Table 3. Adverse events

	Grade 0, *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Total (*n* = 26), *n* (%)
Fever	2 (8)	10 (39)	1 (4)	1 (4)	0	14 (54)
Hypophosphatemia (decreased blood phosphate)	0	0	0	8 (31)	2 (8)	10 (38)
Hypokalemia (decreased blood potassium)	0	0	0	4 (15)	0	4 (15)
Increased urinary β_2 microglobulin	0	4 (15)	0	0	0	4 (15)
Hematuria (occult blood in urine)	0	2 (8)	0	0	0	2 (8)
Increased AST	0	0	2 (8)	0	0	2 (8)
Increased ALT	0	0	1 (4)	1 (4)	0	2 (8)
Increased γ-GTP	0	0	0	1 (4)	0	1 (4)
Increased serum creatinine	0	0	1 (4)	0	0	1 (4)
Anemia (decreased hemoglobin)	0	0	0	0	1 (4)	1 (4)
Hypocalcemia (decreased blood calcium)	0	0	0	0	1 (4)	1 (4)
Nausea	0	1 (4)	0	0	0	1 (4)
Vomiting	0	0	1 (4)	0	0	1 (4)
Blister	0	1 (4)	0	0	0	1 (4)
Pulmonary edema	0	0	0	0	1 (4)	1 (4)
Disturbance of consciousness	0	0	1 (4)	0	0	1 (4)
Hypoesthesia	0	1 (4)	0	0	0	1 (4)
Headache	0	1 (4)	0	0	0	1 (4)
Polyuria	0	0	1 (4)	0	0	1 (4)
Eczema	0	1 (4)	0	0	0	1 (4)

Adverse events where a causal relationship with the study drug could not be ruled out are shown.

and mouth dryness, improved in accordance with decreasing CSC level. The proportions of patients in whom each symptom was improved at day 10 were 88.9% (eight out of nine), 68.2% (15 out of 22), 64.7% (11 out of 17), 75.0% (three out of four), 66.7% (14 out of 21) and 64.7% (11 out of 17), respectively.

Re-treatment with Zoledronic Acid

Seven patients who relapsed within 56 days after having achieved a CR and one patient who did not achieve a CR to the initial treatment were re-treated with a 4 mg dose. The mean baseline CSC before the re-treatment was 12.8 mg/dl (range, 11.7–15.2), while it was 15.3 mg/dl (range, 12.4–18.4) before the initial treatment in these eight patients. After re-treatment with a 4 mg dose, four patients achieved a CR by day 10, including the patient who did not achieve a CR to the initial treatment. These patients were not documented as relapsed until death or the end of study except for the patient with non-CR to the initial treatment, who had increased CSC at day 8 after re-treatment.

Safety

Safety was evaluated in all 26 treated patients. Zoledronic acid 4 mg was well tolerated. Adverse events with which a causal relationship with the study drug could not be ruled out are listed in Table 3. The most frequently observed adverse event was fever (≤38°C). Electrolyte abnormalities suspected to be drug related including grade 3 or 4 hypocalcemia, hypophosphatemia and hypokalemia were observed in 11 patients; however, all patients were asymptomatic. Grade 4 pulmonary edema, as a serious adverse event, was observed 2 days after the first administration of zoledronic acid in a patient with lung cancer who had lymphangitis, pleural effusion and pericardial effusion before the therapy. The pulmonary edema might have been related to the primary cancer and/or hydration, but a causal relationship to infusion of zoledronic acid could not be ruled out completely. No serious adverse events associated with renal toxicity were reported.

DISCUSSION

This study demonstrated the calcium-lowering effect and safety of zoledronic acid in the treatment of HCM in Japanese patients. The CSC level decreased in all patients after zoledronic acid treatment, and 84% of the patients became normocalcemic by day 10. The CR rate of our study was similar to that of large randomized studies of zoledronic acid in patients with HCM reported by Major et al. (84 versus 88%) (5) on the same eligibility and response criteria.

In the above studies by Major et al., subgroup analysis indicated zoledronic acid 4 mg to be equally effective with regard to the CR rate independent of a patient's demographics, such as baseline CSC, PTHrP, presence of bone metastases and cancer type. Although the subgroup analysis of CR rate in this Japanese trial showed some variation, our observation seemed to be comparable considering that the number of patients in each subgroup was small.

Our study demonstrated shorter time to relapse than reported by Major et al. (median, 23 versus 30 days). Duration of CR demonstrated the same tendency (median, 22 versus 32 days). The reason for the difference in duration of response might be due to a difference in patient demographics between these studies. Although the background of the patients including tumor type, sex, age and CSC at baseline were similar, the frequency of elevated (>2 pmol/l) PTHrP in our study was higher than that in the studies by Major et al. (80 versus 23%). Time to relapse was shorter in patients with high PTHrP levels than in patients with low levels. Considering PTHrP is accompanied by enhancement of kidney re-absorption of calcium and activation of osteoclasts, the higher proportion of patients with high PTHrP levels in our study may explain the shorter time to relapse and CR duration compared with the study by Major et al.

It is also noteworthy that the calcium-lowering effect of zoledronic acid 4 mg was retained even if patients had an elevated PTHrP level; nevertheless, it was reported that bisphosphonates such as pamidronate and ibandronate were less effective in reducing the serum calcium level in patients who had a higher PTHrP level (6–10). This important property is presumably due to the more potent pharmacological activity of zoledronic acid.

Currently, pamidronate, incadronate and alendronate are available for treatment of HCM in Japan. Although incadronate and alendronate have not been compared directly in clinical studies, available data indicate that zoledronic acid is more effective. For instance, a single recommended dose of incadronate 10 mg yielded normalization of calcium in 58% of patients with mean initial CSC of 14.2 mg/dl in a Japanese dose response study with HCM (11); and single doses of 5, 10 or 15 mg of alendronate resulted in an overall normalization rate of 74% and a time to relapse of 15 days with an initial CSC of 11.5 mg/dl (12).

The safety profile of zoledronic acid was similar to that of other bisphosphonates. The most frequent adverse events occurring in this study, i.e. transient fever and abnormality of electrolytes, were typical of bisphosphonates as a class. The incidence of these adverse events was generally within the expected range from the previous pamidronate trials (13). Although urinary laboratory abnormalities, such as urinary β_2 microglobulin and hematuria, were reported, no clinically relevant symptoms were observed. No patient developed grade 3 or 4 serum creatinine changes. Bisphosphonates, however, have been associated with impairment of renal function. The risk of renal dysfunction with zoledronic acid was also reported in cancer indications necessitating repeated dosing, but was similar to pamidronate (14). Monitoring of renal function therefore should be routine practice, particularly when patients have underlying or concomitant illnesses associated with renal function impairment. HCM constitutes a potentially life-threatening condition, thus serum creatinine levels of up to 4.5 mg/dl were accepted as baseline level at study entry.

In conclusion, zoledronic acid at a dose of 4 mg is well tolerated, and it effectively induces durable reduction in the corrected serum calcium level and improves the symptoms of HCM in Japanese patients.

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Thermo-Chemo-Radiotherapy for Advanced Gallbladder Carcinoma

Terumi Kamisawa[1], Yuyang Tu[1], Jun-ichi Ishiwata[1], Katsuyuki Karasawa[2]
Tadayoshi Matsuda[2], Tsuneo Sasaki[3], Nobuaki Funata[4], Kouji Tsuruta[5]
Atsutake Okamoto[5], Toshio Takahashi[5]
[1]Department of Internal Medicine, [2]Department of Radiology, [3]Department of Chemotherapy
[4]Department of Pathology, and [5]Department of Surgery
Tokyo Metropolitan Komagome Hospital, Tokyo, Japan
Corresponding Author: Terumi Kamisawa, MD, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, 113-8677 Bunkyo, Tokyo, Japan
Tel: +81 3 3823 2101, Fax: +81 3 3824 1552, E-mail: kamisawa@cick.jp

ABSTRACT

Background/Aims: Many gallbladder carcinomas are detected at an advanced stage, and the outcome of the patients with these tumors is dismal despite aggressive tumor removal. We have treated advanced gallbladder carcinoma with chemoradiotherapy combined with hyperthermia. In this study, clinical effectiveness of thermo-chemo-radiotherapy (TCRT) for advanced gallbladder carcinoma was evaluated in comparison with other treatment modalities.

Methodology: Two hundred and seventy patients with advanced gallbladder carcinoma (Stage VI) were treated. According to treatments received, they were divided into five groups as follows; group 1; 30 patients treated with TCRT, group 2; 19 patients underwent R0-resection, group 3; 39 patients underwent R1,2-resection, group 4; 57 patients treated with chemo- and/or radiotherapy, group 5; 125 patients with only supportive therapy.

Results: In group 1, there were 19 objective responses (5 complete response and 14 partial response) in respect to tumor regression, and 15 (6 complete response and 9 partial response) of 20 patients with obstructed bile duct showed resolution of the bile duct. The survival rate was best in group 2. A significant improvement of long-term survival was exhibited in group 1 and 3 compared to group 4 and 5, and there was no significant difference between group 1 and 3 ($p<0.01$).

Conclusions: TCRT can produce significant response and improvement of survival time in patients with advanced gallbladder carcinoma, and may be a favorable alternative to aggressive surgical approaches.

KEY WORDS:
Hyperthermia; Gallbladder carcinoma; Thermo-chemo-radiotherapy

ABBREVIATIONS:
Thermo-chemo-radiotherapy (TCRT); American Joint Committee on Cancer (AJCC); Cis-platinum (CDDP); 5-Fluorouracil (5-Fu); Methotolexate (MTX); Intraoperative Radiation Therapy (IORT); External Beam Radiation Therapy (EBRT); Complete Regression (CR); Partial Regression (PR); No Change (NC); National Cancer Institute Common Toxicity Criteria (NCI-CTC); Percutaneous Transhepatic Cholangiodrainage (PTCD); Radiotherapy (RT)

INTRODUCTION

Despite recent tremendous advances in diagnostic technologies, many gallbladder carcinomas are detected at an advanced stage when the tumor has already invaded adjacent organs or major vessels. Then, various kinds of combined resection are required to obtain higher resectability and curability. Recently, aggressive surgical approaches, including resection of the liver, pancreas, and major vessels have been challenged, but their results have been discouraging and long-term survivors are the exceptions (1,2).

Hyperthermia has been used in combination with radiation therapy and/or chemotherapy and is considered to be effective for certain type of tumors (3). Since 1985, we have performed triodality treatment with hyperthermia, chemotherapy and radiotherapy (thermo-chemo-radiotherapy: TCRT) for advanced gallbladder carcinoma (4). The aim of this report is to assess the value of TCRT for advanced gallbladder carcinoma in comparison with other treatment modalities.

METHODOLOGY

Patients

We experienced 357 patients with gallbladder carcinoma in Tokyo Metropolitan Komagome Hospital between 1976 and 2001. According to the pTNM system proposed by the American Joint Committee on Cancer (AJCC) (5), 270 cases were advanced gallbladder carcinomas histologically or roentographically confirmed as Stage IV tumors. Stage IV gallbladder carcinoma is defined as tumor extending more than 2cm into liver and/or into two or more adjacent organs (T4), or with metastasis in peripancreatic, periduodenal, periportal, celiac and/or superior mesenteric lymph nodes (N2), or with distant metastasis (M1). Roentographic diagnosis was based on the results of more than three imaging diagnostic techniques: computed tomography, ultrasonography, magnetic resonance cholangiopancreatography, angiography, percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography. Thus, 270 patients were analyzed in this study.

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TABLE 1 Patient Characteristics and pTNM Staging in Each Group

Group	Treatment regimens	No. of patients	Male/ Female	Age (mean SD)	T4N0,1M01	T4N2M0	T4AnyNM1
1	Thermo-chemo-radiotherapy	30	9/21	63.4 8.8	16	6	8
2	R0-resection	19	6/13	65.3 8.6	19	0	0
3	R1,2-resection	39*	12/27	67.7 9.1	13	15	11
4	Chemo- and/or radiotherapy	57	21/36	66.2 9.9	18	12	27
5	Supportive therapy	125	45/80	72.2 10.1	28	30	67
	Total	270	93/177	68.5 9.5	94	63	113

39*: including 13 patients who also underwent intraoperative therapy.

According to treatments received, the 270 patients were divided into five groups as follows: group 1 consisting of 30 patients with nonresectable tumors treated with TCRT, group 2 consisting of 19 patients underwent R0-resection without post-residual tumor microscopically, group 3 consisting of 39 patients underwent R-1,2 resection with post-residual tumor microscopically or macroscopically, group 4 consisting of 57 patients treated with chemo- and/or radiotherapy, group 5 consisting of 125 patients with only supportive therapy. Patient characteristics and T, N, and M categories of each group are summarized in **Table 1.**

Thermo-Chemo-Radiotherapy (TCRT)

The heating equipment was RF-capacitive heating device, Thermotron RF-8 [Yamamoto Vinita company, Osaka, Japan (6)]. The patient lay in the prone position. The target was sandwiched with upper and lower electrodes, and an 8-MHz RF wave was applied. We administered heat to the patient for 40 minutes after the intratumor temperature had risen to 42°C. Intratumor temperature was measured using a needle thermosensor every time. The thermosensor was inserted beside or into the tumor from the skin surface through an 18-G angiocatheter under the aid of ultrasonography. The chemotherapeutic agents employed were cisplatinum (CDDP, 50mg/m^2) in combination with 5-fluorouracil (5-Fu, 800mg/m^2) or methotolexate (MTX, 30mg/m^2) in combination with 5-Fu (800mg/m^2). Hyperthermia and chemotherapeutic agents were administered simultaneously once weekly immediately following radiotherapy at 2 Gy. Usually it started within 15 min after the irradiation (**Figure 1**). Number of heat treatments ranged from 2 to 11 times (mean 4.5). Three cases were retreated.

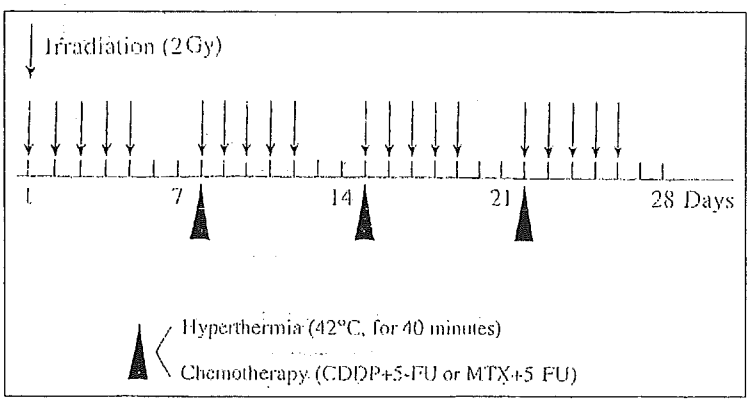

FIGURE 1 Schedule of thermo-chemo-radiotherapy.

Surgical Procedures, Intraoperative Radiation Therapy (IORT), External Beam Radiation Therapy (EBRT), and Chemotherapy

Combined resection of the involved organs such as liver, bile duct, pancreas, duodenum, or colon (31 cases), hepatic resection (39 cases), pancreatic duodenectomy (11 cases), partial resection of transverse colon (14 cases) was performed as far as anatomically possible.

Immediately after tumor removal, a high energy electron beam from a betatron was applied to the resected portions (intraoperative radiation therapy: IORT) was administered to 13 patients whose tumors had spread to the hepatoduodenal ligament or hepatic hilus in attempt to suppress the development of local recurrence (Group 3). The dose of IORT ranged from 18 to 20 Gy with energies of 8 to 12 million electron volts.

External beam radiation therapy (EBRT) was administered five times per week at a dose of 2 Gy per fraction. Total radiation dose ranged from 30 to 60 Gy. EBRT other than TCRT was performed for 13 patients with nonresected tumors.

Chemotherapy not combined with hyperthermia was performed by MTX, CDDP, 5-Fu, mitomycin C, or adriamycin for 49 patients with nonresected tumors.

Response and Toxicity Criteria

The effectiveness of TCRT on nonresectable tumors was evaluated about tumor regression by follow-up CT, and resolution of biliary obstruction by cholangiographies. Tumor regression was graded as complete regression (CR: more than 80% tumor volume reduction), partial regression (PR: more than 50% and less than 80% regression), and no change (NC). Response of stenotic or obstructed bile duct was graded as CR: complete resolution of the bile duct, PR: partial resolution of the bile duct, and NC.

We examined histologically the state of the gallbladder and bile duct, and hematogenous, lymphogenous metastases at autopsy in 11 patients with advanced gallbladder carcinoma treated with TCRT. Modes of hematogenous and lymphogenous metastases were evaluated by high and moderate degree according to the criteria reported before (7).

Side effects were evaluated and graded according

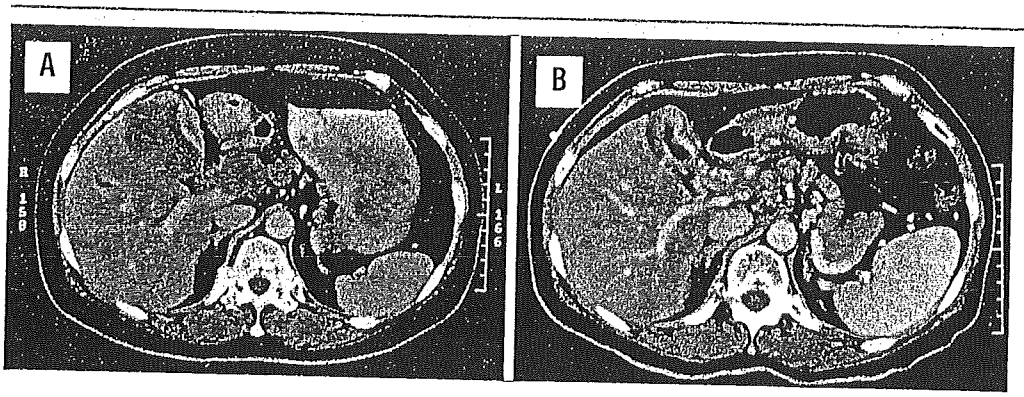

FIGURE 2
CT scan of Case 4. A large gallbladder carcinoma with thickening of the gallbladder wall (A) had almost completely disappeared after TCRT (B).

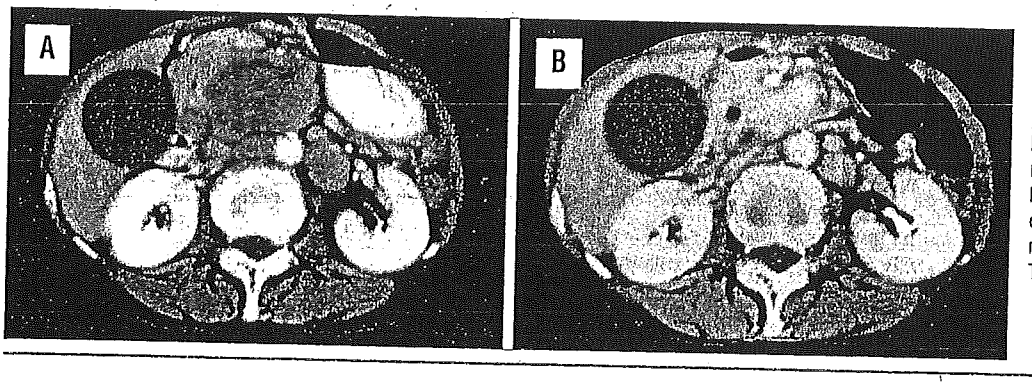

FIGURE 3
CT scan of Case 2. A large peripancreatic lymph node metastasis (A) had completely disappeared four months after TCRT (B).

to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (8).

Statistical Analysis

Life table survival probabilities were calculated using the Kaplan-Meier method. The generalized Wilcoxon test was used to assess the difference in survival rates. A p-value of less than 0.01 was considered statistically significant.

RESULTS

Effectiveness of TCRT

In respect to tumor regression by TCRT, there were 5 CR, 14 PR, and 11 NC. CR rate and CR+PR rate was 17% and 63%. Marked reduction of the gallbladder tumor or lymph node metastasis was observed in some cases after TCRT **(Figures 2 and 3)**.

As for resolution of the bile duct, there were 6 CR, 9 PR, and 5 NC in 20 patients with obstructed or markedly stenotic bile duct. CR rate and response rate was 30% and 75%. In four patients with resolution of the obstructed bile duct, percutaneous transhepatic cholangiodrain (PTCD) could be removed **(Figure 4)**. However, as the four patients developed obstructive jaundice again due to disease progression, we placed self-expandable metallic stent after TCRT into the patency-restored bile duct for prevention of restenosis and the partially resolved bile duct for improvement of patients' quality of life **(Table 2)**.

Long-term Survival Results

Three patients of group 2 survived for more than three years. No patient of group 3, 4 and 5 survived for more than two years, but one patient of group 1 survived for 33 months. Mean survival months (mean±SD) and the 1-year survival rates for patients of groups 1-5 were 9.5±6.3 - 33%, 24.7±26.8 - 79%, 8.4±4.9 - 21%, 5.7±4.2 - 11%, and 3.4±3.5 - 3%, respectively. The survival rate was best in group 2 ($p<0.01$). A significant improvement of long-term survival was exhibited in group 1 and 3 compared to group 4 and 5 ($p<0.01$). The difference of survival rate between group 1 and 3 was not significant **(Figure 5)**.

Histological Findings at Autopsy in Patients Treated with TCRT

In almost all cases, marked hyalinization or fibrosis with necrosis replaced extensively gallbladder tumor and wall, in which suppressed cohesiveness of

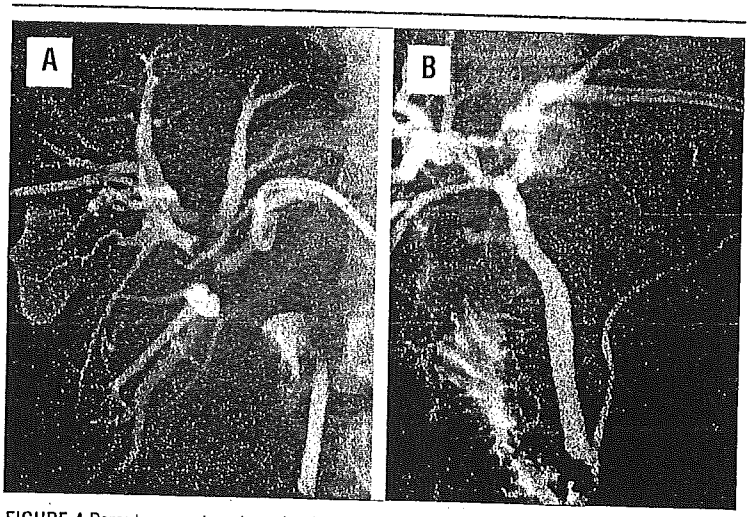

FIGURE 4 Percutaneous transhepatic cholangiography of Case 3. Complete obstruction of the upper bile duct (A) had completely resolved after TCRT (B).

TABLE 2 Results of Thermo-Chemo-Radiotherapy for Advanced Gallbladder Carcinoma

Case	Age	Sex	Stage factors	Tumor regression	Resolution of bile duct	Biliary drainage	Heat sessions	Chemotherapy regimen	Dose of RT (Gy)	Survival months
1	66	f	T4N2	CR	NC	PTCD	x6, x1	MTX, 5-Fu	54	15.5
2	60	f	T4N2	CR	no stenosis	None	x5, x6	MTX, CDDP, 5-Fu	50, 24	33
3	52	f	T4	CR	CR	Withdrawal of PTCD	x6	CDDP, 5-Fu	56	10
4	57	f	T4	CR	CR	PTCD → metallic stent	x5	MTX, 5-Fu	40	5.5
5	62	m	T4M1	CR	no stenosis	None	x5	MTX, 5-Fu	54	10
6	57	m	T4	PR	CR	PTCD	x5, x3	CDDP, 5-Fu	46	21
7	48	f	T4M1	PR	PR	PTCD → metallic stent	x2	CDDP, VP16	40	16
8	64	f	T4	PR	no stenosis	None	x4	MTX, 5-Fu	40	14
9	41	f	T4M1	PR	PR	Withdrawal of PTCD	x3	MTX, 5-Fu	50	13
10	69	f	T4M1	PR	CR	Withdrawal of PTCD	x5	MTX, 5-Fu	50	13
11	83	f	T4	PR	CR	Withdrawal of PTCD	x4	MTX, 5-Fu	50	12.5
12	69	m	T4N2	PR	no stenosis	None	x5	MTX, 5-Fu	50	10.5
13	62	f	T4N2	PR	no stenosis	None	x6	MTX, 5-Fu	54	7
14	65	f	T4	PR	no stenosis	None	x3	CDDP, 5-Fu	50	8 alive
15	70	m	T4	PR	PR	PTCD→ metallic stent	x4	MTX, 5-Fu	56	6.5
16	72	m	T4M1	PR	PR	None	x5	CDDP, 5-Fu	60	5.5
17	72	m	T4	PR	NC	PTCD	x4	CDDP, 5-Fu	46	5
18	73	m	T4N2	PR	no stenosis	None	x6	CDDP, 5-Fu	50	4.5
19	72	f	T4M1	PR	no stenosis	None	x6	MTX, 5-Fu	50	3
20	68	f	T4	NC	CR	PTCD → metallic stent	x4	MTX, 5-Fu	52	5
21	59	f	T4	NC	PR	PTCD → metallic stent	x3	CDDP, 5-Fu	50	13.5
22	72	f	T4N2	NC	PR	PTCD → metallic stent	x2	MTX, 5-Fu	42	12
23	65	m	T4	NC	PR	PTCD	x2	MTX, 5-Fu	50	8.5
24	53	f	T4	NC	PR	PTCD	x4	CDDP, 5-Fu	38	6.5
25	55	f	T4	NC	PR	PTCD → metallic stent	x3	CDDP, 5-Fu	38	6
26	69	f	T4	NC	no stenosis	None	x3	CDDP, 5-Fu	32	4
27	64	m	T4M1	NC	no stenosis	None	x3	MTX, 5-Fu	30	2.5
28	57	f	T4M1	NC	NC	PTCD	x4	MTX, 5-Fu	50	8.5
29	72	f	T4	NC	NC	PTCD	x4	MTX, 5-Fu	32	8
30	57	f	T4M1	NC	NC	PTCD	x4	MTX, 5-Fu	50	3

RT: radiotherapy; CR: complete response; PR: partial response; NC: no change; PTCD: percutaneous transhepatic cholangiodrainage.

carcinoma cells and degenerative cells were sparsely observed. Carcinoma cells were also detected peripherally. Common bile duct of six cases was not completely obstructed, though it was partly obstructed with debris or necrotic mass. Frequency and degree of hematogenous or lymphogenous metastases were not different from other cases **(Table 3)**.

Complication of TCRT

Treatment complications by TCRT were nausea and vomiting (Grade 1-2, 16 cases), gastritis (Grade 2, 7 cases), leukocytopenia (Grade 2, 4 cases; Grade 3, 2 cases; Grade 4, 1 case), thrombocytopenia (Grade 2, 1 case; Grade 3, 1 case), gastric or duodenal ulcer (Grade 2, 2 cases), fistula due to tumor necrosis (2 cases), and hemobilia from ruptured pseudoaneurysm of the hepatic artery (1 case). These complications were successfully treated conservatively.

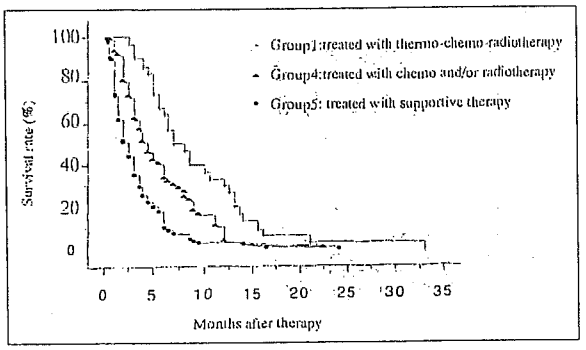

FIGURE 5 Comparison of survival (Kaplan-Meier) according to treatment regimen. There was a significant difference in the survival rate between group 1 and group 4,5 ($p<0.01$).

DISCUSSION

Gallbladder carcinoma carries a poor prognosis, with the only chance for cure lying in early detection and complete surgical resection. The 5-year survival rate following surgery for gallbladder carcinoma has been reported to be between 5 and 13% in the literature (9,10). Such distressing results are due partly to a low resectability rate and late diagnosis but also to certain limitations in the radical removal of the tumors. Therefore, the postoperative recurrence rate is high. Clinical benefit of radical resection for advanced gallbladder carcinoma is still controversial. For advanced gallbladder carcinoma, we have performed TCRT. We have also performed combined resection of the alimentary tract with or without the liver, with adjuvant IORT in some cases, chemotherapy and/or radiotherapy, and supportive therapy for

TABLE 3 Pathological Findings at Autopsy in Patients Treated with Thermo-Chemo-Radiotherapy

		Change of gallbladder wall and tumor				Metastases		
Case	Histology	Necrosis	Hyalinization or fibrosis	Scattered degenerative tumor cells	Bile duct	Liver	Lung	Lymph node
2	well diff. adenoca.	+	++	++	stenosis	++	+	++
6	poorly diff. adenoca.	+	++	++	obstructed	+	-	+
7	poorly diff. adenoca.	+	++	+	stenosis	++	-	++
8	adenosquamous ca.	+	++	+	obstructed	-	-	-
11	well diff. adenoca.	+	+	+	obstructed	+	+	-
15	well diff. adenoca.	+	++	+	stenosis	+	+	+
18	pleomorphic ca.	++	+	+	open	+	+	-
20	well diff. adenoca.	+	++	+	stenosis	+	+	+
21	well diff. adenoca.	++	++	++	stenosis	+	-	-
22	well diff. adenoca.	+	+	+	obstructed	+	+	+
28	well diff. adenoca.	++	++	+	obstructed	+	+	++

well diff. adenoca.: well differentiated adenocarcinoma; poorly diff. adenoca.: poorly differentiated adenocarcinoma; adenosquamous ca.: adenosquamous carcinoma; pleomorphic ca.: pleomorphic carcinoma.

these tumors (4). We analyzed the effectiveness of TCRT for Stage IV gallbladder carcinoma compared with other treatment regimens.

R0-resection was the most beneficial for prolonging survival. However, despite aggressive tumor removal with adjuvant IORT, there was no significant difference in the survival rate between patients treated with R1,2-resection and TCRT.

Most reasons for unresectability for cure in cases without distant metastases are due to the involvement of the hepatoduodenal ligament. Deeply invaded tumors, especially those located in the neck or body of the gallbladder, are apt to spread to the bile duct or the connective tissues in the hepatoduodenal ligament, with encasement of major vessels, or both. Moreover, tumor cells that spread to the ligament often cannot be cleared away completely, even when dissection of the tissue is performed. In nonresected cases, tumor spread to the hepatoduodenal ligament also frequently induces the development of obstructive jaundice which cannot be controlled, resulting in early death from cholangitis. One of the desired strategies for advanced gallbladder carcinoma appears to be control of this involvement of the hepatoduodenal ligament.

Effectiveness of TCRT on nonresctable tumors was surprising. In respect to tumor regression, there were 5 CR cases and 14 PR cases. At autopsy, marked hyalinization or fibrosis with necrosis replaced the gallbladder wall or tumor in almost all cases. Additionally, we observed that biliary obstruction resolved completely in 6, and partially in 9 of 20 patients with obstructive jaundice. TCRT was effective for management of involved hepatoduodenal ligament. In 11 patients, PTCD was able to be removed. Moreover, placement of self-expandable metallic stent into the patency-restored bile duct after TCRT was useful for keeping the longer patent period of the duct.

First of all, we consider why it is effective to combine radiation therapy on chemotherapy with hyperthermia. When the target lesion is heated up to around 42°C, the cancer killing effect of radiation or anticancer drug is enhanced. This fact is well documented by many reports on biological research (11-14). Furthermore, research in the fields of molecular biology and genetics is being conducted actively to clarify the mode of action of hyperthermia (15,16).

There are also many clinical studies that reveal effectiveness of combination treatment of radiation therapy and hyperthermia. In the meantime, European and American researchers are applying microwave therapy to superficial tumors (17) and conducting phase III study to clarify the combined use of hyperthermia (18,19). The effectiveness of thermoradiotherapy for deep-seated tumors has been revealed by prospective randomized studies (16,20). In Japan, the clinical research on hyperthermia is more active than in other countries (21). Especially, stream is RF-capacitive heating for deep-seated tumors. Effective deep heating of chest and upper abdomen with less side effects can be achieved only by RF-capacitive heating equipment (21).

The treatment protocol of TCRT was established and its effectiveness was evidenced by a series of research reports published by Sugimachi and his colleagues. They treated esophageal carcinoma with combination of radiotherapy and chemotherapy and additionally with 6 sessions of intracelial heating. They demonstrated significant improvement in the clinical effectiveness and 5-year survival ratio (22). Furthermore, they applied chemoradiotherapy and TCRT in a randomized control study before operation of esophageal carcinoma. Their phase III study revealed that clinical and histopathological effects were superior in TCRT to chemoradiotherapy (23).

This study established the treatment protocol of TCRT for advanced gallbladder carcinoma, comparing it with four other treatment modalities, and clarifying its effectiveness. We prefer TCRT for patients whose tumors have invaded the hepatoduodenal ligament in place of an aggressive surgical approach.

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Original article

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Phase I–II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer

Y. Ohe[1]*, S. Negoro[2], K. Matsui[3], K. Nakagawa[4], T. Sugiura[5], Y. Takada[6], Y. Nishiwaki[7], S. Yokota[8], M. Kawahara[9], N. Saijo[7], M. Fukuoka[4] & Y. Ariyoshi[10]
On behalf of the Amrubicin SCLC Study Group

[1]*Department of Internal Medicine, National Cancer Center Hospital, Tokyo;* [2]*Department of Clinical Oncology, Osaka City General Hospital, Osaka;* [3]*Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Osaka;* [4]*Department of Medical Oncology, Kinki University School of Medicine, Osakasayama, Osaka;* [5]*Department of Internal Medicine, Aichi Cancer Center Hospital, Nagoya, Aichi,* [6]*Department of Radiology, Hyogo Medical Center for Adults, Akashi, Hyogo;* [7]*Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba;* [8]*Department of Internal Medicine, National Hospital Organization Toneyama National Hospital, Toyonaka, Osaka;* [9]*Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Osaka;* [10]*Aichi Prefectural Hospital, Okazaki, Aichi, Japan*

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Background: Amrubicin, a totally synthetic 9-amino-anthracycline, demonstrated excellent single-agent activity for extensive-stage small-cell lung cancer (ED-SCLC). The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy with amrubicin and cisplatin, and to assess the efficacy and safety at their recommended doses (RD).

Patients and methods: Eligibility criteria were patients having histologically or cytologically proven measurable ED-SCLC, no previous systemic therapy, an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function. Amrubicin was administered on days 1–3 and cisplatin on day 1, every 3 weeks.

Results: Four patients were enrolled at dose level 1 (amrubicin 40 mg/m^2/day and cisplatin 60 mg/m^2) and three patients at level 2 (amrubicin 45 mg/m^2/day and cisplatin 60 mg/m^2). Consequently, the MTD and RD were determined to be at level 2 and level 1, respectively. The response rate at the RD was 87.8% (36/41). The median survival time (MST) was 13.6 months and the 1-year survival rate was 56.1%. Grade 3/4 neutropenia and leukopenia occurred in 95.1% and 65.9% of patients, respectively.

Conclusions: The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC.

Key words: anthracycline, cisplatin, phase I–II, small-cell lung cancer

Introduction

Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumors, and the outcome of SCLC patients is slowly but surely improving. Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 26% 5-year survival rate in limited-stage (LD) patients [1]. Despite the high response rate to combination chemotherapy, however, local and distant failure is very common, especially in extensive-stage (ED) patients. Moreover, resistance to chemotherapeutic agents develops easily after failure of initial treatment. Thus, long-term survivors are still very rare among patients with ED-SCLC. To improve the outcome of SCLC patients, several strategies, such as high-dose chemotherapy, dose-intensive chemotherapy, alternating chemotherapy and introduction of new drugs, have been investigated [2–6]. However, only the introduction of new agents has improved the outcome of SCLC patients. Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin alternating cyclophosphamide, doxorubicin and vincristine had been mainly used for SCLC in North America. Recently, a Japanese trial [Japan Clinical Oncology Group (JCOG) 9511] demonstrated the superiority of the combination of irinotecan and cisplatin for ED-SCLC patients over the combination of etoposide and cisplatin [6]. The development of more active chemotherapy, and especially the introduction of effective new drugs, is therefore essential to improve the survival of SCLC patients.

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor [7–14]. It has antitumor activity, and is more potent than doxorubicin against various mouse experimental tumors and human tumor

Correspondence to: Dr Y. Ohe, Department of Internal Medicine, National Cancer Center Hospital 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-7006; E-mail: yohe@ncc.go.jp

xenografts. Amrubicin and its 13-hydroxy metabolite, amrubicinol, inhibit purified human DNA topoisomerase II [11]. Amrubicinol is 10–100 times more cytotoxic than amrubicin [9]. The potent therapeutic activity of amrubicin is caused by the selective distribution of its highly active metabolite, amrubicinol, in tumors [9]. In an experimental animal model, amrubicin did not exhibit any chronic cardiotoxicity potential, and no deleterious effects on doxorubicin-induced cardiotoxicity in dogs was observed [14]. In a phase II study of amrubicin using a schedule of 45 mg/m^2 on days 1–3 every 3 weeks, in 33 previously untreated ED-SCLC patients, an overall response rate of 76% and a complete response (CR) rate of 9% were reported [15]. Moreover, median survival time (MST) was 11.7 months in the single-agent phase II study of amrubicin. Amrubicin is one of the most active new agents for SCLC. Thus, we conducted a phase I/II study of amrubicin plus cisplatin for untreated ED-SCLC, because cisplatin is considered as one of the most important drugs in the treatment of SCLC. The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy of amrubicin with cisplatin, to assess the efficacy and safety for ED-SCLC at their recommended doses (RD), and to examine the pharmacokinetics of the drug combination.

Patients and methods

Patient selection

Patients with histologically and/or cytologically documented SCLC were eligible for this study. Each patient was required to meet the following criteria: extensive-stage disease [16]; no prior therapy for primary lesion; measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; expected survival time >2 months; age 20–74 years; adequate hematological function [white blood cell (WBC) count 4000–12 000/mm^3, neutrophils ≥2000/mm^3, platelets ≥100 000/mm^3, hemoglobin ≥10 g/dl]; adequate hepatic function [total bilirubin within 1.5× the upper limit of normal; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5× the upper limit of normal]; adequate renal function (creatinine within the upper limit of normal); partial pressure of arterial oxygen 60 torr; no abnormality requiring treatment on electrocardiogram; left ventricle ejection fraction >60%; written informed consent. Patients with symptomatic brain metastasis, pleural effusion that required drainage, non-steroidal anti-inflammatory drug or glucocorticoid use for >50 days, pericarditis carcinomatous, active infection, varicella, superior vena cava syndrome, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), gastric and/or duodenal ulcer, severe heart disease, severe renal disease, active concomitant malignancy, symptomatic pneumonitis and/or pulmonary fibrosis and pregnant/nursing women were excluded. This study was approved by the Institutional Review Board at each hospital.

Patient evaluation

Pretreatment evaluation consisted of complete blood cell counts, differential, routine chemistry measurements, progastrin-releasing peptide (ProGRP), neuron-specific enolase, electrocardiogram, echocardiography, chest radiograph, chest and abdominal computed tomography (CT) scan, whole-brain magnetic resonance imaging (MRI) or CT scan, and isotope bone scan. Complete blood cell counts, differential and routine chemistry measurements were performed at least once a week during the chemotherapy.

Treatment schedule

At level 1, chemotherapy consisted of cisplatin 60 mg/m^2 on day 1 and amrubicin 40 mg/m^2 on days 1–3. Amrubicin was administered as an intravenous injection over 5 min and cisplatin was administered as a drip infusion over 60–120 min with adequate hydration. At level 2 the dose of amrubicin was increased to 45 mg/m^2 on days 1–3. Level 3 was planned with cisplatin 80 mg/m^2 on day 1 and amrubicin 45 mg/m^2 on days 1–3. The chemotherapy was repeated every 3 weeks for four to six courses. Intrapatient dose escalation was not allowed. Administration of granulocyte colony-stimulating factor (G-CSF) was permitted prophylactically for patients expected to experience grade 3 neutropenia during the first course. Prophylactic administration of G-CSF was only permitted at second or later courses.

The administrations of both cisplatin and amrubicin were postponed if patients met the following criteria: WBC <3000/mm^3; neutrophils <1500/mm^3; platelets <100 000/mm^3; AST and ALT >5× the upper limit of normal; total bilirubin >1.5× the upper limit of normal; creatinine >1.3× the upper limit of normal; ECOG PS 3 or 4; active infection; grade 2 or worse non-hematological toxicity, except for alopecia, anorexia, nausea, vomiting or fatigue.

The administrations of both cisplatin and amrubicin were withdrawn if patients met the following criteria: tumor regression <15% after first course or <30% after second course; WBC <3000/mm^3; neutrophils <1500/mm^3; platelets <100 000/mm^3; no recovery from grade 3 or 4 non-hematological toxicity at 6 weeks after the start of previous chemotherapy; abnormality of electrocardiogram requiring treatment for more than 6 weeks; left ventricle ejection fraction <48%; treatment delay of >4 weeks.

The dose of amrubicin was decreased 5 mg/m^2/day if patients met the following criteria: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 neutropenia with fever; platelets <20 000/mm^3 during the previous course. The dose of cisplatin was decreased to 75% if creatinine increased to >1.5× the upper limit of normal during the previous course.

The dose-limiting toxicity (DLT) was defined as follows: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 febrile neutropenia; platelets <20 000/mm^3; grade 3 or worse non-hematological toxicity except for nausea, vomiting, anorexia, fatigue, hyponatremia and infection. Initially, three patients were treated at each dose level. If DLT was not observed in any of the three patients, dose escalation was carried out. If DLT was observed in one of three patients, an additional three patients were entered at the same dose level. If DLT was observed in three or more of six patients, or two or three of the initial three patients, we considered that dose to be the MTD. If DLT was observed in one or two of six patients, dose escalation was also carried out. Dose escalation was determined based only on the data from the first course of chemotherapy.

Response and toxicity evaluation

Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) and tumor markers were excluded from the criteria [17]. CR was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks and no new lesions. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesion, taking as reference the baseline sum longest diameter, the required non-progression in non-target lesions and no new lesions for at least 4 weeks. Stable disease (SD) included: regression of target lesions insufficient to meet the criteria for PR, a <20% increase in the sum of the longest diameter of target lesion, taking as reference the smallest sum longest diameters recorded since the treatment started, the required non-progression in non-target lesions and no new lesions for at least 6 weeks. Progressive disease (PD) indicated a >20% increase in the sum of the longest diameters of target lesion, taking as reference the smallest sum longest diameter recorded since the treatment started

and/or unequivocal progression of existing non-target lesions and/or appearance of new lesions. The evaluation of objective tumor response for all patients was performed by an external review committee.

Toxicity grading criteria of the National Cancer Institute Common Toxicity Criteria (version 2.0) was used for evaluation of toxicity.

Statistical analysis

This study was designed to reject response rates of 70% (P0) at a significance level of 0.05 (one-tailed) with a statistical power of 80% to assess the activity of the regimen as a 85% response rate (P1) at the recommended dose. The upper limit of rejection was 29 responses (CR + PR) among 37 evaluable patients. Overall survival was defined as the interval between the first administration of the drugs in this study and death or the last follow-up visit. Median overall survival was estimated using the Kaplan–Meier method [18].

Table 1. Characteristics of treated patients

	Phase I	Phase II	Total
Number of patients	7	37	44
Gender			
Male	5	31	36
Female	2	6	8
Age (years)			
Median	65	64	64.5
Range	54–73	50–74	50–74
ECOG PS			
0	0	5	5
1	7	32	39
2	0	0	0
Stage			
IIIB	0	2	2
IV	7	35	42
Prior therapy			
Yes	0	1	1
No	7	36	43
Serum ALP			
Normal	7	29	36
Elevated	0	7	7
Serum LDH			
Normal	3	14	17
Elevated	4	23	27
Na			
Normal	6	35	41
Decreased	1	2	3
Number of metastases			
0	0	2	2
1	4	27	31
2	3	6	9
3	0	1	1
4 or more	0	1	1

In one patient, serum ALP level could not be measured.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

Pharmacokinetic analysis

Pharmocokinetic analysis was performed in patients entering the phase I section of this study. One milliliter of the blood was taken from the patients before administration of amrubicin, and at 0 min, 15 min, 1, 2, 3, 4, 8 and 24 h after administration on days 1 and 3 in the first course of chemotherapy. Concentrations of amrubicin and its active metabolite, amrubicinol, in plasma and red blood cells were measured as reported elsewhere [9].

Results

Patient characteristics

Between April 2001 and December 2002, 45 patients with ED-SCLC were enrolled and 44 were treated in this study (Table 1). One patient did not receive the protocol treatment because atrial fibrillation was observed just before administration on day 1 of the first course. All treated patients were assessed for response, survival and toxicity. The median age of the treated patients was 64.5 years (range 50–74). There were 36 males and eight females. Five patients had an ECOG PS 0 and 39 patients had PS 1. Only one patient received surgery for brain metastasis as a prior therapy.

MTD and DLT in the phase I study

Four patients were enrolled at dose level 1 (amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1) and three patients at level 2 (amrubicin 45 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1). Toxicities in the phase I study are listed in Table 2. No DLT were observed during the first course of level 1. At level 2, grade 4 neutropenia for ≥4 days and febrile neutropenia occurred in one patient, and febrile neutropenia and grade 3 constipation occurred in another patient. Consequently, the MTD and RD were determined to be level 2 and level 1, respectively.

Pharmacokinetics of amrubicin and its active metabolite, amrubicinol

Pharmacokinetic parameters of amrubicin in plasma were almost identical on days 1 and 3 at the two dose levels (Table 3). No clear dose relationship in the area under the concentration–time curve (AUC) of amrubicin in the plasma was observed. The AUC of amrubicinol in red blood cells tended to increase on day 3 at both doses (Table 4). No clear dose relationship in the AUC of amrubicinol in red blood cells was observed. Combination with cisplatin did not alter the pharmacokinetics of amrubicin and amrubicinol (data not shown).

Treatment received in patients treated at the RD

Forty-one patients were treated at the RD: amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1. Of 41 patients, 32 (78%) patients received more than three

Table 2. Toxicities during the first course in the phase I study

	Level 1 ($n=4$)					Level 2 ($n=3$)				
Amrubicin	40 mg/m^2 days 1–3					45 mg/m^2 days 1–3				
Cisplatin	60 mg/m^2 day 1					60 mg/m^2 day 1				
	Grade (NCI CTC)					Grade (NCI CTC)				
	0	1	2	3	4	0	1	2	3	4
Leukopenia	0	1	1	2	0	0	0	1	1	1
Neutropenia	0	0	0	2	2	0	0	0	0	3
Febrile neutropenia	4	–	–	0	0	1	–	–	2	0
Hemoglobin	1	1	2	0	0	2	1	0	0	0
Thrombocytopenia	1	2	0	1	0	0	2	0	1	0
Stomatitis	3	0	1	0	0	3	0	0	0	0
Nausea	1	1	2	0	–	1	1	0	1	–
Constipation	3	0	1	0	0	1	0	1	1	0
Hyponatremia	2	1	0	0	1	1	2	0	0	0
Hypocalcemia	3	0	1	0	0	3	0	0	0	0

Dose limiting toxicity at level 2: febrile neutropenia, two patients; grade 4 neutropenia ≥4 days, one patient; grade 3 constipation, one patient.
NCI CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Pharmacokinetics of amrubicin in plasma

Dose	n	Day	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	V_d (l)	CL (l/h)	$AUC_{0-24\,h}$ (ng h/ml)
40 mg/m^2	4	1	0.11 ± 0.04	2.29 ± 0.31	46.6 ± 11.0	13.6 ± 1.8	2995 ± 434
	4	3	0.08 ± 0.01	2.89 ± 0.34	50.0 ± 10.6	11.6 ± 1.9	3511 ± 514
45 mg/m^2	3	1	0.13 ± 0.05	2.39 ± 0.34	56.3 ± 10.6	14.9 ± 1.8	3052 ± 402
	3	3	0.09 ± 0.03	2.27 ± 0.18	51.9 ± 3.7	14.2 ± 2.3	3217 ± 479

$T_{1/2\alpha}$, half-life at distribution phase; $T_{1/2\beta}$, half-life at elimination phase; V_d, volume of distribution; CL, clearance; AUC, area under the concentration–time curve.

courses of chemotherapy, and 10 (31%) of these 32 patients needed dose reduction of amrubicin at the fourth course (Table 5). Of 41 patients, 22 (54%) patients completed four courses of chemotherapy without dose modification. The main cause of dose reduction was myelosuppression, especially leukopenia and neutropenia.

Objective tumor response and overall survival

The objective tumor responses are given in Table 6. Four CRs and 32 PRs occurred, for an objective response rate of 87.8% [95% confidence interval (CI) 73.8% to 95.9%] in 41 patients treated at the RD. The objective response rate for all 44 patients was 88.6% (95% CI 75.4% to 96.2%). The overall survival times of the 41 patients treated at the RD are shown in Figure 1. The MST of the 41 patients was 13.6 months (95% CI 11.1–16.6), with a median follow-up time for eight censored patients of 16.4 months (95% CI 14.2–18.8). The 1- and 2-year survival rates were 56.1% and 17.6%, respectively. The MST of all 44 patients was 13.8 months (95% CI 11.1–16.6). The 1- and 2-year survival rates of all 44 patients were 56.8% and 21.4%, respectively.

Table 4. Pharmacokinetics of amrubicinol in red blood cells

Dose	n	Day	$T_{1/2}$ (h)	$AUC_{0-24\,h}$ (ng·h/ml)
40 mg/m^2	4	1	21.0 ± 3.1	1412 ± 314
	4	3	20.7 ± 4.8	2159 ± 622
45 mg/m^2	3	1	19.6 ± 6.1	1098 ± 277
	3	3	18.1 ± 5.7	2027 ± 332

$T_{1/2}$, elimination half-life; AUC, area under the concentration–time curve.

Table 5. Treatment received in patients treated at the recommended dose

Cycle	n	Amrubicin (mg/m^2)			Cisplatin (mg/m^2)	
		40	35	30	60	45
1	41	41			41	
2	36	30	6		36	
3	33	26	5	2	33	
4	32	22	8	2	32	
5	18	9	5	4	18	
6	13	6	3	4	12	1

Table 6. Response rates

	n	CR	PR	SD	PD	NE	Response rate (%) (95% CI)
All	44	4	35	3	0	2	88.6 (75.4–96.2)
Treated at RD	41	4	32	3	0	2	87.8 (73.8–95.9)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; 95% CI, 95% confidence interval; RD, recommended dose.

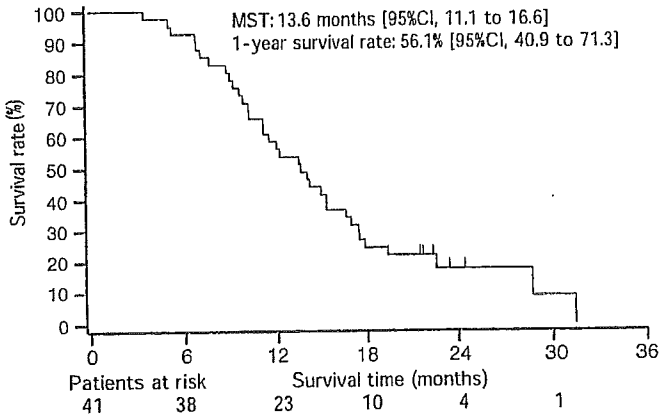

Figure 1. Overall survival of patients with extensive-stage small-cell lung cancer who were treated with amrubicin and cisplatin at the recommended dose. MST, median survival time; 95% CI, 95% confidence interval.

Toxicity in patients treated at the RD

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 7. Hematological toxicity, especially leukopenia and neutropenia, was common and relatively severe. Grade 3 or worse leukopenia and neutropenia occurred in 65.9% and 95.1% of patients, respectively. Febrile neutropenia was observed in two patients at level 2. Grade 3 or worse anemia and thrombocytopenia occurred in 53.7% and 24.4% of patients, respectively. Four patients received platelet transfusions. Common non-hematological toxicities were gastrointestinal toxicity, such as anorexia, nausea, vomiting, constipation, diarrhea and stomatitis. Gastric ulcers developed in three patients. Hepatic and renal toxicity were not common in this study. Grade 3 or worse hyponatremia and hypokalemia occurred in 22% and 9.8% of patients, respectively. One patient developed myocardial infarction; however, cardiac toxicity was not common. No treatment-related deaths were observed.

Discussion

Doxorubicin and epirubicin are classified as active agents for SCLC, for which single-agent activity is a >20% response rate [19]. Doxorubicin has been used as a constituent of combination therapy for SCLC in the CAV (cyclophospamide, doxorubicin and vincristine) and CAP (cyclophosphamide, doxorubicin and cisplatin) regimens. Epirubicin has shown

Table 7. Toxicity in patients treated at the recommended dose ($n=41$)

	Grade (NCI CTC)					Grade 3/4 (%)
	0	1	2	3	4	
Leukopenia	1	0	13	20	7	65.9
Neutropenia	0	1	1	7	32	95.1
Febrile neutropenia	41	–	–	0	0	0.0
Hemoglobin	1	8	10	17	5	53.7
Thrombocytopenia	9	14	8	10	0	24.4
Stomatitis	22	13	5	1	0	2.4
Anorexia	1	14	13	13	0	31.7
Nausea	3	15	14	9	0	22.0
Vomiting	20	8	11	2	0	4.9
Constipation	24	1	13	3	0	7.3
Diarrhea	26	12	1	2	0	4.9
Gastric ulcer	38	0	1	2	0	4.9
Bilirubin	24	12	4	1	0	2.4
Hyponatremia	18	14	–	7	2	22.0
Hypokalemia	31	6	–	4	0	9.8
Hyperkalemia	33	3	4	1	0	2.4
Hypocalcemia	31	5	4	0	1	2.4

NCI CTC, National Cancer Institute Common Toxicity Criteria.

50% and 48% response rates in two clinical studies in 41 and 80 previously untreated patients, respectively, with ED-SCLC [20, 21]. However, currently, combination modalities containing doxorubicin or epirubicin are not being used in the therapy of SCLC, in preference to combination therapy with cisplatin and etoposide. Since amrubicin has shown excellent single-agent activity [15], it can be expected to be superior to other anthracyclines in the treatment of SCLC. Additionally, the present results of combination therapy with cisplatin support the view that amrubicin may be a promising agent that overcomes the therapeutic plateau of SCLC.

Amrubicin is one of the most promising new agents for the treatment of SCLC. In a previous phase II study of amrubicin 45 mg/m^2 on days 1–3 every 3 weeks as a monotherapy for chemonaive ED-SCLC, a 76% overall response rate and 11.7 month MST were observed [15]. The overall response rate and MST were comparable to those achieved with standard combination chemotherapy, such as etoposide plus cisplatin [5, 6]. Moreover, only a few patients treated in the phase II study received salvage chemotherapy consisting of cisplatin and etoposide [15]. The major toxicity of amrubicin as a monotherapy was hematological toxicity: grade 4 leukopenia and neutropenia were seen in 12.1% and 39.4% of patients, respectively, and thrombocytopenia and anemia of grade 3 or worse in 21.2%. Hepatic, renal and cardiac toxicities with amrubicin were not common. Cisplatin is a key drug for the treatment of SCLC and its hematological toxicity, such as leukopenia and neutropenia, is not severe. Thus, we conducted a phase I–II study of amrubicin and cisplatin treatment for chemonaive ED-SCLC to determine the MTD of this combination therapy, to

assess the efficacy and safety of the drugs delivered at their RD in chemonaive ED-SCLC, and to examine pharmacokinetics.

The topoisomerase I inhibitor, irinotecan, is also very effective for SCLC [6]. Combinations of topoisomerase I and topoisomerase II inhibitors, such as irinotecan plus etoposide, have been reported as active combination chemotherapy for SCLC [22]. Thus, combination of irinotecan and amrubicin is another candidate for new combination chemotherapy for SCLC. A phase I study of irinotecan and amrubicin for chemonaive non-SCLC was performed in National Cancer Center Hospital (unpublished data). However, the MTD was less than irinotecan 60 mg/m^2 on days 1 and 8 and amrubicin 35 mg/m^2 on days 2–4, due to relatively severe myelotoxicity. We considered that amrubicin <35 mg/m^2 on days 2–4 with irinotecan 60 mg/m^2 on days 1 and 8 was insufficient to treat SCLC.

In this study, we determined the RD to be amrubicin 40 mg/m^2 on days 1–3 and cisplatin 60 mg/m^2 on day 1 every 3 weeks, and 41 patients were treated at the RD. Main toxicities of this combination chemotherapy were myelosuppression, especially leukopenia and neutropenia, and gastrointestinal toxicities including anorexia, nausea, vomiting, constipation, diarrhea, stomatitis and gastric ulcer. Of 41 patients, 32 (78%) patients received four or more courses of chemotherapy, and 22 (54%) patients completed four courses of chemotherapy without dose modification. One patient developed myocardial infarction; however, other cardiac toxicity, including decrease in left ventricle ejection fraction, was not observed in up to six courses of chemotherapy. The total dose of amrubicin was 720 mg/m^2. Grade 3 or 4 hyponatremia occurred in nine (22%) patients; however, most of the patients were asymptomatic. No unexpected toxicities and no treatment-related deaths were observed in this study. Toxicities observed in this study were manageable.

Four CRs and 32 PRs occurred, for an objective response rate of 87.8% (95% CI 73.8% to 95.9%) in 41 patients treated at the RD. In most patients, ProGRP levels changed in parallel with tumor responses. The MST of the 41 patients was 13.6 months, and the 1-year survival rate was 56.1%. These results were better than recently reported results for irinotecan and cisplatin in chemonaive ED-SCLC: an objective response rate of 84% and MST of 12.8 months [6]. The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC. A possible reason for the better results is overselection of patients, because we used unusual exclusion criteria such as non-steroidal anti-inflammatory drug or adrenal cortical steroid use for >50 days, and gastric and/or duodenal ulcer. However, in a phase II study, this kind of bias is not uncommon.

Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin, alternating with cyclophosphamide, doxorubicin and vincristine, had been considered as standard chemotherapy for SCLC in North America and Japan. A Japanese phase III trial (JCOG 9511) demonstrated that treatment with four cycles of irinotecan plus cisplatin every 4 weeks yielded a highly significant improvement in survival in ED-SCLC patients over standard etoposide plus cisplatin, with less myelosuppression [6]. Based on the results of the JCOG 9511 trial, irinotecan plus cisplatin is considered to be the reference chemotherapy arm for ED-SCLC in future trials in Japan [23]. The JCOG are preparing a phase III clinical trial of amrubicin and cisplatin for previously untreated ED-SCLC to compare combination therapy of irinotecan with cisplatin.

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CLINICAL INVESTIGATION **Lung**

A PHASE II STUDY OF HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) AFTER INDUCTION CISPLATIN (CDDP) AND VINORELBINE (VNR) FOR STAGE III NON-SMALL-CELL LUNG CANCER (NSCLC)

SATOSHI ISHIKURA, M.D.,* YUICHIRO OHE, M.D.,† KEIJI NIHEI, M.D.,* KAORU KUBOTA, M.D.,† RYUTARO KAKINUMA, M.D.,† HIRONOBU OHMATSU, M.D.,† KOICHI GOTO, M.D.,† SEIJI NIHO, M.D.,† YUTAKA NISHIWAKI, M.D.,† AND TAKASHI OGINO, M.D.*

*Divisions of Radiation Oncology and †Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Purpose: The purpose was to assess the feasibility and efficacy of hyperfractionated accelerated radiotherapy (HART) after induction chemotherapy for Stage III non-small-cell lung cancer.

Methods and Materials: Treatment consisted of 2 cycles of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 25 mg/m^2 on Days 1 and 8 every 3 weeks followed by HART, 3 times a day (1.5, 1.8, 1.5 Gy, 4-h interval) for a total dose of 57.6 Gy.

Results: Thirty patients were eligible. Their median age was 64 years (range, 46–73 years), 24 were male, 6 were female, 8 had performance status (PS) 0, 22 had PS 1, 9 had Stage IIIA, and 21 had Stage IIIB. All but 1 patient completed the treatment. Common grade ≥3 toxicities during the treatment included neutropenia, 25; infection, 5; esophagitis, 5; and radiation pneumonitis, 3. The overall response rate was 83%. The median survival was 24 months (95% confidence interval [CI], 13–34 months), and the 2-year overall survival was 50% (95% CI, 32–68%). The median progression-free survival was 10 months (95% CI, 8–20 months).

Conclusion: Hyperfractionated accelerated radiotherapy after induction of cisplatin and vinorelbine was feasible and promising. Future investigation employing dose-intensified radiotherapy in combination with chemotherapy is needed. © 2005 Elsevier Inc.

Non–small-cell lung cancer, Hyperfractionated accelerated radiation therapy, Chemoradiotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death for men and the second for women in Japan. During 2001, approximately 55,000 patients died of lung and bronchus cancer (1). Surgery is the standard of care for patients with Stage I–II non–small-cell lung cancer (NSCLC), but a combination of chemotherapy and thoracic radiotherapy with or without surgery is indicated for the majority of patients with Stage III disease. Cisplatin (CDDP) based chemotherapy with conventional radiotherapy improved survival compared to conventional radiotherapy alone (2–6) and was the standard of care in the 1990s. Recently, concurrent chemoradiotherapy has been revealed to be superior to sequential chemoradiotherapy (7, 8), but it is difficult to give full-dose chemotherapy using newer cytotoxic agents concurrently with radiotherapy, and the optimal combination has not yet been clarified. In the meantime, continuous hyperfractionated accelerated radiotherapy (CHART) with 3 daily fractions to intensify the local effect of radiotherapy has been found to be superior to conventional radiotherapy (9). The survival benefit of CHART was encouraging, but the protocol including treatments on weekends and 6-h intervals between fractions had some difficulties in practicality. Mehta *et al.* introduced hyperfractionated accelerated radiotherapy (HART) (modified CHART) with 3 daily fractions and 4-h interfraction intervals with weekend breaks and also showed promising results similar to those using sequential chemoradiotherapy (10). After these results, we started a Phase II trial to evaluate the feasibility and efficacy of induction chemotherapy with HART for patients with Stage III NSCLC.

METHODS AND MATERIALS

Eligibility criteria

Eligibility criteria included previously untreated patients with pathologically proven NSCLC with clinical tumor-node-metastasis system Stage III, and pathologic N2 was also required for Stage

Reprint requests to: Satoshi Ishikura, M.D., Radiation Oncology Division, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan. Tel: (+81) 4-7133-1111; Fax: (+81) 4-7131-4724; E-mail: sishikur@east.ncc.go.jp

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IIIA; age, 20 to 74 years; performance status (PS) (based on Eastern Cooperative Oncology Group [ECOG] scale) 0 to 1; measurable disease; adequate hematologic (WBC count ≥4,000/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥9.5 g/dL), hepatic (AST and ALT level ≤2 times the upper limit of normal and total bilirubin level ≤ the upper limit of normal), and renal (creatinine ≤1.2 mg/dL and creatinine clearance ≥60 mL/min) functions; PaO_2 ≥70 torr; no pleural and pericardial effusion; radiation field encompassed one-half or less of the ipsilateral lung; and no serious comorbidity. All patients signed written informed consent in accordance with our institutional review board.

Pretreatment evaluation included history and physical examination; serum chemistries (lactate dehydrogenase, alkaline phosphatase, AST, ALT, bilirubin, albumin, creatinine, and calcium); chest radiograph; CT scan of the chest; ultrasound of the abdomen; MRI or CT scan of the brain; and bone scintigraphy.

Treatment details

The treatment consisted of 2 cycles of CDDP 80 mg/m^2 on Day 1 and vinorelbine (VNR) 25 mg/m^2 on Days 1 and 8 every 3 weeks followed by HART; 3 times a day with minimal interval of 4 hours for a total dose of 57.6 Gy in 36 fractions over 2.5 weeks.

Radiation therapy was started after the patient recovered from the toxicity of chemotherapy and was delivered with megavoltage equipment. Lung heterogeneity corrections were not used. The first and third fraction of each day consisted of anterior-posterior opposed fields that encompassed the primary tumor, the metastatic lymph nodes, and the regional lymph nodes with a 1.5 to 2-cm margin. The fraction size was 1.5 Gy. Regional nodes excluding the contralateral hilar and supraclavicular nodes were included in these fractions. However, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The second fraction of each day consisted of bilateral oblique fields that encompassed the primary tumor and the metastatic lymph nodes with a 1.5 to 2-cm margin; the fraction size was 1.8 Gy. Attempts were made to design the field of the second fraction to minimize the irradiated volume of the esophagus without compromising the margin around the tumor or spinal cord.

Toxicity assessment

Patients were observed weekly during treatment to monitor toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity was graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

Follow-up evaluation

The following evaluations were performed until disease progression every 2 months for the first year, every 3 months for the second year, and every 6 months thereafter: physical examination, toxicity assessment, and chest radiograph. CT scan of the chest was performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. Restaging at 6 months after the treatment was also performed with ultrasound of the abdomen, MRI or CT scan of the brain, and bone scintigraphy.

Response assessment

Complete response (CR) was defined as complete disappearance of all measurable and assessable lesions for ≥4 weeks, partial response (PR) was defined as a decrease of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions for ≥4 weeks, and progressive disease (PD) was defined as an increase of 25% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions or the appearance of any new lesion. Stable disease was defined as the remainder of evaluable patients without CR, PR, or PD.

Pattern of failure

Patterns of failure were defined as first site of failure. Local/regional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Statistics

A Simon's two-stage optimal design was used for this study with the assumption that a protocol compliance rate of less than 60% would not be feasible, and protocol compliance rate of 80% or greater with α error of 0.10 and β error of 0.10 would warrant further investigation of this regimen. In the first stage, 11 assessable patients were entered. If fewer than 7 patients completed the treatment, accrual would be stopped with the conclusion that the regimen was not feasible for further investigation. If 7 or more patients completed the treatment, an additional 27 patients would be accrued in the second study. According to this design, this study would be determined to be feasible and be proceeded to a multicenter Phase II study if 27 patients completed the treatment. The actuarial median survival time and 2-year survival were estimated by the Kaplan–Meier method (11).

RESULTS

Patient population

Between July 1999 and March 2001, 30 patients were enrolled in the study. The accrual was stopped, because 29 of 30 patients completed the treatment, and conclusions could be drawn at that time. The patients' median age was 64 years (range, 46–73 years), 24 were male, and 6 were female. The patient and tumor characteristics are summarized in Table 1.

Treatment compliance and toxicity

All patients completed 2 cycles of induction chemotherapy. Six of 30 patients required dose modification, and 13 patients had treatment delay. The median time to start of HART from start of chemotherapy was 49 days (range, 41–62 days). Twenty-nine of 30 patients completed HART, and the median overall treatment time of HART was 17 days (range, 16–22 days). In total, 29 of 30 patients (97%; 95% confidence interval [CI], 83–100%) completed this combined treatment.

The toxicity profile of the treatment is shown in Tables 2 and 3. Common Grade 3 or greater acute toxicities were neutropenia, 25 (83%); infection, 5 (17%); esophagitis, 5 (17%); and radiation pneumonitis, 3 (19%). There were 2 cases of treatment-related death due to radiation pneumonitis. As of the date of this analysis, 2 cases with Grade

Table 1. Patient and tumor characteristics

Number of patients	30
Age	
Median	64
Range	46–73
Gender	
Male	24
Female	6
Performance status	
0	8
1	22
Weight loss	
<5%	25
≥5%	5
Tumor and lymph nodes	
T1N2	3
T1N3	1
T2N2	5
T2N3	5
T3N2	1
T4N0	1
T4N1	4
T4N2	9
T4N3	1
Stage	
IIIA	9
IIIB	21
Histology	
Squamous	13
Nonsquamous	17

3 s.c. tissue fibrosis and 1 case with spontaneous rib fracture were observed as late toxicities.

Response and survival

Of 30 patients, 2 achieved CR, and 23 achieved PR with a response rate of 83% (95% CI, 65–94%). Five patients remained in a stable disease state, and there were no PD patients. With a median follow-up period of 40 months for surviving patients, the median survival and the 2-year and 3-year survivals (Fig. 1) were 24 months (95% CI, 13–34 months), 50% (95% CI, 32–68%), and 32% (95% CI, 15–49%), respectively. The median progression-free survival and the 1-year progression-free survival (Fig. 2) were 10 months (95% CI, 8–20 months) and 47% (95% CI, 29–65%), respectively.

Pattern of failure

At the time of this analysis, 22 of 30 patients (73%) showed tumor progression, 2 patients (7%) had died as a result of treatment, and 6 patients (20%) were alive without disease progression. The patterns of first failure were as follows: local/regional only, 13 (43%); local/regional and distant, 4 (13%); distant only, 5 (17%).

DISCUSSION

In the 1970s, treatment of locally advanced NSCLC was by conventional radiotherapy alone. In the 1980s, sequential chemotherapy and conventional radiotherapy were revealed to be superior to conventional radiotherapy alone. In the 1990s, optimal sequences of chemoradiotherapy and radiation fractionation were investigated. The West Japan Lung Cancer Group compared sequential vs. concurrent radiotherapy with induction CDDP, vindesine, and mitomycin (7). In an RTOG 9410 trial, induction CDDP and vinblastine plus sequential standard radiotherapy, CDDP and vinblastine plus concurrent standard radiotherapy, and CDDP and etoposide plus concurrent twice-daily hyperfractionated radiotherapy were compared (8). Both trials showed similar results; concurrent chemoradiotherapy was superior to the sequential approach and achieved 5-year survivals for concurrent and sequential approach of approximately 20% and 10%, respectively. However, twice-daily hyperfractionated radiotherapy, which seemed to be promising in a preceding RTOG 9015 trial (12), failed to show a survival advantage over standard once-daily radiotherapy, and concurrent chemotherapy and once-daily radiotherapy is the standard of care today. Recently, a Czech randomized Phase II trial (13) suggested a similar advantage of the concurrent approach using CDDP and VNR, a newer cytotoxic agent. However, there remains some argument that newer cytotoxic agents cannot be delivered as full-dose chemotherapy with concurrent radiotherapy, and the survival advantage of newer cytotoxic agents over old ones has not yet been demonstrated in Stage III NSCLC patients. The optimal schedule and fractionation of thoracic radiotherapy in combination with chemotherapy also remains to be determined.

Another promising regimen was altered fractionation of radiotherapy such as CHART or HART, 3 times a day with a fraction interval of 4 to 6 hours over 2.5 weeks or less. CHART was developed at Mount Vernon Hospital, United Kingdom, in the 1980s. It was designed to combine both a shortening of the overall treatment time of radiotherapy, which is analogous to the concept of dose intensification of cytotoxic chemotherapy, and a reduction in dose per fraction. The rationale was to overcome accelerated repopulation of the tumor during the course of radiotherapy, which may lead to local failure, and to reduce normal tissue toxicities that depend on the dose per fraction. After the results of a randomized trial that showed survival benefits of CHART over conventional

Table 2. Hematologic toxicities (n = 30)*

	Grade					
	0	1	2	3	4	≥Grade 3 (%)
Leukopenia	1	3	8	16	2	18 (60)
Neutropenia	3	0	2	6	19	25 (83)
Thrombocytopenia	20	7	1	2	0	2 (7)
Anemia	1	10	16	3	0	3 (10)

* National Cancer Institute–Common Toxicity Criteria version 2.

Table 3. Nonhematologic toxicities (n = 30)*

	Grade						
	0	1	2	3	4	5	≥Grade 3 (%)
Acute toxicity							
Nausea	7	16	4	3	0	0	3 (10)
Vomiting	23	3	4	0	0	0	0
Infection	20	3	2	5	0	0	5 (17)
Esophagitis	1	11	13	4	1	0	5 (17)
Pneumonitis	18	4	5	1	0	2	3 (10)
Late radiation morbidity†							
Esophagus	26	1	0	0	0	0	0
Heart	26	0	1	0	0	0	0
Lung	9	13	5	0	0	0	0
Subcutaneous tissue	17	6	2	2	0	0	2 (7)
Bone	26	0	0	0	1	0	1 (3)

* National Cancer Institute–Common Toxicity Criteria version 2.
† Three patients died within 90 days of the beginning of radiotherapy.

radiotherapy (9), the Department of Health in the United Kingdom recommended CHART as the radiotherapy schedule of choice in inoperable NSCLC, and a CHART implementation group was formed to facilitate its introduction throughout the United Kingdom (14). There were difficulties in changing departmental working hours and a lack of sufficient financial support in UK hospitals to introduce CHART into routine practice (15), although it was suggested that CHART gave more benefit than any sequential combination of conventional radiotherapy and chemotherapy with minimally increased toxicity. To make the accelerated regimen more widely applicable, Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less (CHARTWEL) and HART were introduced and were found to be as effective as CHART. Both CHARTWEL and HART showed improved survival over conventional radiotherapy, but the local tumor control was still unsatisfactory. Radiation dose escalation and use of chemotherapy combined with CHARTWEL/HART were also investigated to improve the local control and survival. Saunders *et al.* (16) reported on CHARTWEL combined with induction chemotherapy (17). In that study, 113 patients were enrolled, and dose escalation from 54 Gy to 60 Gy with or without chemotherapy was successfully achieved. Locoregional control at 2 years was 37% and 55% for CHARTWEL 54 Gy and 60 Gy alone, respectively, compared with 72% in those treated with 60 Gy and induction chemotherapy. These results suggested that chemotherapy improved locoregional control, but unfortunately they failed to show a statistically significant survival advantage, because of the relatively small number of patients and imbalanced tumor characteristics enrolled in each arm. The advantage of dose-escalated CHARTWEL against conventional radiotherapy is currently being investigated in a German Phase

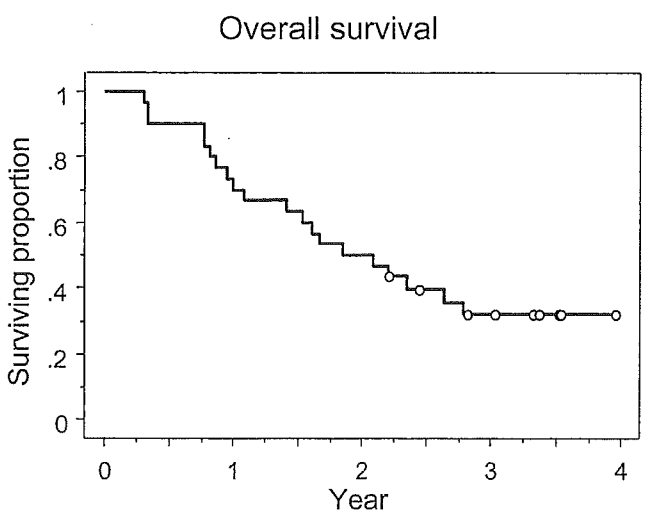

Fig. 1. Overall survival for all patients enrolled in this study.

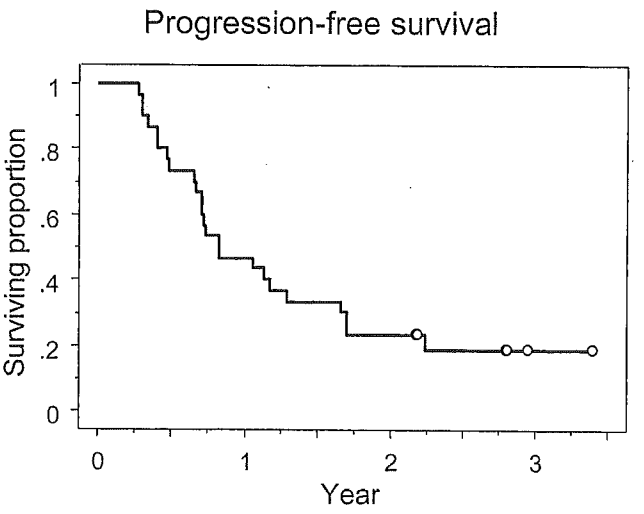

Fig. 2. Progression-free survival for all patients enrolled in this study.

III trial (18). Belani *et al.* reported the results of a randomized Phase III trial (19) that compared conventional radiotherapy with HART after induction chemotherapy (ECOG 2597). This study randomized 119 patients and unfortunately was closed because of slow accrual, but the results were provocative: The median survival time and the 2-year survivals for conventional radiotherapy and HART were 13.7 months and 33% vs. 22.2 months and 48%, respectively. These results seemed to be reliable despite the modest number of patients, because the median survival time of 13.7 months for the conventional radiotherapy arm was similar to that of a sequential chemoradiotherapy trial (2). The optimum chemotherapy regimen in combination with radiotherapy has not yet been determined, and we used a CDDP/VNR regimen instead of the carboplatin/paclitaxel regimen used in the ECOG 2597 trial. Both regimens are standards for advanced-stage NSCLC (20, 21). The compliance and toxicity profiles of chemotherapy in our study were acceptable, the incidence of esophagitis after HART was less than we expected, and the survival figure was nearly identical to that of the ECOG 2597 trial. This suggests that HART after induction CDDP/VNR or carboplatin/paclitaxel can achieve reproducible and promising results.

The pattern of failure in our study showed that local failure was still high (17 of 30, 57%) compared with distant metastasis (9 of 30, 30%), and further improvement of local control is needed. Future directions may include further dose intensification of radiotherapy and introduction of molecular-targeted agents. Recent innovation of information technology has made it possible to use sophisticated three-dimensional conformal radiotherapy (3DCRT). This can deliver intensified radiation doses to the tumor while minimizing the doses to the normal tissues that prevented further dose escalation using conventional two-dimensional radiotherapy. There have been several reports evaluating dose-intensified 3DCRT (22–25), and the technique is now under investigation in combination with cytotoxic chemotherapy in the Radiation Therapy Oncology Group trial (RTOG L-0117). Currently, molecular-targeted agents are being investigated most enthusiastically in Phase II and Phase III trials (26–29). It will be determined in the near future whether or not the combination of these agents has a survival impact. However, the optimal combination of these agents, newer cytotoxic agents, radiation fractionation, and 3DCRT will still need to be determined. Further investigation employing dose-intensified radiotherapy will be necessary to make a great leap in the treatment of locally advanced NSCLC.

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