Ann Hematol (2014) 93:1895–1901
DOI 10.1007/s00277-014-2137-6

ORIGINAL ARTICLE

Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study

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Received: 14 April 2014 / Accepted: 6 June 2014 / Published online: 20 June 2014
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Abstract We conducted a phase II trial of concurrent chemoradiotherapy (CCRT) followed by 2 cycles of L-asparaginase-containing chemotherapy for patients who were newly diagnosed with stages IE and IIE nasal extranodal NK/T cell lymphoma (ENKTL). CCRT consisted of 40–44 Gy of radiotherapy with weekly administration of 30 mg/m^2 of cisplatin for 4 weeks. Two cycles of VIDL (etoposide (100 mg/m^2), ifosfamide (1,200 mg/m^2), and dexamethasone (40 mg) from days 1 to 3, and L-asparaginase (4,000 IU/m^2) every other day from days 8 to 20) were administered sequentially. CCRT yielded a 90 % overall response rate without significant side effects in 30 patients, including 20 patients with complete response (CR); however, two patients showed distant disease progression. After CCRT, VIDL chemotherapy showed an 87 % final CR rate (26/30). Although grade III or IV hematologic toxicity was frequent during VIDL chemotherapy, no treatment-related mortality was observed, and L-asparaginase-associated toxicity was manageable. With a median follow-up of 44 months, 11 patients showed local (n=4) and distant (n=7) relapse or progression. The estimated 5-year progression-

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free and overall survival rates were 73 and 60 %, respectively. In conclusion, CCRT followed by L-asparaginase-containing chemotherapy is a feasible treatment for newly diagnosed stages IE/IIE nasal ENKTL.

Keywords Extranodal NK/T cell lymphoma · Chemotherapy · Radiotherapy · L-Asparaginase

Introduction

Extranodal natural killer (NK)/T cell lymphoma (ENKTL) is a rare subtype of non-Hodgkin lymphoma (NHL) with a dismal prognosis. As the majority of ENKTL cases present as localized disease, particularly involving the nasal or paranasal area [1–3], the treatment of localized disease has been an important issue. Traditionally, radiation therapy alone or anthracycline-based chemotherapy followed by radiation therapy has been adopted for localized ENKTL; however, these approaches yielded a long-term survival of just 40–50 %, even in stages I/II disease [4, 5]. Recently, two prospective phase II trials using concurrent chemoradiotherapy (CCRT), including the Japan Clinical Oncology Group (JCOG) study with radiation therapy (50 Gy) and three courses of concurrent dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) and our group's (CISL) trial of CCRT followed by etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) were published. Although those studies used different chemotherapy regimens and radiation doses, they produced promising outcomes resulting in 70–80 % overall survival [6, 7]. In our previous phase II trial, we found a complete response (CR) rate of 80 % after the sequential application of CCRT and three cycles of VIPD as adjuvant systemic chemotherapy [6]. However, frequent occurrences of grades 3 and 4 hematologic toxicities during the adjuvant VIPD therapy seemed to be too toxic for localized disease, although hematologic and nonhematologic toxicities were minimal during CCRT. Thus, we designed a new trial by maintaining the scheme of CCRT for induction and modifying the post-CCRT chemotherapy to reduce its toxicity and increase efficacy. The modification of post-CCRT chemotherapy was as follows. First, we reduced the number of chemotherapy cycles, as most patients from our previous trial achieved a good response after CCRT [6]. Next, we added L-asparaginase instead of cisplatin, because the efficacy of L-asparaginase was proved in previous clinical trials [8–10]. In addition, we recommended up front high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) for high-risk patients, because previous data suggested that ASCT might be helpful for first-time CR patients who are at risk of relapse, although the role of up front ASCT remains controversial [11]. Given that the central nervous system (CNS) involvement is rare in localized nasal ENKTL, CNS prophylaxis was not included [12]. Herein, we report the results of our phase II study of CCRT followed by L-asparaginase-based chemotherapy for newly diagnosed localized ENKTL (CISL08-01).

Materials and methods

Patients

Eligibility criteria included newly diagnosed ENKTL based on the presence of histological features and immunohistochemistry results, including cytoplasmic CD3+, CD20–, and CD56+ positive for cytotoxic molecules and positive for Epstein–Barr virus (EBV) in in situ hybridization. No patients received any kind of treatment for ENKTL, and all had measurable disease. Patients were 18 years of age or older, and their disease state was Ann Arbor stage IE or IIE. Additional eligibility criteria were the following: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; hemoglobin ≥9.0 g/dL; absolute neutrophil count ≥1,500/μL and platelet count ≥100,000/μL; serum creatinine ≤1.5 mg/dL and creatinine clearance ≥50 mL/min; total bilirubin<two times the upper limit of normal; and aspartate transferase<three times the upper limit of the normal. Patients who had any coexisting medical diseases with sufficient severity to prevent full compliance with the study protocol, such as heart failure or acute, active infection, were excluded from the study. Considering the adverse effects of L-asparaginase, patients who had a history of acute pancreatitis were also excluded. ENKTL cases with nonnasal sites, such as the skin or the gastrointestinal tract, were excluded, even if they had localized disease.

Study design and objectives

The CCRT consisted of radiation therapy with 36–44 Gy per 18–22 fractions and weekly administration of 30 mg/m^2 cisplatin for 4 weeks. The first response evaluation was performed 3 to 4 weeks after the completion of CCRT. Responders to CCRT received 2 cycles of VIDL chemotherapy: daily intravenous administration of etoposide (100 mg/m^2), ifosfamide (1,200 mg/m^2), and dexamethasone (40 mg) for 3 days, followed by intramuscular injection of L-asparaginase (4,000 IU/m^2) every other day from days 8 to 20 (total of seven doses). VIDL chemotherapy was repeated every 4 weeks, and the final response evaluation was performed 3 to 4 weeks after the completion of the second cycle of VIDL. As a consolidation treatment, up front ASCT was recommended for the patients at high risk of relapse, which was defined as having two or three of the following risk factors at diagnosis: presence of B symptoms, elevation of serum LDH, and lymph node involvement [1]. The primary endpoint was complete response rate, including complete

response-unconfirmed (CR-u) by investigator review, and the secondary objectives included overall survival, progression-free survival, and toxicity. All patients provided written informed consent. The study was reviewed and approved by the institutional review board at each participating institute and was registered at ClinicalTrials.gov (NCT01007526).

Assessment of response and toxicity

Assessments included complete blood count, determination of serum lactate dehydrogenase (LDH) levels, bone marrow aspiration and trephine biopsy, endoscopic examination of the nasal and oral cavities by otorhinolaryngologists, CT scanning or magnetic resonance imaging of the involved lesions, and CT scanning of the chest and abdomen–pelvis. All of these studies were performed before treatment and after completion of CCRT and VIDL, and they were then repeated every 3 to 6 months thereafter, to monitor relapse, for 2 years. Subsequently, survival status was monitored at each participating institute, and evaluation of disease status to monitor relapse was performed at the physicians' discretion. For prognostic factor analysis, prognostic models reported previously, such as the International Prognostic Index (IPI), NK/T cell lymphoma prognostic index (NKPI), and local tumor invasiveness (LTI), were evaluated. Quantitative polymerase chain reaction of EBV DNA in the peripheral blood was also performed, as proposed previously [1, 13–15]. The treatment response was assessed according to the International Working Group response criteria [16]. Toxicity was evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0. Dose modification of cisplatin during CCRT, as well as that of etoposide and ifosfamide, was performed as reported previously [6]. The treatment schedule of L-asparaginase was also modified based on the decision of investigators according to the occurrence of grade 4 hematologic or grade 3 nonhematologic toxicities.

Statistics

The sample size was determined based on CR rates according to Simon's optimal two-stage design [17]. Assuming a target and a lower activity level of 0.90 (p1) and 0.70 (p0), respectively, an accrual of six patients was required in the first stage. If four CR cases were observed, the trial would be continued. The planned accrual was 27 patients, in which CR was observed in 22 patients. This design provided a probability of 0.05 of accepting a treatment worse than p0 and a probability of 0.20 for rejecting a treatment better than p1. Assuming a dropout rate of 10 %, the size of the study population was set at 30 individuals. The association between patient characteristics and treatment response was analyzed using the chi-squared test. The Kaplan–Meier method was used to calculate progression-free survival (PFS) and overall survival (OS), and survival curves were compared via the log-rank test. A two-sided P value <0.05 was considered significant. PFS was defined as the time from the date of enrollment to the date of documented disease progression or any kind of death, whereas OS was measured from the date of enrollment to the date of death from any cause and was censored at the date of the last follow-up visit.

Results

Patient characteristics

Thirty patients were enrolled in the study from April 2008 to February 2010. The median age at diagnosis was 47 years (range 22–71 years), and the most common primary site was the nasal cavity. Eight patients had involvement of the nasal cavity as well as of the nasopharynx or oropharynx, and, as each of these sites was counted as extranodal involvement, these patients were determined to have two extranodal involvement sites. Five patients showed an adjacent bone invasion that was defined previously as LTI [14]. A circulating EBV DNA level was detected in 10 patients (median number 6,775 copies per microliter; range 87–30,800), whereas 18 patients showed less than the detected level (Table 1). All patients were determined as having a low or low-to-intermediate risk of IPI, whereas six patients belonged to groups III or IV of the NKPI.

Response to treatment

During CCRT, all but one patient received radiation therapy according to the protocol. Thus, the median dose of radiation was 40 Gy: 23 patients received 40 Gy, six received 44 Gy, and only one received 50 Gy. Among them, 27 patients responded to CCRT, including 18 cases of CR, two cases of CR-u, and seven cases of PR. However, the two patients who received 44 Gy showed disease progression outside the radiation target volume: one case of lung metastasis and another case of liver metastasis (Fig. 1). Thus, there was no significant association between the radiation therapy dose and response (P=0.114). After completion of CCRT, a total of 28 patients, including one patient with SD after CCRT, received VIDL chemotherapy. After 2 cycles of VIDL chemotherapy, CR was achieved in eight patients who showed CR-u, PR, or SD after CCRT; however, one patient with PR after CCRT remained as PR even after 2 cycles of VIDL. The other patient who achieved CR after CCRT progressed outside of the radiation target volume (both parotid glands and neck nodes) after the first cycle of VIDL. Therefore, the final CR rate was 86.7 %

Table 1 Characteristics of patients

Characteristics		Number	Percent
Age (years)	≤60	24	80
	>60	6	20
Sex	Male	20	67
	Female	10	33
Performance status	ECOG 0/1	29	97
	ECOG 2	1	3
Ann Arbor stage	I	21	70
	II	9	30
Serum LD	Normal	22	73
	Increased	8	27
B symptoms	Absence	21	70
	Presence	9	30
EBV titration (copies/μL)	Negative	18	60
	Positive	10	33
	Unknown	2	7
LN involvement	Absence	24	80
	Presence	6	20
Primary site	Nasal cavity	18	60
	Nasopharynx or oropharynx	4	13
	Nasal cavity and naso- or oropharynx	8	27
Local tumor invasion	No	25	83
	Yes	5	17
Extranodal involvement	0/1	22	73
	≥2	8	27
IPI	Low	18	60
	Low to intermediate	12	40
NK prognostic index	Group I	14	47
	Group II	10	33
	Group III	5	17
	Group IV	1	3

ECOG Eastern Cooperative Oncology Group, *LD* lactate dehydrogenase, *EBV* Epstein–Barr virus, *LN* lymph node, *IPI* International Prognostic Index, *NKPI* NK/T cell lymphoma prognostic index

(26/30) after CCRT and VIDL, and disease progression was found in three patients (Fig. 1).

Toxicity and treatment completion of CCRT and VIDL

There were no cases of grades III or IV hematologic toxicity during CCRT, and the majority of nonhematologic toxicities, such as nausea, vomiting, and anorexia, were less than grade 3 (Table 2). A few patients developed grade 1 facial edema and oral pain. However, stomatitis was the most serious toxicity in some patients. Thus, the fourth administration of cisplatin was delayed 1 week in one patient who developed grade 4 stomatitis. However, all patients completed the planned course of radiation therapy and cisplatin administration without dose reduction. When we summarized the toxicity profiles of VIDL chemotherapy, we found that 24 patients developed at least one episode of grades III (n=6) or IV (n=18) leukopenia (Table 2). Although some patients had grades III or IV nonhematologic toxicities, such as nausea, stomatitis, or general weakness, these were manageable with supportive care. L-Asparaginase-associated hepatic transaminase elevation was also manageable, as the majority of cases were grade I (n=10) or grade II (n=4). Three patients who experienced grade III hepatotoxicity recovered with supportive care. In addition, no patient had L-asparaginase-associated acute pancreatitis or coagulopathy. Thus, there was no treatment-related mortality. All patients completed the planned 2 cycles of VIDL chemotherapy, with the exception of one patient who progressed after the first cycle of VIDL chemotherapy. The dose of etoposide and ifosfamide was reduced to 75 % of the original dose in only one patient who showed persistent grade II leukopenia after CCRT. Dexamethasone was administered to all patients without dose reduction. However, 1 cycle of L-asparaginase was skipped in two patients who developed grade III hepatic toxicity and grade III weakness, respectively. The other patient also stopped the administration of L-asparaginase from day 12 during the first and second cycle because of the development of grade III stomatitis and febrile neutropenia.

ASCT and relapse

One patient with PR and four patients with CR after the completion of CCRT and VIDL chemotherapy underwent up front ASCT (Fig. 1). Although they all achieved CR after ASCT, three patients relapsed and died, with one local relapse (nasal cavity) and two distant relapses (colon and central nervous system). Three patients relapsed within 1 year after VIDL chemotherapy, with one local relapse (nasal cavity) and two distant relapses (liver and forearm skin). They all died in spite of salvage chemotherapy. Two patients showed delayed local relapse (nasal cavity) 40 and 44 months after their enrollment, respectively. They are still alive after rescue by salvage treatment. Thus, 19 patients never experienced disease relapse, whereas 11 patients showed local (n=4) or distant (n=7) relapse or progression (Fig. 1). The occurrence of relapse or progression was not significantly associated with characteristics at diagnosis or risk factors of prognostic models, such as the IPI, NKPI, or LTI. Among the four patients mentioned above who were not able to receive a full dose of VIDL chemotherapy, only one patient showed distant relapse in the forearm skin.

Survival outcomes

The last survival data update was performed in May 2013. With a median follow-up duration of 44 months (95 %

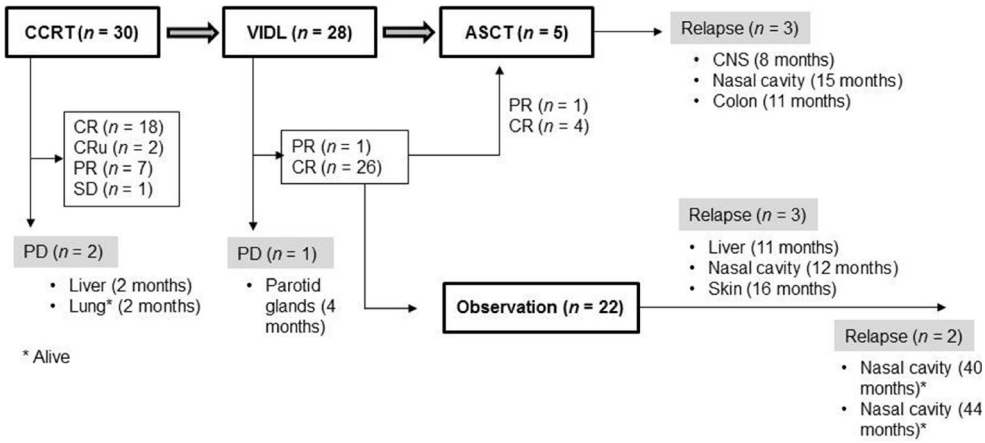

Fig. 1 Summary of response and relapse or progression

confidence interval: 41–47 months), the median OS and PFS were not reached. The 5-year OS and PFS were 73 and 60 %, respectively. A univariate analysis showed an absence of significant association between OS and PFS and patient characteristics, such as age, stage, serum LDH, number of extranodal involvement sites, EBV DNA titer, LTI, etc. ($P>0.05$). The IPI model also failed to show a significant association with OS and PFS ($P>0.05$). The NKPI model showed a trend of poor OS and PFS in patients who had any risk factors for NKPI (groups 2–4) compared with patients without risk factors for NKPI (group 1) (Fig. 2).

Table 2 Toxicity profiles

Toxicity	Concurrent chemoradiation				VIDLchemotherapy			
	G1	G2	G3	G4	G1	G2	G3	G4
Hematologic toxicity								
Anemia	2				4	5	3	
Leukopenia	2	1			1	1	6	18
Thrombocytopenia	2				7	3	3	1
Febrile neutropenia							5	
Nonhematologic toxicity								
Nausea	12	3			11	8	2	1
Vomiting	4	3			8	5		
Diarrhea		2			2	2		
Anorexia	8	2			10	5		
Constipation	5				6	2		
Stomatitis	4	5	4	1	5	5	5	1
General weakness			1		2	4	2	
Insomnia					3	2		
Edema	2				3	1		
Dizziness	1				2	1		
Myalgia	1				2			
Fatigue	1				1	1		
Pain	2	1				3	1	
Xerostomia	1							
Epistaxis	2							
Peripheral neuropathy	1							
Skin rash	1				1	1		
Transaminase elevation	1				10	4	3	

The numbers represent the number of patients who developed the maximal toxicity during their treatment period. Empty spaces mean that no patient developed a toxicity

G grade

Discussion

The treatment of localized ENKTL has been a troublesome issue in the management of NHL because it frequently shows resistance to anthracycline-based chemotherapy, and local radiation therapy often fails to prevent systemic disease relapse or progression [18]. The goal of this study was to develop a more effective and tolerable treatment strategy for localized nasal ENKTL compared with the treatments reported previously, because regimens such as VIPD and DeVIC resulted in severe marrow suppression or mucositis [6, 7]. Our new regimen, i.e., 2 cycles of VIDL chemotherapy, produced a better CR rate (87 %) than did our previous regimen, i.e., 3 cycles of VIPD chemotherapy (80 %, 24/30). Furthermore, there was no treatment-related mortality in this study, whereas two deaths associated with infectious complications were found in our previous study [6]. However, this study included three cases of disease progression after CCRT and the first cycle of VIDL chemotherapy, which all occurred outside the radiation target volume. Eight cases of relapse occurred in the nasal cavity ($n=4$) and distant sites, including the colon, liver, skin, and central nervous system (Fig. 1). Considering that distant relapses occurred relatively early, disease relapse outside the radiation target volume might be associated with microscopic metastasis at time of diagnosis, and these cases might be a main cause of treatment failure in patients with localized nasal ENKTL. Our study included two cases of local

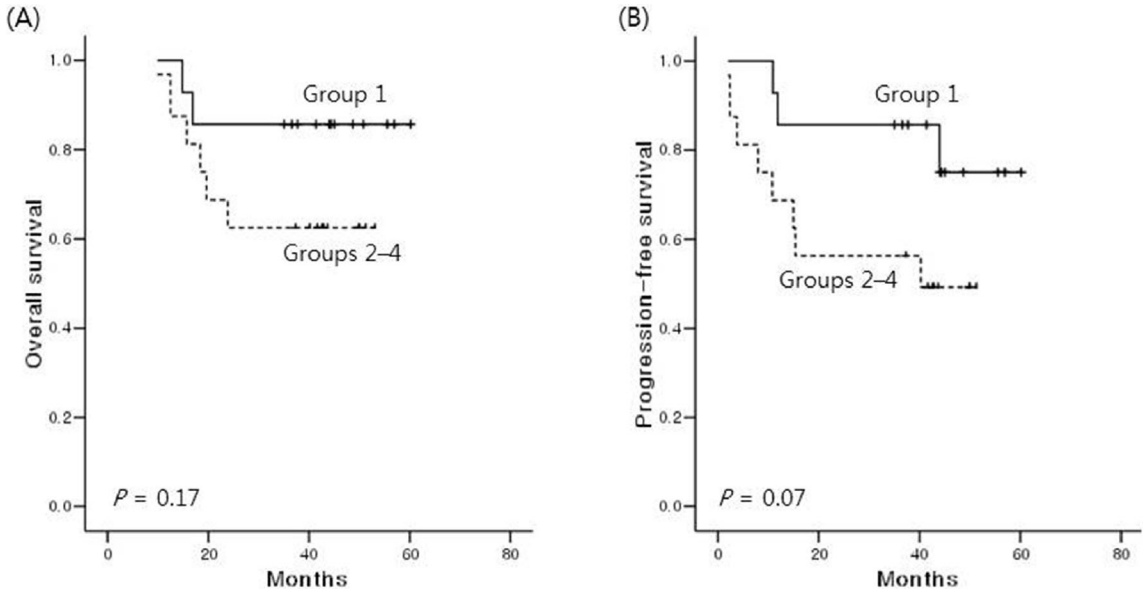

Fig. 2 Comparison of overall survival (**a**) and progression-free survival (**b**) between group 1 and Groups 2–4 of NKPI

relapse that occurred more than 40 months after the first diagnosis (Fig. 1). Although most relapses occur early in the treatment course [2], our late relapse was not uncommon because a previous case series also reported late relapse of ENKTL [19, 20]. These late relapses seemed to have developed mainly in local sites around the initial primary site and responded well to salvage treatment, such as reirradiation or chemotherapy. Our two patients with late relapses were alive after salvage treatment at the time of the current analysis. Recently, the updated analysis of the JCOG trial of DeVIC (updated in December 2011, median follow-up of 67 months) reported no disease progression after the first analysis.[21] Thus, those authors reported a 70 % 5-year OS and a 63 % 5-year PFS, which were comparable to our survival outcomes. Although the causes of late relapse in our current study were not clear, it might have been associated with the difference in radiation dose, as our median radiation dose was lower than that of the JCOG trial of DeVIC.

In this study, we recommended up front ASCT for patients who had two or more risk factors for NKPI; however, only two out of the six patients with≥two risk factors actually underwent ASCT. Among them, one patient relapsed and died in spite of ASCT, whereas the other five patients were still alive without evidence of disease. According to the physicians' decision, two patients who had one risk factor underwent ASCT; however, they all died of distant relapse in the central nervous system and colon (Fig. 1). Thus, our data do not seem to support the role of up front ASCT for nasal ENKTL. However, considering that a certain portion of the patients experienced treatment failure because of systemic progression, the usefulness of up front ASCT should be addressed in the future in a well-designed clinical trial. The L-asparaginase-containing chemotherapy regimen, VIDL, was tolerable in terms of toxicity. Although it still resulted in grades III or IV hematologic toxicity in the majority of patients, no treatment-related mortality was found (Table 2). This might be due to the reduced number of chemotherapy cycles and the omission of cisplatin. Furthermore, the dosage of L-asparaginase (4,000 IU/m^2) in VIDL was lower than that of SMILE (6,000 IU/m^2). This might be associated with the occurrence of manageable toxicity related to L-asparaginase, including acute pancreatitis. Thus, our combination of L-asparaginase with etoposide, ifosfamide, and dexamethasone is effective and tolerable for patients with localized nasal ENKTL.

As the number of patients was too small to allow identification of prognostic factors, our analysis of these factors failed to show a significant prognostic association. Thus, unfavorable parameters reported previously, such as serum LDH, EBV DNA titer, and LTI, were not associated with relapse or poor survival. Furthermore, the prognostic models, such as IPI and NKPI, also failed to show any significant association with poor prognosis. Considering that these prognostic models and unfavorable parameters were developed based on the clinical data of patients who were treated mainly with old-fashioned treatments, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), the lack of prognostic models and factors in this study may imply the requirement for new prognostic models for ENKTL in the era of nonanthracycline-based chemotherapy and radiation therapy.

In conclusion, CCRT followed by L-asparaginase-containing chemotherapy, VIDL, is a feasible treatment for newly diagnosed stages IE/IIE nasal ENKTL. However, considering that local and distant relapse remain as its major obstacles, a further clinical trial is warranted.

Conflicts of interest The authors declare that they have no conflict of interest.

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