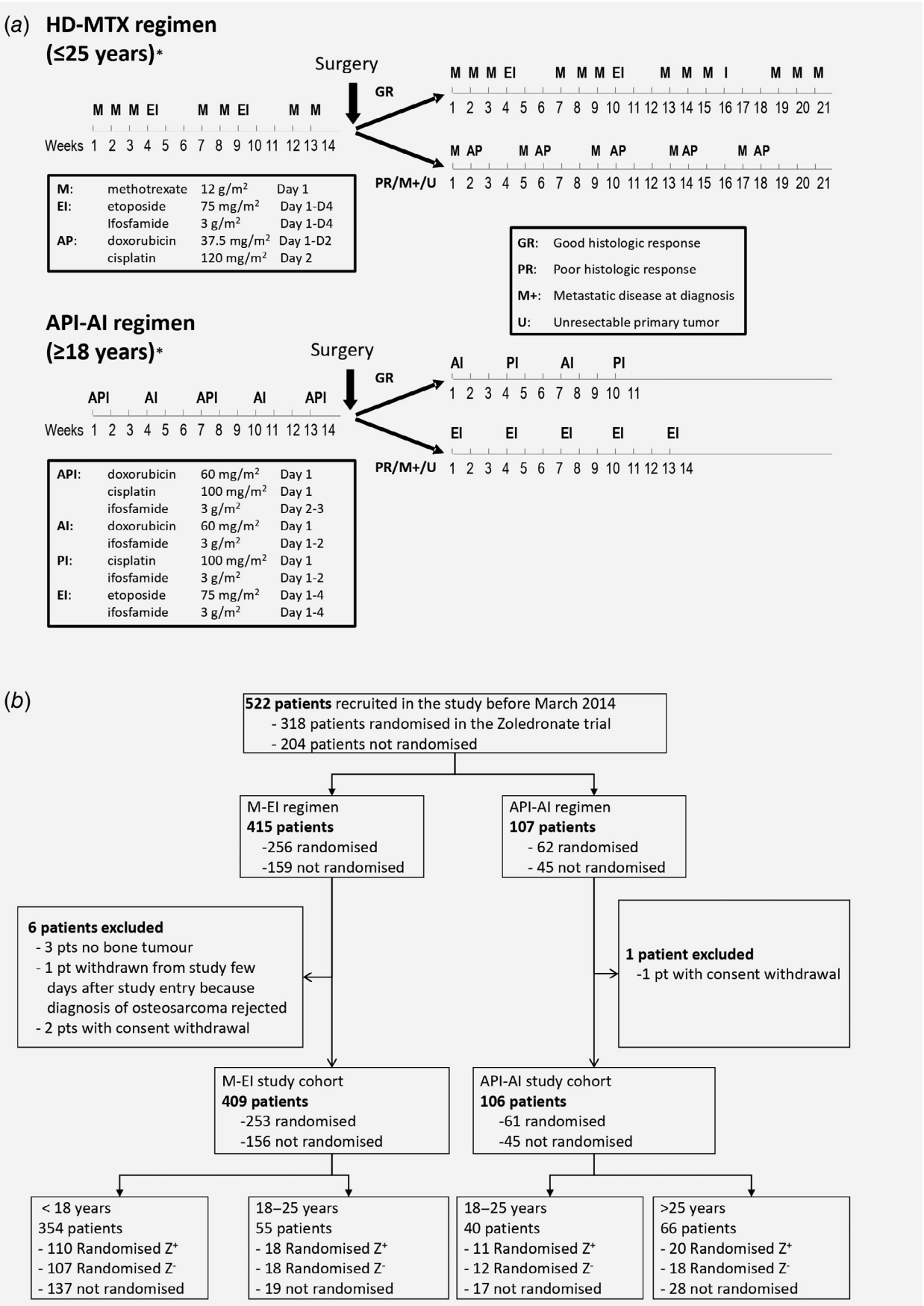

Figure 1. Legend on next page.

age ≤50 years; with normal haematological, renal, cardiac and hepatic functions. Written informed consent was obtained from patients and/or their parents/guardians before enrolment.

Patients younger than 18 years were treated with the methotrexate, etoposide and ifosfamide (M-EI) regimen, patients older than 25 years with the doxorubicin, cisplatin and ifosfamide (API–AI) regimen. Patients aged 18–25 received either HDMTX-EI or API–AI, according to the predetermined centre's choice at the start of the study.

Treatment and follow-up

Preoperative chemotherapy based on API–AI regimen was administered over 13 weeks, and consisted of three courses of API (doxorubicin 60 mg/m^2 with ifosfamide 6 g/m^2 and cisplatin 100 mg/m^2) and two courses of AI (doxorubicin 60 mg/m^2 with ifosfamide 6 g/m^2), every 3 weeks. Patients with a good histological response to preoperative chemotherapy (i.e., <10% viable tumour cells) and with no distant metastases, were classified as standard-risk and received two courses of AI alternating with two courses of PI (cisplatin 100 mg/m^2 and ifosfamide 6 g/m^2). Patients with a poor histological response, initial distant metastases, initial surgery and/or nonresectable primary tumour were classified as high-risk and received five cycles of etoposide and ifosfamide (EI). The planned duration of treatment varied from 31 to 34 weeks according to the postoperative regimen (Fig. 1).

In addition to these chemotherapy regimens, randomised patients assigned to the zoledronate group also received 10 monthly intravenous infusions of zoledronate (four preoperative and six postoperative), at a fixed dose of 4 mg per infusion for patients older than 25 years. In patients aged 18–25 years, the zoledronate dose was 0.05 mg/kg per infusion for the first two courses, then 4 mg per infusion for the remaining eight courses. Patients with operable lung metastases at the time of surgery of the primary tumour also had their lung metastases resected.

During preoperative chemotherapy, the absence of tumour progression was assessed at weeks 7 and 14 with standard X-ray and magnetic resonance imaging (MRI) of the primary tumour, and a chest X-ray (or a thoracic computed tomography [CT]-scan for patients with initial lung nodules). After completion of the postoperative chemotherapy, a chest X-ray was scheduled every 2–3 months for the first 3 years, then every 4 months for the following 2 years, and yearly thereafter. Yearly assessment of the primary site by radiography was recommended. These investigations were completed if necessary by CT-scan, MRI, bone scans and histology.

Endpoints

Event-free survival (EFS) was defined as the time from the start of preoperative chemotherapy until disease progression, relapse, secondary malignancy or death from any cause, or to the last follow-up visit for patients in first complete remission. Progression during preoperative chemotherapy was not considered as progression if complete remission was obtained with surgery. OS was defined as the time from the start of preoperative chemotherapy until death from any cause.

Modifications of preoperative chemotherapy treatment were classified as minor if the patient received at least four API or AI cycles, or equivalent (doxorubicin–cisplatin–cyclophosphamide, doxorubicin–cyclophosphamide), with no other drug; and considered major in all other cases. Postoperative modification was classified as minor if the patient received at least four API or AI cycles, or equivalent (doxorubicin–cisplatin–cyclophosphamide, doxorubicin–cyclophosphamide); all other modifications were classified as major. Dose-intensity during preoperative chemotherapy was computed for patients enrolled in the randomised trial (details in Supporting Information Fig. S1). We used the method published by Wampler and Fryer,[16] multiplying the overall dose strength by the delay factor, where the dose strength represents the fraction of the planned dose and the delay factor is the component resulting from delays in treatment courses. As chemotherapy regimens comprised multiple agents, the overall dose strength was the sum of the dose strength of each protocol drug. A similar weight of 1 was assigned to doxorubicin, ifosfamide and cisplatin.

Adverse events were only evaluated for randomised patients. The evaluation occurred after each chemotherapy course, using a list of 25 selected items and graded by the common terminology criteria for adverse events (CTCAE) version 3.0. A free-text area was available in the case report form to document other adverse events. Acute toxicity was analysed using the maximum grade observed during preoperative and postoperative chemotherapy for each class of toxicity. All Grade 4 haematological toxicities and Grade 3/4 of all extrahaematological toxicities were considered severe.

Statistical analysis

Descriptive statistics were used to describe the population. EFS and OS were evaluated using Kaplan–Meier method. Cox models were used to identify prognostic factors of EFS in univariate and multivariate analyses, first considering baseline characteristics, then including the histological response to preoperative chemotherapy.

Figure 1. (*a*) Backbone OS2006/API–AI chemotherapy scheme according to age group and decision of each participating centre. In addition to the above chemotherapy regimen, patients assigned to the zoledronate group (Z+) received 10 monthly intravenous infusions of zoledronate (four preoperative and six postoperative) at a dose of 4 mg per infusion in patients older than 25 years, 0.05 mg/kg per infusion for the first two courses, then 4 mg per infusion for the remaining eight courses in patients aged 18–25.[15] Patients assigned to the standard group received chemotherapy alone (Z–). (*b*) Flowchart of randomised and nonrandomised patients.

Estimates are provided with 95% confidence intervals (CI). All tests were two-sided, with the analyses performed using SAS 9.4. Data will be made available upon reasonable request.

Results

Population

Between 06/2007 and 02/2014, 107 patients treated with API–AI were enrolled in the OS2006 study (Fig. 1*b*). One patient was excluded from the analysis following withdrawal of consent. The study population thus consisted of 106 patients from 20 centres (2 paediatric and 18 medical oncology centres). Of these, 61 patients participated in the randomised zoledronate trial: 31 patients received zoledronate and 30 did not.

Median age was 30.2 years (range 18.1–67.1), with 66 patients older than 25 years. One patient had a constitutional syndrome predisposing to cancer (fibrous dysplasia), one patient had a family history of cancer and three patients had a personal history of cancer. Patient and tumour characteristics of the population are detailed in Table 1. The primary tumour was mainly located in the limbs (74%), with a median size of 9 cm (range 1–26), and synchronous metastases were present in 28 patients (26%), mostly pulmonary metastases (n = 20).

Treatment

The median time interval between the biopsy and the start of chemotherapy was 28 days (interquartile range [IQR] 18–36).

Preoperative chemotherapy was administered as per protocol in 70 patients (66%). Modifications were minor in 30 patients (28%) and major in six patients (6% including two patients aged 50): due to suspected early progression in one case, toxicity in four patients (infection in one and hematotoxicity in three), and for another reason in one patient. The median dose-intensity of preoperative chemotherapy was 0.84 (IQR 0.74–0.92), with no significant difference observed according to age (≤25 years, 25–40 years and ≥40 years, Supporting Information Fig. S1). The median duration of preoperative chemotherapy was 12.1 weeks (IQR 12–13). The median time interval between the end of preoperative chemotherapy and surgery was 30 days (IQR 24–38).

Nine patients did not have surgery of their primary osteosarcoma: one patient had a confirmed early progression and eight patients with nonresectable tumours received radiotherapy as local treatment. In addition, surgical records were missing in one patient following early consent withdrawal. Overall, 96 patients (91%) underwent surgery of which 82 (85%) had conservative surgery. Margins were reported as radical/wide in 73 evaluable patients (77%). Histological response was evaluable in 95 patients and was classified as a good histological response in 36 patients (38%, 95% CI, 28–48%), corresponding to 34% of the study population (36/106 patients, 95% CI, 25–43%).

Overall, 91 patients started postoperative chemotherapy within a median of 28 days from surgery (IQR 21–35), and the median overall treatment duration was 32.6 weeks (IQR 29.4–37.0). Overall 57/91 patients (62%) received postoperative treatment as per-protocol or with a minor modification (3/27 standard-risk patients, 11%, and 6/64 high-risk patients, 9%). Thirty-four patients had a major modification of postoperative chemotherapy regimen, mainly due to toxicity or progression. Fifteen patients did not receive the planned postoperative chemotherapy, three patients because of refusal of postoperative chemotherapy (consent withdrawal), three because of early progression, five due to toxicity (haematotoxicity in three, renal toxicity and encephalopathy in one each), two due to post-surgery complications and two for unknown reason.

Table 1. Patient characteristics

	n = 106(%)
Gender (female)	33 (31%)
Age at study entry: median (range)	30 (18–67)
18–25 years	40 (38%)
26–39 years	42 (40%)
≥40 years	24 (23%)
Personal medical history or predisposing syndrome[1]	5
Primary tumour site	
Limb	78 (74%)
Axial (trunk /head and neck)	28 (26%)
Primary tumour size (MD = 7)	
<10 cm	56 (57%)
≥10 cm	43 (43%)
Histological subtype (MD = 4)	
Conventional	94 (92%)
Telangiectasic	1 (1%)
Surface high-grade	1 (1%)
Other[2]	6 (6%)
Pathological fracture at diagnostic (MD = 4)	2 (2%)
Initial staging	
Localised	78 (74%)
Metastatic	28 (26%)
Metastatic sites (possibly associated)	
Lung[3]	20 (19%)
Distant bone	2 (2%)
Skip metastases[4]	6 (6%)
Other	8 (8%)

[1]Fibrous dysplasia (n = 1), familial history of colon cancer with no genetic assessment (n = 1), osteosarcoma as a second cancer after basal cell carcinoma (n = 1) or desmoid-type fibromatosis (n = 1) or giant cell tumour of bone (n = 1).
[2]Low-grade periosteal osteosarcoma (n = 2), Giant cells osteosarcoma (n = 1), Other (no more details available; n = 3).
[3]Lung metastases were defined by at least one nodule >1 cm, ≥2 nodules of 5–9 mm or ≥5 nodules.
[4]Skip metastasis was defined as a bone lesion in the same bone as the primary tumour. Transarticular lesions were not counted as skip metastases but as distant bone lesions. Skip metastases were combined with distant metastases in two patients (lung metastases in both patients) whereas four patients presented skip metastases without distant lesion.
Abbreviation: MD, missing data.

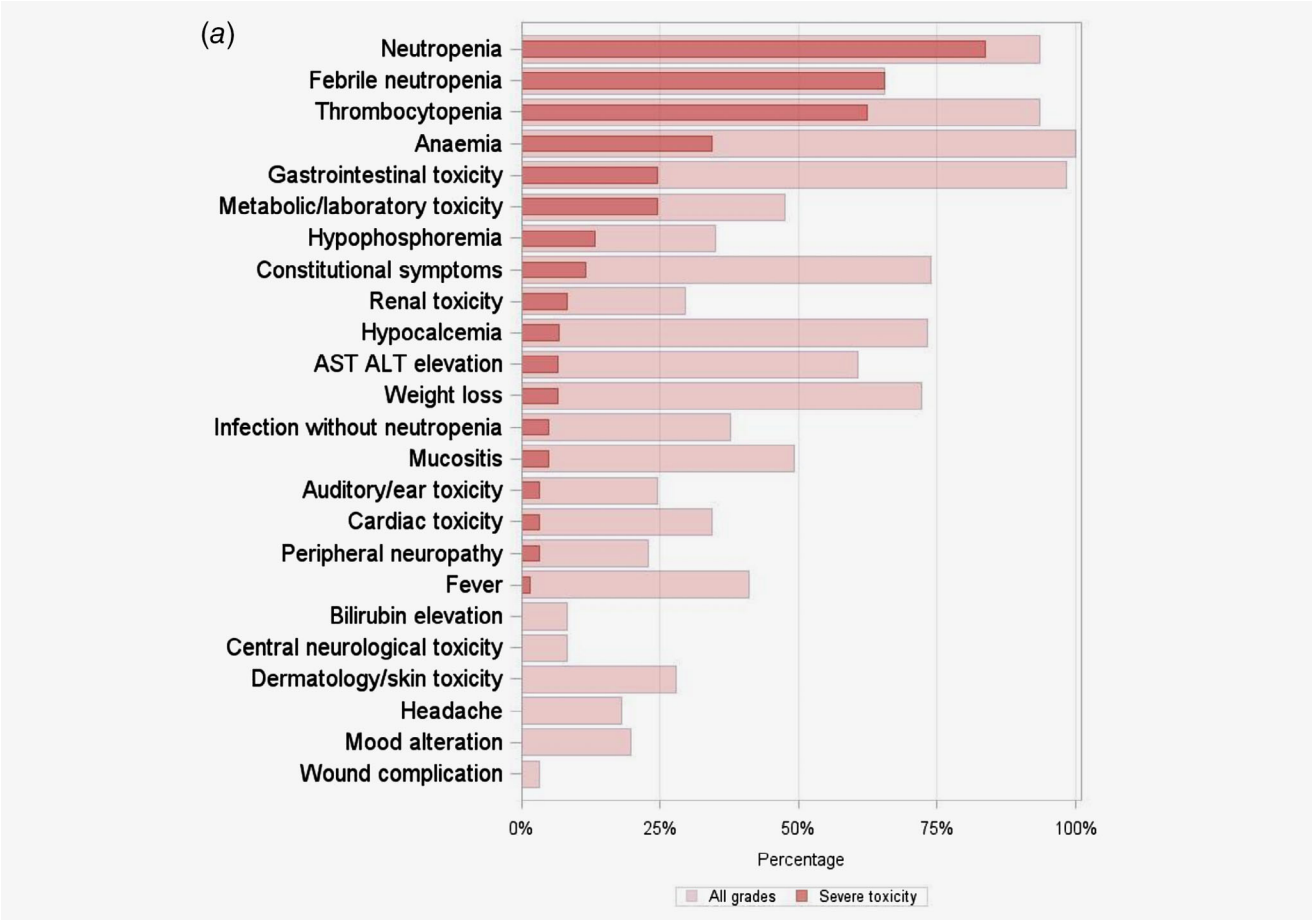

Figure 2. (*a*) The overall proportion of patients who had an adverse event, any grade (light red) and a severe adverse event (dark red) among the 61 patients treated with API–AI regimen of OS2006 and enrolled in the zoledronate randomised trial (per protocol population of the randomised trial). Grade-4 haematological toxicities and grades ≥3 of all extrahaematological toxicities were considered as severe toxicities. The adverse event types are ordered by decreasing value of the proportion of patients experiencing a severe adverse event. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase. (*b*) The proportion of patients who had an adverse event, any grade (light blue patient aged ›25 years and light red for younger patients) and a severe adverse event (dark blue for patients ›25 years and dark red for younger patients) according to the age group. Relative Risks with 95% CIs of severe adverse event, in older patients compared to younger patients. The adverse event types are ordered by decreasing value of the relative risk. The relative risks were not computed for the nine last categories (auditory/ear toxicity, bilirubin elevation, central neurological toxicity, dermatology/skin toxicity, fever, headache, mood alteration, weight loss, and wound complication) as there was no severe toxicity reported in one class of age or both. Details of grades are given in Supporting Information Table S1. [Color figure can be viewed at wileyonlinelibrary.com]

Safety

All 61 adults included in the randomised part of the study were evaluable for safety, whereas the 45 nonrandomised adult patients registered in the database were managed according to national recommendations, without the same required level of completion regarding toxicities of chemotherapy. Figure 2 presents adverse events in the 61 randomised patients: most of them experienced at least one episode of severe acute toxicity (Fig. 2*a*), with neutropenia in 84%, febrile neutropenia in 66% and thrombocytopenia in 62%. A severe renal toxicity was reported in five patients (8%), with three Grade 3 and two Grade 4. Severe acute hearing impairment and peripheral neuropathy were rare events: each type of toxicity was reported in two patients. No severe central neurotoxicity was reported. A mild to moderate cardiac toxicity was reported in 19 patients, two patients experienced a transient and reversible episode of Grade 3 cardiotoxicity. No patient died from any adverse event. We observed no significant difference in incidence of severe acute toxicity between patients aged >25 years and younger patients (Fig. 2*b* and Supporting Information Table S1).

Outcome

Outcomes were recorded for all 106 patients in the dedicated database, whatever their participation in the randomised study. At cut-off date, with a median follow-up of 4.8 years (range 0.2–8.1), 54 events were reported: 53 progressions/relapses (4 local, 41 distant metastases and 8 combined) and 1 second

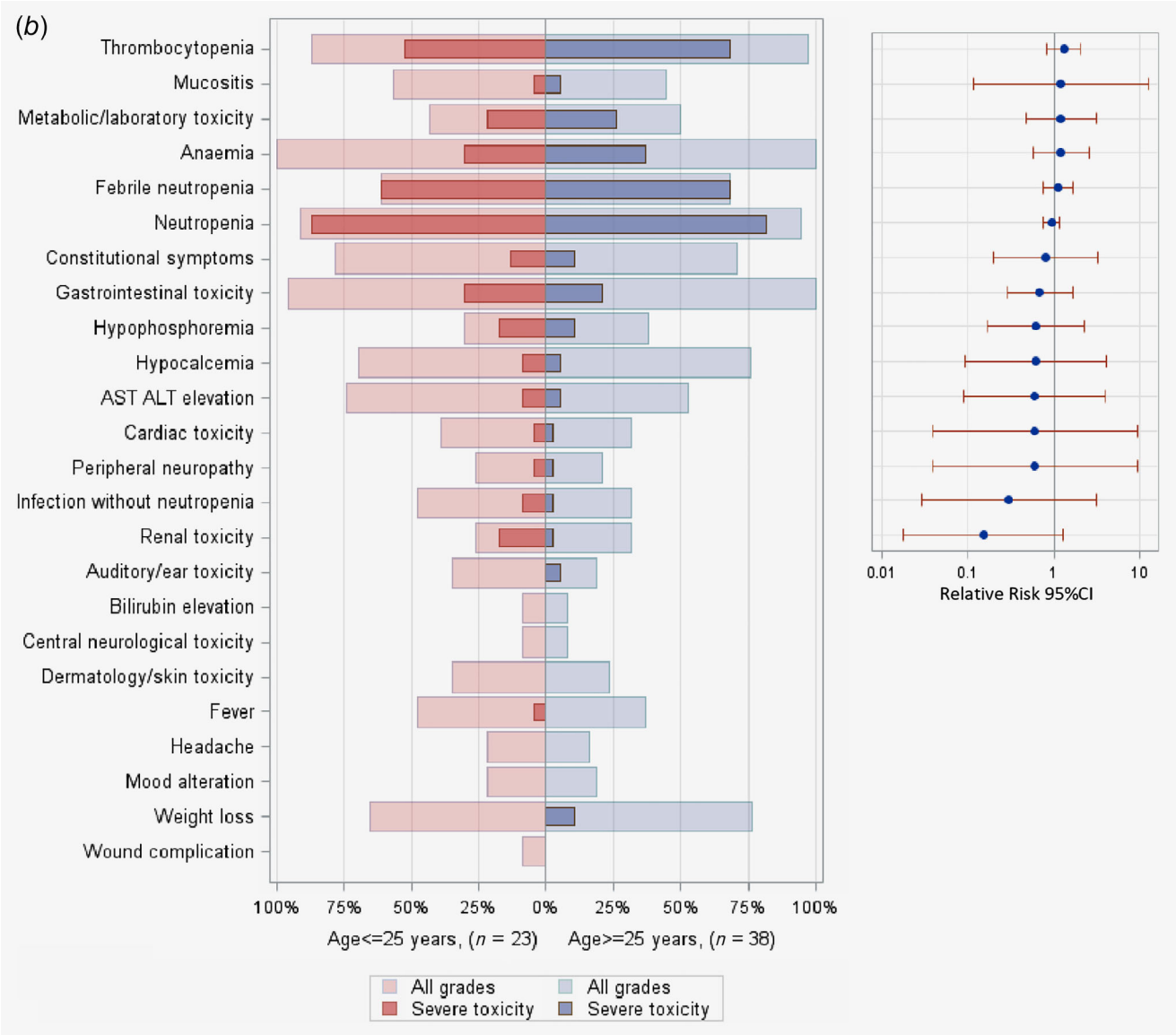

Figure 2. Continued [Color figure can be viewed at wileyonlinelibrary.com]

malignancy as first event (gastric adenocarcinoma 4 years after the diagnosis of osteosarcoma in a 48-year old patient with prior skin basal cell carcinoma). The 3- and 5-year EFS were 52% (95% CI 42–61) and 46% (95% CI 36–56), respectively (Fig. 3*a*). Excluding a patient with a suspected early progression with complete remission obtained by surgery, a progression on treatment was reported in eight patients: during preoperative chemotherapy in one patient (local and metastatic progression) and afterwards in seven patients (four metastatic, and three local and metastatic progressions).

A total of 40 deaths from osteosarcoma were reported. The 3- and 5-year OS were 66% (95% CI 56–75) and 57% (95% CI 47–67), respectively (Fig. 3*a*).

Considering the 61 patients randomised to receive zoledronate or not, the 5-year EFS and 5-year OS rates were not significantly different between patients treated with or without zoledronate, and from the 45 nonrandomised patients (Supporting Information Table S2).

Prognostic analyses

In the univariate analysis of baseline characteristics, gender, age and primary tumour site were not significantly associated with EFS (Table 2). Primary tumour size (≥10 cm *vs.*<10 cm, Fig. 3*b*) and initial staging (metastatic *vs.* localised disease, Fig. 3*c*) were significantly associated with outcome (EFS) in multivariate analysis: HR = 2.53 (95% CI: 1.43–4.49) and HR = 3.26 (95% CI: 1.8–5.91), respectively. These parameters remained significant in multivariate analysis including the histological response in the 95 operated patients. Poor histological response was not associated with more events, neither in

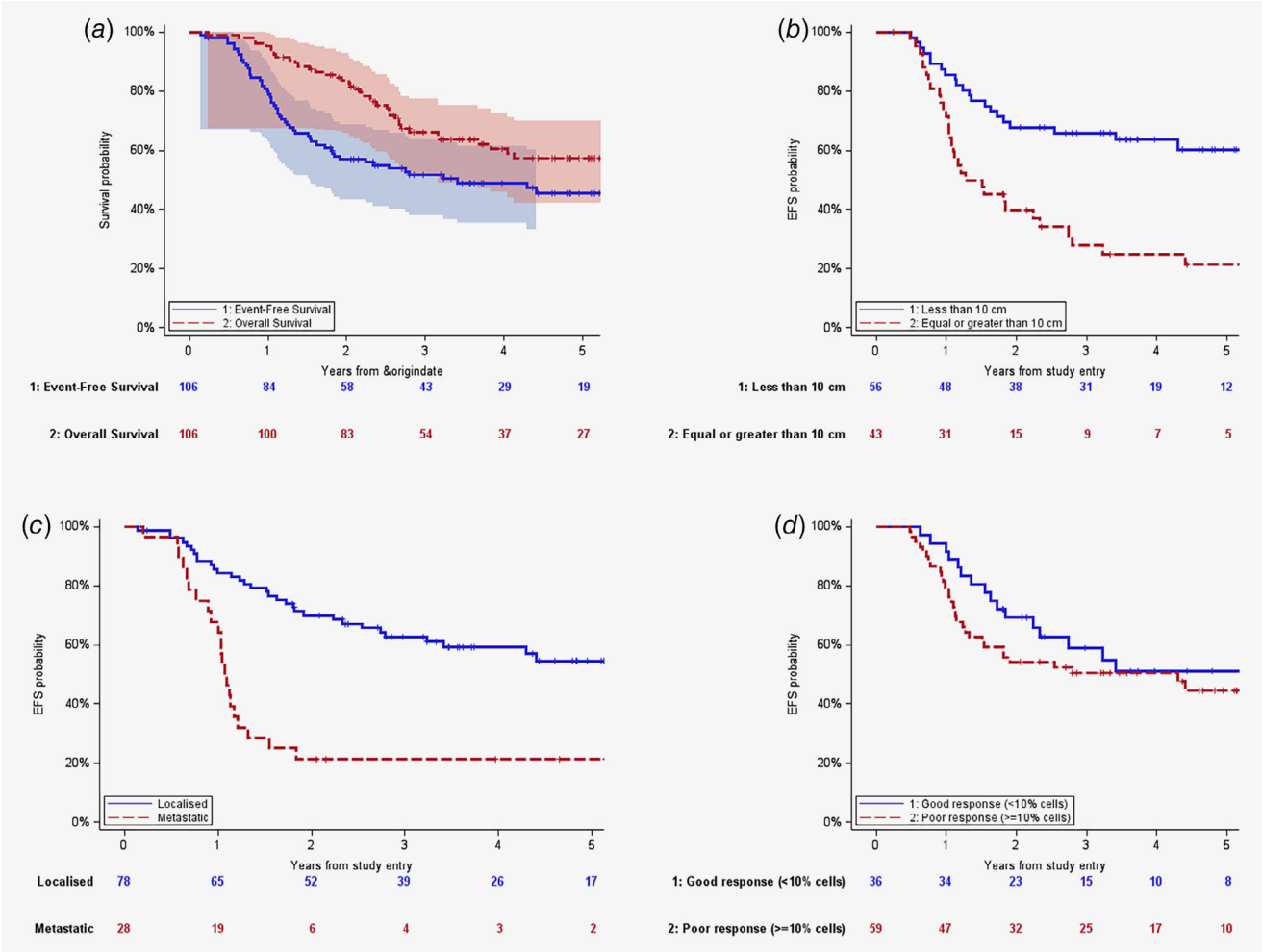

Figure 3. (*a*) Kaplan–Meier estimate of event-free and overall survival of the 106 patients. The shadowed bands represent the 95% Hall–Wellner confidence bands. (*b*) Kaplan–Meier estimate of event-free survival according to tumour size, in the 99 patients with information available: less than 10 cm ($n = 56$) *vs*. equal or greater than 10 cm ($n = 43$). (*c*) Kaplan–Meier estimate of event-free survival according to the initial staging, in the 106 patients: metastatic disease ($n = 28$) *vs*. localised disease ($n = 78$). (*d*) Kaplan–Meier estimate of event-free survival according to the histological response, in the 95 patients who underwent surgery after neo-adjuvant chemotherapy: good histological response (<10% viable cells, $n = 36$) *vs*. poor histological response (≥10% viable cells, $n = 59$). [Color figure can be viewed at wileyonlinelibrary.com]

univariate analysis (Fig. 3*d*) nor in multivariate analysis, after controlling for prognostic factors at diagnosis (Table 3). Patients with metastatic disease had a very poor outcome, with 5-year EFS of 21.4% (95% CI 10.2–39.5) and 5-year OS of 14.5% (95% CI 4.6–37.7).

Discussion

This population of 106 adult osteosarcoma patients were treated in France over a period of almost 7 years (2007–2014). Compared to the randomised OS2006 trial cohort,[15] there were more males (69% *vs*. 57%), primary tumours were more often axial (26% *vs*. 8%), and synchronous metastases were more present at diagnosis (26% *vs*. 17%).

In patients who had preoperative and postoperative chemotherapy with the API–AI regimen of OS2006 protocol, the toxicity was manageable with no toxic death. However, a longer follow-up is needed to assess the long-term toxicity. The toxicities observed were mainly haematological with no significant difference in acute toxicities observed between patients younger than 25 years and those older than 25 years. Major modifications of the preoperative chemotherapy were less frequent (6%) than in patients treated with the MTX-based regimen (15%), from which five patients died from adverse events.[17]

The median dose-intensity in the preoperative setting was 84%, whereas it reached 90 and 89% in the two API–AI French phase II studies,[13,14] and ranged from 78% to 94% in older trials testing non-MTX-based chemotherapy regimens.[12,18,19]

The median treatment duration from the start of preoperative chemotherapy was 31 weeks (IQR 28–37) in the API–AI protocol, and 37.4 weeks (IQR 34.7–39.9) for patients treated with the MTX-based regimen.[17] This was expected since the

Table 2. Prognostic analyses of EFS

			Univariate analysis		Multivariate analysis of baseline characteristics		Multivariate analysis including histological response and initial staging	
	No. of events/ No. of patients	5-year EFS (95% CI)	HR (95% CI)	*p*-value (Wald)	HR (95% CI)	*p*-value (Wald)	HR (95% CI)	*p*-value (Wald)
Gender				0.11		0.73		
Female	14/33	51% (32; 69)	1		1		–	
Male	40/73	44% (33; 55)	1.64 (0.89–3.02)		1.12 (0.6–2.08)		–	
Age at study entry				0.60				
18–25 years	21/40	45% (30; 61)	1		–		–	
26–39 years	19/42	53% (37; 67)	0.87 (0.47–1.62)		–		–	
≥40 years	14/24	37% (20; 59)	1.24 (0.63–2.45)		–		–	
Primary tumour site				0.90				
Limb primary	40/78	44% (33; 57)	1		–		–	
Axial primary	14/28	49% (31; 67)	1.04 (0.57–1.91)		–		–	
Primary tumour size (MD = 7)				0.0003		0.001		0.0004
Less than 10 cm	21/56	60% (46; 73)	1		1		1	
Equal or greater than 10 cm	31/43	21% (11; 37)	2.83 (1.62–4.96)		2.53 (1.43–4.49)		3.0 (1.64–5.51)	
Initial staging				<0.0001		<0.0001		0.0001
Localised	32/78	55% (43; 66)	1		1		1	
Metastatic	22/28	21% (10; 40)	3.44 (1.97–6.0)		3.26 (1.8–5.91)		3.46 (1.83–6.54)	
Histological response (MD = 11)[1]				0.33				0.17
Good response (<10% cells)	16/36	51% (34; 68)	1		–		1	
Poor response (≥10% cells)	31/59	44% (31; 58)	1.35 (0.74–2.47)		–		1.55 (0.83–2.88)	

[1]Histological response was evaluable in 95 patients who underwent surgery after preoperative chemotherapy; it was not evaluated in 10 patients who did not undergo surgery as part of first-line treatment and in one patient who had initial surgery at diagnosis.

Table 3. Impact of initial staging (a) and histological response (b) on EFS and OS, in the 95 patients who underwent surgery after neoadjuvant chemotherapy

	Event-free survival analysis				Overall survival analysis			
	No. of events/ No. of patients	5-year EFS (95% CI)	HR (95% CI)	*p*-value (Wald)	No. of deaths/ No. of patients	5-year OS (95% CI)	HR (95% CI)	*p*-value (Wald)
(a) Initial staging								
Risk group (MD = 7)				<0.0001				<0.0001
Localised and <10 cm	16/47	63% (48; 76)	1		12/47	72% (55; 84)	1	
Localised and ≥10 cm	15/26	34% (18; 55)	2.06 (1.02–4.18)		7/26	67% (45; 83)	1.21 (0.48–3.07)	
Metastatic	21/26	19% (9; 38)	4.88 (2.50–9.53)		19/26	14% (4; 37)	5.67 (2.69–11.96)	
(b) Histological response								
Risk group (MD = 11)				0.0004				<0.0001
Localised disease and good histological response	8/26	64% (43–81)	1		3/26	90% (70; 97)	1	
Localised disease and poor histological response	21/45	49% (33–65)	1.85 (0.82–4.17)		14/45	62% (45; 76)	3.27 (0.93–11.42)	
Metastatic	18/24	25% (12–45)	4.83 (2.08–11.23)		16/24	21% (8; 44)	11.63 (3.31–40.91)	

postoperative schedule with the MTX-based regimen was longer for both good and poor responders. A shorter duration of treatment may be associated with better compliance, notably in the adolescent and young adult population.[20]

Only 9/106 patients did not undergo surgery. For eight patients, the primary tumour was deemed not resectable. The surgery was conservative with adequate margins (radical or wide) in the majority of patients, taking into account the high proportion of axial tumours (26%), as compared to the 8% in the randomised trial,[15] and 6% in the MTX-based population.[17]

Median time interval between the biopsy and the start of preoperative chemotherapy, between end of preoperative chemotherapy and surgery and between surgery and the start of postoperative chemotherapy are quite longer for adult patients (28, 30 and 28 days, respectively), compared to paediatric patients (14, 14 and 16 days),[17] and adolescent and young adult patients (23, 23 and 23 days).[20] These differences may reflect differences in practices between paediatric and medical oncology centres, but also factors associated with age: delayed diagnosis, treatment compliance, incidence and severity of toxicities and differences in host and tumour biology.[21]

A good histological response was noted in 36/95 evaluable patients (38%), consistent with the 47% and 37% rate of good responders in the API–AI phase II trials,[13,14] and in line (29–50%) with prior osteosarcoma trials testing alternative regimen to MTX.[12,18,19] With a median follow-up of 4.8 years, the 5-year EFS rate was 46% and the 5-year OS rate was 57% in the 106 patients analysed. These results are in the lower range of those reported in the literature in patients treated without MTX, with 5-year EFS rates from 39% to 57% and 5-year OS rates from 55% to 64%.[12,18,19] However, the population enrolled in these previous non-MTX-based large EOI studies presented two noteworthy differences: age was limited to 40 years and all patients had a nonmetastatic and resectable disease of the extremities. On the contrary, patients with metastatic disease at diagnosis and/or aged up to 50 were eligible in our study, known to have a poorer prognosis.[6]

In this small series of patients, the size of the primary and the presence of metastases at diagnosis were correlated with EFS in univariate and multivariate analyses. In the 95 operated patients following preoperative chemotherapy, patients can be divided into three risk groups regarding the initial staging and the histological response to chemotherapy. As in the MTX population,[17] patients with metastases and/or poor histological response display a poor prognosis that may reflect inherent resistance to chemotherapy. However, the lack of histological response to chemotherapy alone may no longer explain the poor long-term outcome of these patients: biological and immune approaches are needed to better understand the mechanisms of chemoresistance in order to find the best way to improve outcomes in these patients. The ancillary studies from the OS 2006 trial are ongoing: tumour and blood samples are studying the role of genomics, transcriptomics, pharmacogenomics, tumour microenvironment and immunology in this patient population.

Since the OS2006 study enrolled patients aged from 5 to 50 years, close collaboration between French paediatricians and medical oncologists was essential. This collaboration was reinforced by the national sarcoma network ResOs/NetSarc funded by the French National Cancer Institute. The generation of a network of experts in reference centres is optimising the management of sarcoma patients and improves the outcome, as was recently demonstrated for soft tissue sarcoma patients.[22]

When we designed the OS2006 trial, a risk-adapted postoperative chemotherapy strategy had not demonstrated any survival benefit in osteosarcoma patients. Despite this, we designed the OS2006 trial to expose high-risk patients to all cytotoxic agents considered as effective, adjusted to age category.[23,24]

In the EURO-B.O.S.S. study on chemotherapy in bone-sarcoma patients aged over 40, the 5-year OS was 66% in osteosarcoma patients with localised disease (29% for pelvic tumours and 70% for extremities), and 22% in patients with synchronous metastases.[25] Only 21% of patients were good responders after induction chemotherapy. Toxicity was higher in older patients, with around 25% of patients with renal or neurotoxicity, and delayed MTX elimination in 23%.

The API–AI regimen avoids MTX toxicity in adult patients with osteosarcoma; this attitude corresponds to the ESMO guidelines that recommend that osteosarcoma patients may require tailored regimens.[26] The present study adds one piece to the puzzle toward obtaining the optimal chemotherapy regimen for adults with osteosarcoma.[27] However, the limited number of patients precludes any definitive conclusion on the impact of chemotherapy regimen on the outcome and long term morbidity.

In this series of 106 adult patients with osteosarcoma, API–AI proved feasible with no excess of toxicity, and favourable activity despite poor-prognosis factors. The biological and immunological studies based on tumour and blood samples from patients aged from 5 to 50 years will hopefully allow us to develop tailored strategies in this rare cancer.

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