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ORIGINAL ARTICLE

Short-term low-volume hydration in cisplatin-based chemotherapy for patients with lung cancer: the second prospective feasibility study in the Okayama Lung Cancer Study Group Trial 1201

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Abstract
Objective We previously reported the feasibility of short-term low-volume hydration in patients with advanced lung cancer who received cisplatin-based chemotherapy (Jpn J Clin Oncol 2013). We sought to determine the clinical usefulness of a more convenient hydration method, evaluating the safety and efficacy of shorter-term and lower-volume hydration.
Method Chemonaïve patients with advanced lung cancer who were ≤75 years and reserved an adequate renal function for cisplatin use (≥60 mg/m^2) were eligible. An intravenously administered hydration of 1700 ml in ~3.5 h with 1500 ml of orally administered hydration was investigated. The primary endpoint was the proportion of patients without grade 2 or worse renal toxicity in the first cycle.
Results A total of 45 patients were registered, all of whom were evaluable for renal toxicity. The median baseline creatinine score was 0.70 mg/dl, and the median cisplatin dose on day 1 was 75 mg/m^2. In the first cycle, one patient (2 %) developed grade 2 creatinine toxicity, and thus, the proportion of patients with less than grade 2 was 98 % (the lower limit of 95 % confidence interval; 93 %), which met the primary endpoint. Five patients (11 %) had grade 1 or greater nephrotoxicity, three of whom successfully recovered. The objective response rate was 24 % and median progression-free survival 5.8 months.
Conclusion This prospective study demonstrated the safety and efficacy of shorter-term lower-volume hydration.

Keywords Cisplatin · Lung cancer · Hydration

Introduction

Cisplatin-based chemotherapy is the standard of care for advanced non-small-cell lung cancer based on its survival advantage seen in randomized trials and meta-analyses [1–3]. On the other hand, nephrotoxicity is the most problematic adverse event [4], and in Japan, the high-volume hydration of 2500–5000 ml has been routinely used in daily clinical practice to avoid renal toxicity. However, this high-volume hydration method could impair patient's quality of life (QOL) because it necessitates long infusion time. The development of serotonin antagonists and neurokinin-1-receptor antagonist has remarkably improved gastrointestinal toxicity induced by cisplatin, which could guarantee hydration orally. We conducted a prospective study successfully showing the feasibility of short-term small-volume hydration with a total of 2.5 L in a period of 4.5 h with orally administered hydration [5], which enabled to cisplatin use in the outpatient setting. However, we felt that such hydration was still somewhat bothersome for both patients and medical staff in terms of administration, which potentially complicated patients' QOL in the outpatient setting. To test whether hydration venously could shift further toward hydration orally, we evaluated the safety of shorter-term, lower-volume hydration in patients with advanced lung cancer.

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Methods

Patients

Eligibility criteria were as follows: age ≤75 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1, pathological diagnosis of lung cancer, inoperable locally advanced or metastatic or recurrent disease, no prior cytotoxic chemotherapy except prior adjuvant chemotherapy completed ≥1 year earlier, capacity to drink ~1 L per day, and adequate hematologic, cardiac, liver, and renal function (including both serum creatinine level below the institutional upper normal limit and a creatinine clearance of ≥60 ml/min). Exclusion criteria were radiographic signs of active interstitial pneumonia, symptomatic brain metastasis, or uncontrolled third-space fluid retention. Those who were treated with the split schedule of cisplatin or with the cisplatin–etoposide regimen that required drip infusion even on days 2 and 3 were also excluded.

Treatment

Patients were to receive cisplatin-based chemotherapy with a cisplatin dose of ≥60 mg/m^2 per day. The treatment schedule was designed as shown in Table 1. Cisplatin was diluted in 500 ml normal saline solution and administered over 1 h. Magnesium sulfate, the key agent for preventing renal toxicity, was supplemented at 4 mEq both before and after cisplatin administration. Mannitol, an osmotic diuretic, was infused just before cisplatin administration. A total of 1.7 L of hydration was administered in ~3 h. Patients were strongly recommended to drink 1.5 L of water on day 1 and 1 L on days 2 and 3 to avoid dehydration, which may potentially lead to renal failure [10]. This treatment was repeated every 3 or 4 weeks for four to six cycles unless disease progression or unacceptable toxicity was observed or the patient refused further treatment. Maintenance therapy with pemetrexed or bevacizumab was accepted after four cycles of cisplatin. All patients received the first cycle in an inpatient setting to precisely evaluate safety, and subsequent cycles were given in an outpatient setting if possible.

Assessment of toxicity

All toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, which contains two types of grading systems for creatinine toxicity; we primarily used one, which is based on the upper limit of the normal range (ULN) for serum creatinine at each institute (ULN-based) because we and others had previously used it [5, 6].

Endpoints

The primary endpoint was patients who underwent cisplatin-based chemotherapy without developing grade 2 or greater renal toxicity based on serum creatinine levels during the first cycle; we principally checked toxicity in each cycle until the day the next cycle was initiated. We also assessed it in the last cycle in each patient until day 30 or the day when the poststudy treatment was subsequently initiated. Renal toxicity during all cycles was recorded. The secondary endpoints were response rate, other toxicities, and survival rate. As for response, the Response Evaluation Criteria in Solid Tumors (RECIST; ver. 1.1) was applied.

This study was conducted in compliance with the principles of the Declaration of Helsinki, and the protocol was approved by the Okayama University institutional review

Table 1 Preplanned schedule of short-term low-volume hydration in cisplatin-based chemotherapy on day 1

Chemotherapeutic and hydration agents		Dosage
Antiemetic premedication	Normal saline solution with palonosetron 0.75 mg, dexamethasone 9.9 mg, magnesium sulfate 4 mEq	100 ml (15 min)
Cytotoxic agents	Normal saline solution[a] with an anticancer agent that would be combined with cisplatin	500 ml (1 h)
Diuresis	20 % mannitol	150 ml (15 min)
Cisplatin	Normal saline solution with cisplatin ≥ 60 mg/m^2	500 ml[b] (1 h)
Hydration	1/4 normal saline solution with magnesium sulfate 4 mEq, KCl 4 mEq	200 ml (30 min)
Total		1700 ml (3 h)

The venous line was kept with 250 ml of normal saline throughout the infusion. Dose schedules for cisplatin and anticancer agents combined with cisplatin were based on the latest National Comprehensive Cancer Center guidelines. In the case of triplet chemotherapy with bevacizumab, it was diluted in 100 ml of normal saline and was administered after the completion of 5)

[a] Vinorelbine, pemetrexed, and gemcitabine were diluted in 50, 100, and 100 ml of normal saline (5, 10, and 30 min), respectively. In addition, 250 ml of normal saline solution was administered

[b] A total of 500 ml with cisplatin and normal saline solution

board (Approval No. 10365). All patients gave written informed consent before entering the study.

Statistical consideration

Safety and efficacy were assessed in subsequent cycles. A minimax design was used to determine whether there was sufficient evidence that the treatment completion rate was at least 90 % (clinically feasible) versus at most 75 % (clinically infeasible), accepting alfa and beta of ≤10 % each. The estimated accrual number was 40 patients. This regimen was to be rejected when <35 of the 40 cases successfully completed the cycle. With an assumed 10 % dropout rate, a total of 45 patients were needed. Overall survival was defined as the interval between the date of enrollment in this study and death or the last follow-up visit. Progression-free survival was defined as interval between the date of enrollment in this study and progressive disease or death. Survival distribution was estimated using the Kaplan–Meier method. All statistical analyses were conducted with STATA/SE version 11.0 software (College Station, TX, USA).

Results

Patients

Between July 2012 and April 2014, 45 patients were registered. Table 2 lists their demographics and details of baseline renal function, which were similar to those of patients recruited in the prior trial [5]. Eighteen patients (40 %) had epidermal growth factor receptor (EGFR) mutations, and two patients (4 %) had fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK). Of these, 14 (70 %) had already received tyrosine kinase inhibitor for their specific mutations in their first-line setting. All patients were followed up sufficiently during this defined period.

Table 2 Patient characteristics and baseline renal function ($n = 45$)

Demographics of patients and tumors		
Age (years)	Median (range)	66 (34–72)
Sex	Male/female	28 (62 %)/17 (38 %)
ECOG PS	0/1	26 (58 %)/19 (42 %)
Histology	Adenocarcinoma	38 (84 %)
	Squamous cell carcinoma	2 (4 %)
	Small-cell carcinoma	3 (7 %)
	NSCLC/unclassified	2 (4 %)
Stage	IV/recurrence	37 (82 %)/8 (18 %)
Driver mutation status	EGFR mutation	18 (40 %)
	EML4-ALK	2 (4 %)
	Not detected	21 (47 %)
	Not assessed	4 (9 %)
Key baseline laboratory data		
Serum Cr level (mg/dl)	Median (range)	0.70 (0.45–0.94)
eGFR (ml/min/1.73 m^2)	Median (range)	79.7 (60.9–111.0)
CrCl (ml/min)	Median (range)	97.2 (64.0–145.2)

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *NSCLC* non-small-cell lung cancer, *EGFR* epidermal growth factor receptor, *EML4* echinoderm microtubule-associated protein-like 4, *ALK* anaplastic lymphoma kinase, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *Cl* clearance

Renal toxicity

During the first cycle, the cumulative follow-up time of the 45 patients was 1233 days. Of these, one patient (2 %) developed grade 2 creatinine toxicity, and thus, the proportion of patients with less than grade 2 was 98 % [lower limit of the 95 % confidence interval (CI); 93 %], which met the primary endpoint (Table 3). Despite appropriate supportive care, this patient did not recover completely from this toxicity, even on day 34 (serum creatinine level 1.17 mg/dl). It was decided he could not tolerate further cycles of cisplatin administration. He dropped out of the protocol and received poststudy treatment of carboplatin-based chemotherapy. Four patients (9 %) developed grade 1 toxicity, and the median worst creatinine score (range) and median time to develop grade 1 or lower toxicity (range) were 1.19 mg/dl (0.80–1.83 mg/dl) and 9 days (3–10 days), respectively (Table 3b).

Regarding renal toxicity during all cycles, the cumulative follow-up time for assessment was 4725 days. No patient developed grade 2 or worse toxicity in the second cycle or later. Seven patients (16 %) developed grade 1 toxicity, two of whom did not recover to grade 0 (best serum creatinine level recovered after developing grade 1 toxicity of 1.12 mg/dl and 0.81 mg/dl) among the four cycles; the other five of seven patients recovered successfully from renal toxicity within a median of 64 days.

Treatment delivery

The delivery of cisplatin-based chemotherapy is summarized in Table 4. The median cisplatin dose on day 1 in the first cycle was 75 mg/m^2 (range 60–80 mg/m^2). Thirty-two patients (72 %) received regimens including pemetrexed. Thirty patients (67 %) were able to accomplish the designated four cycles of chemotherapy, whereas the remaining 15 failed to complete it mainly due to toxicity ($n = 8$), which included renal toxicity just in one patient, as described above. The other seven patients who temporarily developed grade 1 renal toxicity were able to continue

Table 3 Creatinine toxicity among the 45 patients

	First cycle	All cycles
Serum Cr grade in the CTCAE ver. 4.0		
Grade 0 (%)	40 (89 %)	37 (82 %)
Grade 1 (%)	4 (9 %)	7 (16 %)
Grade 2 (%)	1 (2 %)	1 (2 %)
Grade 1 or less (%)	44 (98 %)	44 (98 %)
With the lower limit of 95 % CI	93 %	93 %
Serum Cr score		
Worst Cr score (mg/dl), median (range)	0.79 (0.46–1.83)	0.81 (0.54–1.83)
Time to develop the worst Cr score, median (range)	9 days (3–30)	65 days (3–170)
Cr score at the end of study treatment (mg/dl), median (range)	0.69 (0.43–1.17)	0.72 (0.50–1.17)

Creatinine toxicity was evaluated with ULN-based value, and the ULN at our institute is ≤1.1 mg/dl for men and ≤0.8 mg/dl for women

Cr creatinine, *CTCAE* Common Terminology Criteria for Adverse Events, *CI* confidence interval, *ULN* upper limit of the normal range

Table 4 Regimen for cisplatin-based chemotherapy treatment

Treatment delivery	
Anticancer agents	
Cisplatin dose at the first cycle (mg/m^2; day 1), median (range)	75 (60–80)
Agents combined with cisplatin	
Pemetrexed	16 (36 %)
Pemetrexed and bevacizumab	16 (36 %)
Docetaxel	4 (9 %)
Vinorelbine	4 (9 %)
Irinotecan	3 (6 %)
Gemcitabine	2 (4 %)
Total number of cycles administered, median (range)	4 (1–6)
No. of patients receiving	
Four cycles or more	30 (67 %)
Three cycles	4 (9 %)
Two cycles	6 (13 %)
One cycle	5 (11 %)
Reasons for failure to receive the designated four cycles ($n = 15$)	
Toxicity	8 (53 %)
Gastrointestinal toxicity	5
Ototoxicity	2
Renal toxicity	1
Disease progression	6 (40 %)
Patient wish	1 (7 %)
No. of patients receiving unplanned hydration during the first cycle	12 (27 %)
Time to initiation of its administration, median (range)	Day 5 (2–8)
Duration of administration in days, median (range)	5 days (1–12)
Volume of unplanned hydration, median (range)	1000 ml/day (500–2000)

further cycles of therapy. Six patients (15 %) needed reduced cisplatin dose in the second cycle or a later, the reason mainly being hematologic toxicity, such as grade 3–4 neutropenia, and febrile neutropenia. Twelve (27 %) of the 45 patients needed unscheduled hydration during the first cycle, mainly due to gastrointestinal toxicity. Median volume of unplanned hydration was 1000 ml/day (range 500–2000 ml/day) (Table 4).

Other toxicities

Toxicitiy of grade 3 or greater is listed in Table 5, which was mainly hematological toxicity (grades 3–4 neutropenia of 20 %); other hematological toxicities were less common. Grades 3–4 severe nonhematological toxicities included nausea/vomiting (16 %) and infection (9 %). Hyponatremia developed in six patients (13 %) in the first cycle but was reversible with the appropriate supportive care. Hepatotoxicity and gastric ulcer occurred reversibly in one patient each.

Response and survival

Tumor response was observed in 11 patients, with an overall response rate of 24 %, whereas 17 patients (38 %) achieved stable disease. Seven patients (16 %) had a non-evaluable response because of early discontinuation of the protocol therapy principally due to adverse events. At the time of analysis performed in February 2015, progression and death were observed in 35 and 16 patients, respectively. Median progression-free survival (PFS) was 5.8 months, and the rate at 6 months was 46 % (Fig. 1a). Median overall survival (OS) was 21.6 months (Fig. 1b).

Discussion

During the first cycle, the proportion of patients with less than grade 2 creatinine toxicity was 98 % (lower limit of 95 % CI; 93 %), which met the primary endpoint. One patient (2 %) developed grade 2 renal toxicity, with his worst creatinine level being 1.83 mg/dl and best recovered level 1.17 mg/dl; four patients (9 %) developed grade 1 renal toxicity. Furthermore, no patient developed grade 2 or worse toxicity in the second cycle or later. Seven (16 %) had grade 1 toxicity, all of whom were able to receive further cycles of therapy. Twelve (27 %) patients needed unplanned hydration during the first cycle, mainly due to gastrointestinal toxicity. Overall response rate was 24 %, and median PFS and OS were 5.8 and 21.6 months, respectively.

To date, there has been no formal Japanese study regarding the safety of short-term low-volume hydration—only standard higher-volume hydration. The Japanese government has not dealt with this issue and has no strong desire to recommend long hydration. We previously reported a feasibility of relatively short-term low-volume hydration [5], but it seemed that the optimal hydration volume was still undetermined. Also, we assumed that venously administered hydration might further shift toward orally administered hydration, potentially leading to further improvement in the patient's QOL. These issues prompted us to conduct the study reported here. This study population was totally different from that registered in our previous study between November 2010 and February 2012 [5].

In this study, grade 2 renal toxicity was observed just in one (2 %) patient throughout treatment cycles, which seemed better than that in traditional long-term high-volume hydration (>4 L in approximately half a day) (6–7 %) [6, 7] and almost identical with that in our prior study or other study of short-term and low-volume hydration (1.6–2.5 L in 4–4.5 h) (0–2 %) [5, 8], despite no direct comparison. Although cisplatin-induced renal disorder could be prevented by appropriate hydration [9], there is still no consensus on a standard hydration method. The current study results might shed light on this long-standing debate.

Dehydration due to cisplatin-induced emesis can also be a threat for nephrotoxicity [10]. Indeed, in this study, 16 % of patients developed grade 3 or worse nausea/vomiting (Table 5), most of whom needed unscheduled hydration. Possibly owing to the appropriate extra hydration, we could maximally avoid severe nephrotoxicity. The proportion of those with extra hydration in this study was consistent with that in our and others' previous studies [5, 8]; we should be aware of such subset of patients in this hydration method and the need for proactive additional hydration based on thorough follow-up, especially for emesis that develops early. In addition, further development of antiemetic therapy shall make it more likely to guarantee orally administered hydration and thus facilitate treatment continuance.

Among the other adverse events, hyponatremia developed in 13 % of patients in our study (Table 5), more frequently than in our previous short-hydration study (9 %) [12]. We used water for orally administered hydration, which would have led to a lack of sodium intake. This adverse event would improve with the use of a saline

Table 5 Adverse events other than renal toxicities in all courses ($n = 45$)

	Grade 3	Grade 4	Grades 3/4 (%)
Hematological			
Leucopenia	7	2	9 (20 %)
Neutropenia	6	7	13 (29 %)
Hemoglobin	2	0	2 (4 %)
Thrombocytopenia	2	0	2 (4 %)
Nonhematological			
Febrile neutropenia	2	0	2 (4 %)
Infection	4	0	4 (9 %)
Nausea/vomiting	7	0	7 (16 %)
Hyponatremia	3	3	6 (13 %)
Hepatotoxicity	1	0	1 (2 %)
Gastric ulcer	1	0	1 (2 %)
Treatment-related death			0

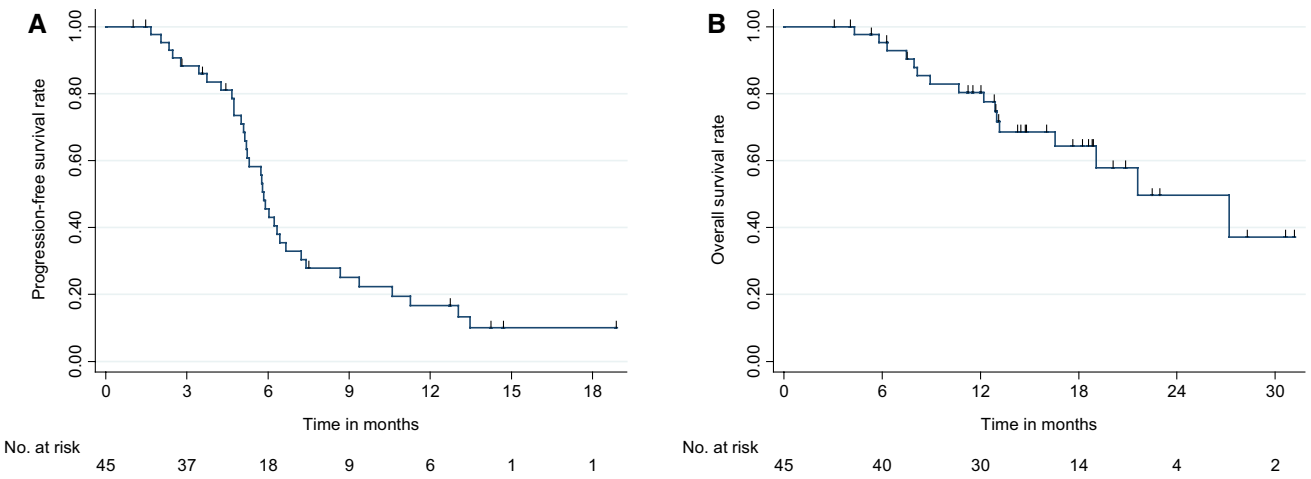

Fig. 1 Survival curves: **a** progression-free survival and **b** overall survival in the 45 patients

solution. Further investigation regarding this issue is warranted.

Regarding efficacy, the overall response rate in this study (30.1–33.1 %) was somewhat lower than that reported in previous studies. This was attributable to seven patients (16 %) having had a nonevaluable response because of early discontinuation of therapy principally due to adverse events. As for survival, our results were almost compatible with existing data in the standard-hydration regimen in patients wtih advanced lung cancer, with a median PFS time of 4.0–4.7 months [11]. Our efficacy data was also consistent with our previous study of short-term low-volume hydration that showed median PFS of 6.9 months [12]. Overall, the hydration method reported here seems to retain the efficacy produced by cisplatin-based chemotherapy.

This study had some limitations, especially its small sample size, potentially leading to selection bias. It is advisable to further investigate the safety and efficacy of short-term low-volume hydration using multicenter large-scale observational data to ensure the generalizability of our data. Also, we did not enforce the evaluation of QOL change during cisplatin chemotherapy, which would be one of the important factors for cancer patients. Furthermore, we assessed the efficacy in patients with non-small-cell lung cancer and small-cell lung cancer together. Thus, our data should be cautiously interpreted.

In conclusion, this prospective study demonstrated the safety and efficacy of shorter-term lower-volume hydration in cisplatin-based chemotherapy.

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Conflict of interest KN has received honoraria from Eli Lilly Japan. KH has received honoraria from Eli Lilly Japan, Nippon Kayaku, AstraZeneca, Pfizer, Daiichi-Sankyo Pharmaceutical, Boehringer-Ingelheim, Taiho Pharmaceutical, Chugai Pharmaceutical, and Sanofi-Aventis. KK has received honoraria from Eli Lilly Japan, Nippon Kayaku, AstraZeneca, Daiichi-Sankyo Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, and Sanofi-Aventis. All other authors declare that they have no conflicts of interest relating to this study.

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