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ORIGINAL ARTICLE

Comparison of carboplatin plus etoposide with amrubicin monotherapy for extensive-disease small cell lung cancer in the elderly and patients with poor performance status

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Keywords
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Abstract

Background: Carboplatin plus etoposide (CE) is a standard treatment for elderly patients with extensive-disease small cell lung cancer (ED-SCLC). However, amrubicin monotherapy (AMR) may be a feasible alternative. We compared the efficacies and safety profiles of CE and AMR for ED-SCLC in elderly patients and chemotherapy-naive patients with poor performance status (PS).

Methods: The records of SCLC patients who received CE or AMR as first-line chemotherapy were retrospectively reviewed and their treatment outcomes evaluated.

Results: Eighty-four patients (median age 72 years; 42 each received CR and AMR) were analyzed; 34 patients had a PS score of 2. There were no significant differences in patient characteristics between the treatment groups. The median progression-free survival rates of patients in the CE and AMR groups were 5.8 and 4.8 months, respectively ($P = 0.04$); overall survival was 14.0 and 8.5 months, respectively ($P = 0.089$). Twenty-three CE group patients received AMR as second-line chemotherapy; their median overall survival from first-line chemotherapy was 18.5 months. Grade 3 or higher neutropenia occurred more frequently in patients treated with AMR (64% vs. 40%; $P = 0.02$), as did febrile neutropenia (14% vs. 7%).

Conclusions: CE remains a suitable first-line treatment for ED-SCLC in elderly patients or those with poor PS in comparison with AMR.

Introduction

Despite being one of the most chemo-sensitive solid tumor types, small-cell lung cancer (SCLC) has an extremely poor prognosis.[1] Most patients relapse because of the emergence of drug-resistant tumor cells even after remarkably successful induction therapy.[2–4] Approximately half of all SCLC patients in Japan are aged > 70 years,[5] and the Japan Lung Cancer Society recommends carboplatin plus etoposide (CE) as a treatment for elderly patients with SCLC.[6] Previous clinical trials have indicated that combination chemotherapy consisting of reduced or split doses of cisplatin plus etoposide (SPE) can be safe and effective for SCLC in elderly patients or patients with poor performance status (PS).[7,8] Subsequently, the Japan Clinical Oncology Group reported the results of a phase III trial that showed that the SPE regimen could be an alternative to standard CE for the treatment of extensive-disease (ED)-SCLC in elderly patients and those with poor PS.[9] Thus, CE and SPE regimens are administered as standard therapies for elderly Japanese patients with ED-SCLC.

Amrubicin hydrochloride is a fully synthetic 9-amino-anthracycline that is converted to its active metabolite

amrubicinol in the liver. Amrubicin inhibits DNA topoisomerase II and exerts a cytotoxic effect by stabilizing a topoisomerase-II-mediated cleavable complex. Its potency as a DNA intercalator is approximately one-tenth that of doxorubicin.[10,11] The catatonic activity of amrubicinol in vitro is 18–220-fold more potent than that of its parent compound.[12] The anti-tumor activity of amrubicin against several human tumor xenografts implanted in nude mice is more potent than that of the representative anthracycline doxorubicin, with almost no cardiotoxicity.[13,14] One study showed amrubicin to be active against chemo-naïve SCLC;[15] the patients had a response rate of 79% and a median survival duration of 11 months. These results support examining amrubicin monotherapy (AMR) as a viable SCLC treatment. Our previous retrospective study showed that amrubicin produced a response rate of 70%, progression-free survival (PFS) of 6.6 months, and a median survival duration of 9.3 months for ED-SCLC in elderly patients or those with poor PS.[16]

However, the efficacy of AMR in patients with SCLC has not been sufficiently compared to CE. Therefore, the aim of this study was to retrospectively evaluate the efficacy and safety of CE and AMR for ED-SCLC in elderly patients or those with poor PS.

Methods

Patient selection and data collection

The eligibility criteria for this retrospective study were: histologically or cytologically proven SCLC; stage IV disease (as defined by the Union for International Cancer Control 7th edition Tumor Node Metastasis classification); age ≥ 70 years or Eastern Cooperative Oncology Group PS ≥ 2; received CE combination therapy or AMR as first-line treatment at Kitasato University Hospital between March 2010 and December 2016; and measurable target lesions on imaging examination by chest radiography, computed tomography (CT) of the chest and abdomen, or by other procedures such as magnetic resonance imaging (MRI) of the head, positron emission tomography (PET), or combined PET/CT imaging. Patients aged < 70 years or with a PS of 2 were excluded as single-dose administration of cisplatin was not considered feasible in this subset. The institutional ethics review board of the Kitasato University Hospital approved this study. Informed consent was not required because of the retrospective nature of the study.

Treatment

In clinical practice, the treatment regimen for ED-SCLC (CE or AMR) was selected at the discretion of the attending physician. Carboplatin was intravenously administered on day 1 at a dose calculated using the Calvert formula in which the target area under the curve (AUC) was 5 mg/min/mL. The patients' glomerular filtration rates (required for the Calvert formula) were derived from the serum creatinine level using the Cockcroft-Gault method. Etoposide was administered intravenously at 80 mg/m^2 on days 1–3 every three weeks. Amrubicin dissolved in 20 mL normal saline was administered once intravenously as a 5 minute infusion on days 1–3 every three weeks. The amrubicin dose was 40 mg/m^2/day. The treatment regimen was repeated for four to six cycles at the attending oncologists' discretion (i.e. after 4 cycles, the oncologist decided whether a fifth and sixth cycle was appropriate) and continued until disease progression, unacceptable adverse events, or the patient's request.

Response evaluation

Lesions were evaluated using plain chest radiography, CT of the chest and abdomen, PET or bone scintigraphy, and CT or MRI of the cranium. To evaluate the tumors, CT imaging of the chest and abdomen was performed at least every two cycles. PET or bone scintigraphy, as well as CT or MRI of the cranium, were performed at six month intervals or earlier if patients exhibited significant tumor-associated symptoms. Tumor control was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. The best overall response and maximum tumor control were recorded as the tumor response.

Toxicity assessment and treatment modification

Toxicity was graded according to Common Terminology Criteria for Adverse Events, version 4.0. At our institution, the criteria for dose reduction (common to both regimens) were grade 4 neutropenia lasting ≥ 4 days, febrile neutropenia, and grade 4 thrombocytopenia. If any of these events occurred, the amrubicin dose was reduced by 5 mg/m^2/day while carboplatin and etoposide doses were reduced to a target AUC of 4 mg/min/mL and 60 mg/m^2/day, respectively, in subsequent cycles. Patients received supportive care as required. The treatment protocol specified that 50 μg/m^2/day or 2 μg/kg/day recombinant human granulocyte colony-stimulating factor (G-CSF) should be used in accordance with national health insurance coverage in Japan. Indications for G-CSF administration were as follows: (i) fever (in principle, body temperature > 37.5°C) with a neutrophil count of ≤ 1000/mm^3; (ii) a neutrophil count of 500/mm^3; and (iii) fever with a neutrophil count of ≤ 1000/mm^3 or a neutrophil count of 500/mm^3 during the previous course followed by a neutrophil count of ≤ 1000/mm^3 after completing the same chemotherapy.

Table 1 Differences in patient characteristics according to type of chemotherapy

Patient characteristics	Carboplatin/ etoposide (*n* = 42)	Amrubicin monotherapy (*n* = 42)	*P*
Gender			
Male/Female	39/3	32/10	0.03
Age (years)			
Median (range)	72 (42–82)	71 (50–91)	0.84
Smoking history			
Current/former	21/21	21/21	1.0
ECOG PS score			
0–1/2 (all patients)	28/14	22/20	0.18
0–1/2 (over 70 years)	17/9	19/6	0.41
LDH (U/L)			
Median (range)	254 (158–1903)	257 (131–870)	0.39
Na (mmol/L)			
Median (range)	138 (115–143)	138 (106–145)	0.20
Cr (mg/dL)			
Median (range)	0.81 (0.52–1.48)	0.71 (0.43–2.86)	0.23
GFR (Cockcroft-Gault)			
Median (range)	70.9 (36.7–121.2)	80.1 (17.9–116)	0.39
Stage			
IVa/IVb	9/33	9/33	1.0
Brain metastasis			
Yes/No	4/38	5/37	0.72
Number of metastatic lesions			
Median (range)	1 (0–6)	1 (0–5)	0.79
Number of cycles			
Median (range)	4 (1–6)	4 (1–6)	

ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; LDH, lactate dehydrogenase.

Statistical analyses

Patient characteristics and response rates following first-line therapy were compared using chi-square, Fisher's exact, and Mann–Whitney *U* tests. PFS was defined as the interval between the date of initiation of first-line chemotherapy to that of disease progression or patient death. Overall survival (OS) was defined as the interval between the date of initiating first-line chemotherapy to that of patient death or the last follow-up. Survival curves were plotted using the Kaplan–Meier method. Differences in PFS and OS according to the type of first-line therapy were analyzed using the log-rank test. Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). *P* values < 0.05 were considered significant.

Table 2 Clinical response to chemotherapy

Response	Total (*n* = 84)	Carboplatin/ etoposide (*n* = 42)	Amrubicin monotherapy (*n* = 42)	*P*†
Complete response	1	1	0	
Partial response	54	27	27	
Stable disease	16	9	7	
Progressive disease	12	5	7	
Not evaluable	1	0	1	
Response rate, %	65.4	66.7	64.3	0.82
95% CI	55.5–75.9	52.4–81.0	49.8–78.8	

†Chi-square test. CI, confidence interval.

Results

Patient characteristics

Eighty-four patients who were treated between March 2010 and December 2016 were identified in this retrospective cohort study; all were included in the efficacy and safety analyses. The patients' demographic data are shown in Table 1. Forty-two patients were enrolled in each of the CE and AMR groups; there were significantly more men than women in the CE than the AMR group, but otherwise there were no significant differences in patient characteristics between the groups. Nine and six elderly patients with poor PS were included in CE and AMR groups, respectively. Five patients with interstitial lung disease and three patients with cardiovascular complication, including arrhythmia and ischemic heart disease, were treated with CE. Only four patients (2 in each group) had received palliative radiotherapy (whole-brain irradiation for brain metastases) before treatment.

Response

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 1, 54, 16, and 12 patients, respectively. The tumor response was not evaluable in one patient because of early termination of the treatment protocol after he refused treatment beyond the first cycle of AMR. The overall response rate was 65.4% (95% confidence interval [CI] 55.5–75.9%) (Table 2). In the CE group, CR and PR were observed in 1 and 27 patients, respectively, representing a 66.7% response rate (95% CI 52.4–81.0). In the AMR group, 27 achieved a PR, representing a 64.3% response rate (95% CI 49.8–78.8%) (Table 3). There was no significant difference in the response rates between the groups ($P = 0.82$).

Survival

The median follow-up duration was 10.2 months. The median PFS and OS rates for all patients were 5.4 (95% CI 4.4–6.4) and 10.5 (95% CI 7.6–13.4) months, respectively. The median PFS rates of the CE and AMR groups were 5.8 (95.0% CI 4.9–6.7) and 4.8 (95.0% CI: 4.1–5.5) months, respectively; the difference was significant ($P = 0.04$) (Fig 1a). The corresponding median OS rates were 14.0 (9.1–18.9) and 8.5 (5.4–11.6) months, respectively ($P = 0.089$) (Fig 1b). In

Table 3 Second and third-line chemotherapy after disease progression

Chemotherapy regimen	Carboplatin plus etoposide (*n* = 40)	Amrubicin (*n* = 42)
Second-line therapy	26 (65%)	25 (60%)
Amrubicin	23	2
Carboplatin + etoposide	2	17
Carboplatin + irinotecan	—	1
Cisplatin + irinotecan	—	3
Irinotecan	—	2
Carboplatin + paclitaxel	1	—
Third-line therapy	9 (23%)‡	12 (29%)

†Two patients continued first-line therapy. ‡Four patients continued second-line therapy.

addition, in elderly patients with poor PS, PFS rates were 3.1 and 3 months in the CE and AMR groups, respectively. Refractory relapse was observed in 19 patients (47%) in the CE and 27 patients (64%) in the AMR group after first-line chemotherapy, showing a higher tendency for refractory relapse after AMR than CE treatment ($P = 0.09$).

Second-line chemotherapy was administered to 65% of patients in the CE and 60% in the AMR group; the types of regimens were substantially different between the groups (Table 3). The proportions of patients who received third-line chemotherapy were 23% in the CE and 29% in the AMR group. Post-progression survival duration was 6.2 (95% CI 3.1–9.3) in the CE and 3.8 (95% CI, 1.6–6.0) months in the AMR group ($P = 0.26$). Twenty-three CE group patients received AMR as second-line chemotherapy and achieved median OS of 18.5 (95% CI 11.7–25.3) months (Fig 2).

Toxicity

The patients' toxicity profiles are summarized in Table 4. The most common adverse events were hematological toxicities, such as neutropenia and leukopenia. Grade 3 or higher neutropenia occurred in 40% of patients in the CE compared to 64% in the AMR group ($P = 0.02$). Febrile neutropenia occurred in 14% of patients in the AMR and 7% in the CE group. The total number of cycles was 149 in the CE and 153 in the AMR group. The median number of chemotherapy cycles per patient was four (range 1–6) in both groups. Dose reduction to a target AUC of 4 mg/min/mL of carboplatin and 60 mg/m^2/day of etoposide was required in six patients (14%) in the CE group because of grade 4 neutropenia lasting ≥ 4 days in four patients and febrile neutropenia in two; however, none of the patients required a subsequent dose reduction. Dose reduction to 35 mg/m^2/day was required in eight patients (19%)

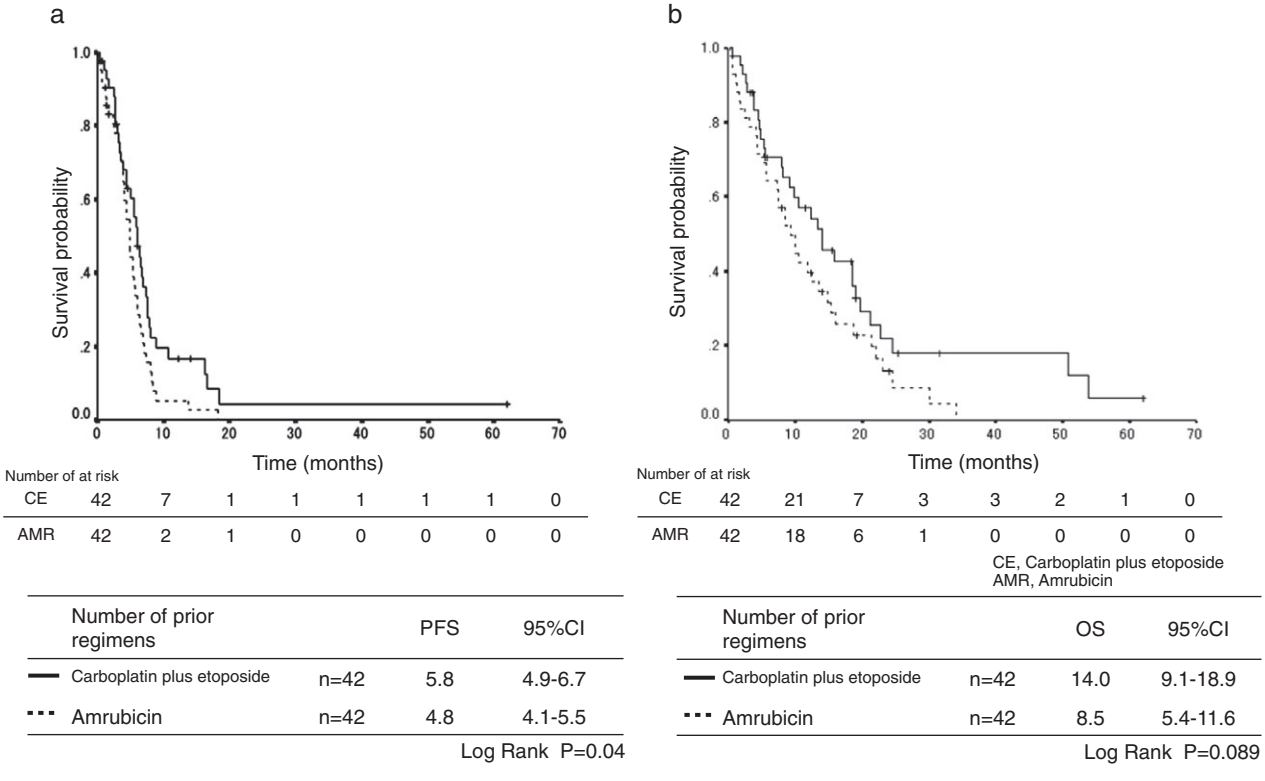

Figure 1 Kaplan–Meier plots of survival. (**a**) Progression-free survival (PFS) and (**b**) overall survival (OS) according to treatment regimen. AMR, amrubicin; CE, carboplatin + etoposide; CI, confidence interval.

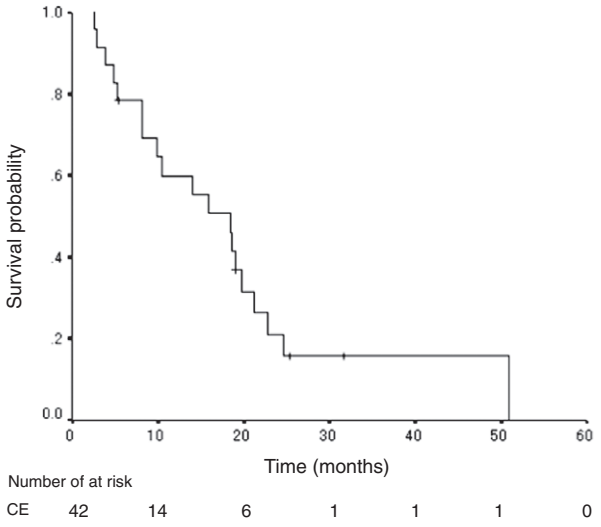

Figure 2 Overall survival of carboplatin + etoposide group patients who received amrubicin as second-line chemotherapy.

in the AMR group because of grade 4 neutropenia lasting ≥ 4 days in five patients and febrile neutropenia in six (3 patients experienced both adverse effects); two patients required a subsequent dose reduction to 30 mg/m^2/day because of grade 4 neutropenia lasting ≥ 4 days. Reasons for protocol discontinuation included PD (n = 81), severe toxicity (n = 2 in the AMR group), and patient refusal (n = 1 in the CE group). While one patient in the AMR group experienced grade 3 pneumonitis, non-hematological toxic effects were relatively mild, and no treatment-related deaths occurred in either group.

Discussion

Patients administered CE achieved significantly longer PFS than those administered AMR. Moreover, OS tended to be longer in the CE than in the AMR group, although this result was not significant. Notably, patients in the CE achieved better PFS and OS than those in the AMR group, even though patients with comorbidities such as interstitial lung disease, arrhythmia, and ischemic heart disease were all included in the CE group. On the other hand, PFS was relatively short in extremely fragile elderly patients with poor PS (3.1 and 3 months in the CE and AMR groups, respectively), indicating that a satisfactory benefit cannot be expected regardless of the type of first-line chemotherapy in these extremely fragile patients. The response rates after CE and AMR treatment were equivalent, and were consistent with data from recent phase II and III studies.[8,9,17,18] However, the rate of refractory relapse tended to be higher in the AMR than the CE group, indicating that the anti-cancer effect might be better sustained by CE treatment despite the equivalent response rates.

The Japanese Pharmaceuticals and Medical Devices Agency approved the use of AMR for SCLC in December 2002 as a first-line chemotherapy option for patients with ED-SCLC. In a phase III trial of patients with SCLC, amrubicin significantly improved the response rate compared to topotecan and improved survival, especially in refractory patients.[19–22] Based on that trial, amrubicin is the standard second-line chemotherapy for ED-SCLC in Japan. Regarding the AMR dose, Onoda *et al.* found that 40 mg/m^2 showed significant activity and acceptable toxicity in previously treated SCLC patients.[22] Another study found that

Table 4 Toxicities

	Carboplatin/etoposide (n = 42) Grade			Amrubicin (n = 42) Grade			
Adverse event	≤ 2	3 (4)	%	≤ 2	3 (4)	%	*P*
Leukopenia	21	15 (4)	45	20	12 (8)	48	0.5
Neutropenia	23	14 (3)	40	13	17 (10)	64	0.02
Thrombocytopenia	23	9 (3)	29	13	5 (2)	17	0.15
Anemia	21	4 (0)	10	14	2 (0)	5	0.34
Febrile neutropenia	—	3 (0)	7	—	6 (0)	14	0.24
Fatigue	14	0 (0)	0	6	0 (0)	0	—
Nausea	12	2 (0)	5	3	1 (0)	3	0.5
Constipation	11	0 (0)	0	3	0 (0)	0	—
Anorexia	8	4 (0)	10	7	4 (0)	10	1.0
Diarrhea	1	0 (0)	0	0	0 (0)	0	—
Mucositis	1	0 (0)	0	0	0 (0)	0	—
AST/ALT	9	0 (0)	0	3	0 (0)	0	—
Total bilirubin	1	0 (0)	0	1	0 (0)	0	—
Creatinine	6	0 (0)	0	1	0 (0)	0	—
Uric acid	1	0 (0)	0	1	0 (0)	0	—
Pneumonitis	0	0	0	1	0	0	—

†Fisher's exact test. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

amrubicin was efficacious against relapsed ED-SCLC at 35–40 mg/m^2.[23,24] However, administration of amrubicin at 45 mg/m^2, while effective, produced intolerable toxicities and even treatment-related deaths in separate studies.[25,26] Thus, the amrubicin dose is critical to avoid severe or febrile neutropenia. Accordingly, we selected 40 mg/m^2 as a starting dose for SCLC in elderly patients and those with poor PS, as well as for relapsed patients. A previous study summarized seven cases of interstitial lung disease (ILD) induced by AMR from among 100 SCLC patients treated with this anti-cancer agent; the incidence rate of ILD in patients without pre-existing pulmonary fibrosis was 3%.[27] This was consistent with the incidence of ILD induced by amrubicin in our present study (2.4%). While non-hematologic adverse events were mild and consistent with historical data in both groups, dose reduction was more frequent in the AMR (19%) than in the CE (10%) group because of severe or febrile neutropenia.[9,16]

Sekine *et al.* previously reported results from a very valuable randomized phase III study indicating that higher incidences of febrile neutropenia and ILD ≥ grade 3 occurred after treatment with amrubicin and concluded that 40–45 mg/m^2 AMR is toxic and intolerable in elderly Japanese patients with ED-SCLC.[28] In addition, no significant differences in OS and objective response rate between the CE and AMR groups were observed in this phase III study. The results of our study support the results of the phase III study, thus it is reasonable to continue to select CE as first-line chemotherapy for SCLC in elderly patients or in those with poor PS.

Crucially, patients in our study who received AMR as second-line chemotherapy after CE achieved OS of 18.5 months. Imai *et al.* reported that post-progression survival has a greater impact on OS in elderly patients with lung cancer including ED-SCLC after first-line chemotherapy, suggesting that subsequent treatments in elderly ED-SCLC patients affect OS.[29,30] Moreover, Imai *et al.* showed that AMR was safe and effective for relapsed elderly patients with ED-SCLC.[31] Therefore, it is reasonable to conclude that CE is more suitable as first-line chemotherapy, based on historical data, while AMR is appropriate as second-line chemotherapy for ED-SCLC in elderly patients and those with poor PS.[9,18]

There were several limitations to this study. First, the results cannot be considered definitive because of the retrospective single-center design and relatively small sample size. However, our data affirm the benefits of using CE as a standard regimen for elderly patients with ED-SCLC, as previously demonstrated.[9] Second, because the treatment regimen for ED-SCLC patients was decided at the discretion of the physicians in charge, bias in the categorization of patients into CE and AMR groups cannot be excluded. Nevertheless, there were no significant differences in patient characteristics between the groups. Third, although the patients included in this study were elderly or poor-risk, data regarding their quality of life were not evaluated.

In conclusion, our data affirm that CE should remain standard chemotherapy for ED-SCLC in elderly patients and those with poor PS, while AMR is an appropriate second-line chemotherapy regimen.

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Disclosure

No authors report any conflict of interest.

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