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Chemotherapy for Small-Bowel Adenocarcinoma at a Single Institution

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Abstract

Purpose. Small-bowel adenocarcinoma (SBA) is rare.
No standard chemotherapy for this type of cancer has
yet been established. At Cancer Institute Hospital
(CIH), the chemotherapy regimen used for colorectal
cancer is initially used for patients with SBA, followed
by that used for gastric cancer.

Methods. Patients with advanced or recurrent SBA who
had been treated with chemotherapy in CIH were
retrospectively analyzed. The first-line treatments were
fluoropyrimidines used alone or in combination with
other drugs, such as 5-fluorouracil plus leucovorin (FL),
UFT-E, or TS-1. The second-line treatment was irino-
tecan (CPT-11) monotherapy.

Results. Fluoropyrimidine-based regimens, mainly FL,
were used for 10 patients. Seven patients received the
second-line CPT-11 regimen. Disease control was seen
in five patients (50%) with the first-line chemotherapy
and in three (43%) with the second-line. The median
overall survival time was 12 months (range 3–39). The
treatments were generally tolerated. Gastrointestinal
symptoms were the most common adverse effects.

Conclusions. Fluoropyrimidines as the first-line and
CPT-11 as the second-line chemotherapy yielded low
response, although the adverse effects were mild. The
FOLFOX and FOLFIRI regimens such as those used
for metastatic colorectal cancer are potential alternative
strategies. Extensive trials are needed to develop stan-
dard chemotherapy with new drugs.

Key words Small bowel · Adenocarcinoma · Chemo-
therapy · 5-Fluorouracil · Irinotecan

Introduction

Small-bowel adenocarcinoma (SBA) is a rare cancer.
Patients suffering from this type of tumor are likely to
have a poor prognosis.[1-3] No efficacious standard che-
motherapy has been developed that can prolong sur-
vival. No aggressive large-scale clinical trial has been
undertaken in Japan because of the rarity of this cancer
in comparison to other forms of gastrointestinal cancer.
In general, empirical chemotherapy regimens estab-
lished for gastric and colorectal cancer have been used
for SBA, with unsatisfactory results.

Patients and Methods

Patients

Patients diagnosed with unresectable or recurrent SBA
were treated with chemotherapy between August 2001
and March 2006. The patients' data were retrieved
from the tumor registry at Cancer Institute Hospital
and the extracted patients' records were reviewed
retrospectively.

Chemotherapy

The chemotherapeutic strategy of SBA was discussed
and fluoropyrimidine-based chemotherapies were
chosen as the first-line, followed by irinotecan (CPT-11)
monotherapy as the second-line in the regular Digestive
Cancer Board Meeting.

Toxicity and Efficacy Evaluation

Adverse effects were evaluated and graded according
to the National Cancer Institute Common Toxicity
Criteria.[4] The response was assessed using computed
tomography (CT) according to the RECIST criteria,

every 12 weeks. The data of toxicity and tumor evaluation were analyzed retrospectively from the medical records and the examination films of each patient.

The progression-free survival time and overall survival time were defined as the time between the date of treatment initiation and the date of diagnosis of disease progression or death with the date at which the patient was last confirmed to be alive, respectively, using the Kaplan–Meier method.[5]

Results

Study Population

Ten patients with advanced SBA received chemotherapy between August 2001 and March 2006. The characteristics of all evaluated patients are detailed in Table 1. The median age was 60 years (range 37–77). The performance status scores varied from 0 to 2. The locations of the primary small-bowel adenocarcinoma were 7 in the duodenum, 1 in the jejunum, and 2 in the ileum. The metastatic or recurrent sites when chemotherapy for SBA was begun were 4 in the local region, 4 in the liver, 4 in the peritoneum, and 4 in the paraaortic lymph nodes. Six patients underwent a noncurative operation as the primary treatment followed by chemotherapy, and one patient underwent chemotherapy immediately.

Response and Survival

Fluoropyrimidine-based regimens were carried out on 10 patients. A 5-fluorouracil plus leucovorin (FL) regimen was used as the first-line treatment for seven patients: four of those received the Mayo Clinic regimen; 5-fluorouracil (5-FU), $500\,mg/m^2$ of body-surface area and leucovorin (LV), $20\,mg/m^2$ for 5 days; three received the Roswell Park Memorial Institute (RPMI) regimen, weekly for 6 weeks followed by a 2-week rest period; D,L-leucovorin (D, L-CF; $500\,mg/m^2$ in a 2-h infusion) with 5-FU ($600\,mg/m^2$ i.v. bolus) 1 h after the D, L-CF infusion began and the others were treated with oral drugs: UFT-E 300 mg/body, twice daily every day; TS-1 $40\,mg/m^2$ twice daily on days 1 through 28 every 42 days. Seven patients received the second-line CPT-11 regimen, $150\,mg/m^2$, given biweekly, after a confirmed diagnosis of disease progression during the first-line chemotherapy (Table 2).

The antitumor response to the first-line chemotherapy was partial response (PR) in one patient, stable disease (SD) in four patients, and progressive disease (PD) in four patients. The response to the second-line chemotherapy was three patients in SD and four in PD (Tables 3 and 4). The median progression-free survival

Table 1. Patient characteristics ($n = 10$)

Characteristics	No. of patients
Median age, years (range)	60 (37–77)
Male/female	6/4
ECOG performance status: first-line/second-line	
0	7/3
1	1/1
2	2/3
Primary site	
Duodenum (papilla of Vater)	7 (3)
Jejunum	1
Ileum	2
Metastatic sites	
Liver	4
Nodal (Para-aortic lymph node)	4
Peritoneum	4
Locoregional	4
Histological differentiation	
Adenocarcinoma	10
Well-differentiated	1
Moderately differentiated	1
Poorly differentiated	1
Unknown	7
Operation method ($n = 9$)	
Bypass	3
Partial resection	4
Pancreatoduodenectomy	2
Tumor size (mm)	
< 40/40–80/unknown	2/2/6
Depth of invasion	
SS/SE/SI/unknown	2/1/1/6
Extent of lymph node metastasis	
N0/N1/N2/N3/N4/Nx	3/1/0/1/4/1
Lymphatic invasion	
Positive/negative/unknown	1/1/8
Venous invasion	
Positive/negative/unknown	1/1/8
Curability of surgery ($n = 9$)	
A/B/C	2/1/6

ECOG, Eastern Cooperative Oncology Group

following the first-line fluoropyrimidine-based regimen and the second-line CPT-11 was 81 days (range 27–666) and 71 days (range 14–935), respectively. The median overall survival time was 12 months (range 3–39). Six patients succumbed to tumor progression with systemic disease, three are still alive, and one was transferred to another hospital for supportive care (Fig. 1).

Safety

The adverse effects are summarized in Tables 5 and 6. Both treatments were generally tolerated. Gastrointestinal symptoms were the most common in both regimens; two patients had grade 3 nausea. Grade 3 neutropenia was only seen in one patient undergoing the CPT-11 regimen and no other severe hematologic toxicity occurred.

Table 2. Treatment and survival

Patient	Age (years)/Sex	Primary site	Regimens	PFS (days)	Survival time (months)
1	42/M	Jejunum	FL (Mayo)	63	12 (dead)
			CPT-11	52	
2	68/F	Papilla Vater	FL (Mayo)	27	3 (dead)
			CPT-11	14	
3	38/F	Duodenum	FL (Mayo)	34	39 (dead)
			CPT-11	935	
4	37/M	Duodenum	FL (Mayo)	226	12 (dead)
			CPT-11	82	
5	54/M	Papilla Vater	UFT-E	49	7*
			CPT-11	216	
6	77/F	Ileum	S-1	666	28 (alive)
7	67/F	Jejunum	FL (RPMI)	164	16 (dead)
			CPT-11	21	
8	66/M	Papilla Vater	FL (RPMI)	248	12 (dead)
9	70/M	Ileum	FL (RPMI)	377	19 (alive)
10	47/M	Duodenum	FL (RPMI)	81	6 (alive)
			CPT-11	71	

*This patient was transferred to another hospital for supportive care
PFS, Progression-free survival; FL, 5-fluorouracil plus leucovorin; RPMI, the Roswell Park Memorial Institute

Table 3. Response rates to the fluoropyrimidine-based regimen ($n = 10$)

Status	N (%)
Complete response	0 (0)
Partial response	1 (10)
Stable disease	4 (40)
Progressive disease	4 (40)
Not evaluable for response	1 (10)

**Table 4.** Response rates to the CPT-11 regimen ($n = 7$)

Status	N (%)
Complete response	0 (0)
Partial response	0 (0)
Stable disease	3 (42.9)
Progressive disease	4 (57.1)
Not evaluable for response	0 (0)

Table 5. Toxicity profile for the fluoropyrimidine-based regimen

Toxicity	All grades (%)	Grade 3/4 (%) ($n = 9$)
Diarrhea	3 (33.3)	0 (0)
Stomatitis	0 (0)	0 (0)
Alopecia	0 (0)	0 (0)
Nausea	6 (66.7)	1 (11.1)
Infection	0 (0)	0 (0)
Hand-foot syndrome	0 (0)	0 (0)
Fever	0 (0)	0 (0)
Fatigue	3 (33.3)	0 (0)
Anemia	2 (22.2)	0 (0)
Neutropenia	0 (0)	0 (0)
Thrombocytopenia	0 (0)	0 (0)

Table 6. Toxicity profile for the CPT-11 regimen

Toxicity	All grades (%)	Grade 3/4 (%) ($n = 7$)
Diarrhea	3 (42.9)	0 (0)
Stomatitis	0 (0)	0 (0)
Alopecia	2 (28.6)	0 (0)
Nausea	4 (57.1)	1 (14.3)
Infection	0 (0)	0 (0)
Hand–foot syndrome	0 (0)	0 (0)
Fever	0 (0)	0 (0)
Fatigue	2 (28.6)	0 (0)
Anemia	3 (42.9)	0 (0)
Neutropenia	1 (14.3)	1 (14.3)
Thrombocytopenia	0 (0)	0 (0)
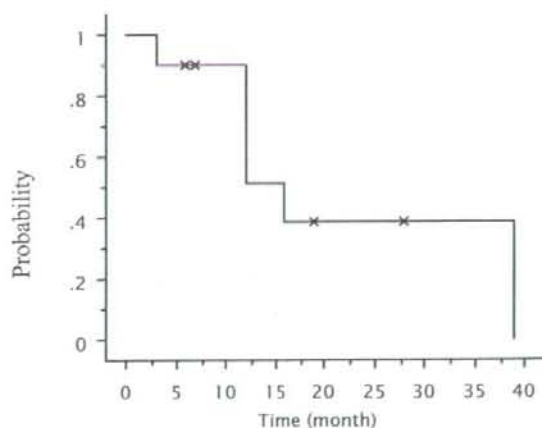
Fig. 1. The overall survival of 10 patients treated with chemotherapy against small-bowel adenocarcinoma

Discussion

Small-bowel tumors are often difficult to diagnose preoperatively. Adenocarcinoma is the most common histology, with a poor prognosis in comparison to carcinoid tumors.[6-8]

Surgery is the usual primary treatment for small-bowel tumors.[6,9,10] For malignancies, standard segmental resections or, if necessary, an extended radical resection including the adjacent organs or as much of the mesentery as is reasonable are recommended. Palliative operations are performed in oncologic emergencies such as gastrointestinal bleeding, obstruction, or perforation. Frost et al. reviewed 30 years of experience with small-bowel adenocarcinoma in their institute and reported the 10-year survival rates of all stages — stage I, II, III and a subgroup of 10 patients (one stage I, seven stage II, two stage III) — undergoing a pancreaticoduodenectomy to be 24%, 75%, 25%, 0%, and 30%, respectively.[9] Talamonti et al. reported their review of 129 surgically treated patients with small-bowel cancer and the prognostic factors for this rare cancer. The 5-year survival rate for an adenocarcinoma was 37%, in which the median survival of patients treated with a curative resection was better than patients with palliative surgery (37 months and 10 months, respectively).[10] According to the reports, late stage was a prognostic factor, while tumor location, size, and patient age were not significant. In addition, aggressive achievement of a sufficient surgical margin and if necessary, extended surgery such as a pancreaticoduodenectomy, are recommended to reduce the risk for local or peritoneal recurrence.

Of the three patients receiving a curative resection in the current study, two underwent a pancreaticoduodenectomy. However, intraoperative extended lymph node metastases were seen in one patient, resulting in para-aortic lymph node metastases. The other patient underwent a partial duodenectomy and the tumor microscopically invaded the serosa, concluding with peritoneal metastases and bilateral ovarian metastases.

In previous reports, few instances of effective chemotherapy and only a small number of large-scale clinical trials have been reported. Gibson et al. administered the FAM regimen (5-FU, mitomycin C, doxorubicin, 5-FU, 600 mg/m² on days 1, 8, 29, and 36; mitomycin C, 10 mg/m² on day 1; and doxorubicin, 30 mg/m² on days 1 and 2) in 38 patients with SBA. In that study, the response rate was 18.4%, including two complete responses; the median survival time was 8 months.[11] Jigyasu et al. also reported their experience using FAM-based regimens at the M.D. Anderson Cancer Center for 14 patients; the MST was 9 months, which was also inadequate.[12] Crawley et al. reported the Royal Marsden experience with protracted venous infusion of 5-FU

administration in eight SBA patients with a response rate of 37.5%, including one complete response (CR). The MST and PFS were 13 and 7.8 months, respectively.[13] Polyzos et al. reported the use of irinotecan as salvage chemotherapy for SBA, mentioning irinotecan as a potentially key drug for metastatic SBA similar to metastatic colorectal cancer.[14] Locher et al. assessed the efficacy of 5-FU and either platinum compounds (cisplatin, carboplatin, oxaliplatin) or irinotecan in patients with advanced SBA. Using a combination of 5-FU and platinum compounds, the overall response rate was 21% and median progression-free and overall survival 8 and 14 months, respectively, with tolerable toxicity. The combination of 5-FU and irinotecan as a second line treatment resulted in 50% disease stabilization with 5 months as the median progression-free survival. But no response was seen in the second-line 5-FU and cisplatin chemotherapy, and the need to try a 5-FU-irinotecan combination chemotherapy as the first-line treatment was indicated.[15] Onodera et al. reported a case of small-bowel adenocarcinoma with extensive lymph node metastases, which showed CR for 10 months after palliative surgery by use of 5-FU and methotrexate sequential chemotherapy.[16] The regimen is generally used for advanced gastric cancer patients who have poor performance status or are unable to receive the current intensive chemotherapy regimens such as S-1 combined regimens.[17-19]

In the current study, an oral fluoropyrimidine agent or bolus 5-FU/LV as the first-line and CPT-11 monotherapy as the second-line, such as the regimen used for metastatic colorectal cancer, were chosen for almost all of the patients. For that reason, no standard chemotherapy against gastric cancer has been established in recent years though both 5-FU and irinotecan were approved and bolus 5-FU/LV had been the standard treatment for first-line metastatic colorectal cancer (mCRC) and CPT-11 monotherapy for the second line until 2004 in Japan, which was applied to SBA patients. This study revealed this strategy to be insufficient against SBA. The FOLFOX or FOLFIRI regimens which have been the new standard for mCRC in Japan since the approval of infusion of 5-fluorouracil and oxaliplatin in early 2005, are being considered for the treatment of SBA.[20,21] In the present cases, fluoropyrimidines as the first-line chemotherapy produced low response, but S-1 showed some potential, although the treatment was used in only one patient. The efficacy of S-1 or S-1 combined chemotherapy against gastric cancer was demonstrated in 2007, which also provides another indication for application to SBA.[18,19]

Therefore, more intensive chemotherapy is required against this rare malignancy to improve its present poor prognosis. In addition, aggressive surgery to achieve a sufficient surgical margin, followed by adjuvant chemo-

therapy in the later stages, is essential to reduce recurrence. Extensive trials to develop a standard chemotherapy regimen for SBA using capecitabine, oxaliplatin, CPT-11, or S-1 with new drugs such as vascular endothelial growth factor (VEGF) antibodies and epidermal growth factor receptor (EGFR) antibodies, which have been initiated for colorectal cancer, should therefore be started for SBA.[22,23]

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ORIGINAL ARTICLE

Increased incidence of interstitial pneumonia by CHOP combined with rituximab

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Abstract Several authors have reported interstitial
pneumonia (IP) during rituximab plus cyclophosphamide,
doxorubicin, vincristine, and prednisone (R-CHOP) ther-
apy, while others have encountered *Pneumocystis jirovecii*
pneumonia during rituximab-combined bi-weekly CHOP.
Herein, we report that 13 of 90 (14%) patients developed IP
during R-CHOP therapy, compared with none of 105
patients treated with CHOP alone as a historical control.
There were no differences in baseline data between patients
undergoing the two therapies. Among R-CHOP-treated
patients, serum β-D-glucan was increased in 8 of 12 (75%)
IP patients compared with none of 30 non-IP patients
examined. In five IP patients who underwent sputum
evaluation, two were positive for *P. jirovecii* by the poly-
merase chain reaction and another two were positive for
Candida albicans. No other organisms were detected as
causative pathogens. Treatment with steroids, sulfameth-
oxazole-trimethoprim (ST), and antifungals was effective.

Our results suggest that R-CHOP raises the incidence of IP,
possibly through increasing the susceptibility to *P. jirovecii*
and fungal infection. The need for prophylactic antifungals
and ST during R-CHOP should be evaluated by random-
ized controlled trials.

1 Introduction

Rituximab, a chimeric mouse–human monoclonal antibody
against CD20, is used for monotherapy, as well as com-
bination chemotherapy, against CD20-positive B-cell non-
Hodgkin's lymphoma (NHL), and its efficacy has been
demonstrated with a low incidence of adverse effects [1].
There have been several case reports of interstitial pneu-
monia (IP) in patients treated with rituximab, and allergic
mechanisms or increased susceptibilities to infection have
been suggested [2–7]. Recently, IP has been shown to be
caused by *Pneumocystis jirovecii* (*P. carinii* pneumonia,
PCP) during treatment with rituximab plus bi-weekly
cyclophosphamide, doxorubicin, vincristine, and predni-
sone (R-CHOP-14) with or without etoposide [8, 9]. These
reports indicated that PCP occurred in the immunosup-
pressive state induced by rituximab or dose-intense agents.
However, IP development in rituximab-treated patients has
not been systematically analyzed, and its incidence and
etiology in such patients therefore remain unclear.

Here, we compared the incidence of IP in 90 B-cell
NHL patients treated with rituximab-combined CHOP
(R-CHOP) with that in 105 similar patients treated with
CHOP alone as a historical control. IP was diagnosed in 13
of 90 patients treated with R-CHOP compared with none of

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the 105 patients receiving CHOP alone, and the incidence was significantly higher in R-CHOP-treated patients. The characteristics of IP patients were analyzed, and the possible etiology is discussed.

2 Patients and methods

A total of 90 patients with CD20-positive B-cell NHL undergoing R-CHOP therapy between April 2005 and October 2006 and 105 patients with B-cell NHL who received CHOP therapy between June 2000 and December 2004 at our institute were compared regarding their characteristics and the incidence of IP by t-tests and Fischer's exact test. The study protocol and sampling were approved by the Institutional Review Board of the Cancer Institute Hospital. Due to the retrospective nature of this study, written informed consent was not obtained from any patients.

Histological diagnosis was confirmed by an expert hematopathologist (K.T.), and staging was performed according to the Ann Arbor classification. For patients with stages Ib-IV, CHOP chemotherapy was repeated six times in both treatment groups, and a standard dose of rituximab (375 mg/m^2) was administered on day 1 of each cycle for patients who received R-CHOP. For patients with stage Ia, CHOP or R-CHOP chemotherapy was repeated for three cycles and rituximab was continued as for patients with stages Ib-IV, which was followed by radiotherapy. Antifungals and sulfamethoxazole-trimethoprim (ST) were not administered prophylactically to patients treated with either RCHOP or CHOP therapy, because PCP or fungal infection has not been proven to be aggravated by the addition of rituximab to CHOP.

We performed chest and abdominal computed tomography (CT) to evaluate the response of each lymphoma to treatment. Furthermore, chest X-rays and CT were carried out in patients who developed a high fever and dyspnea during or after treatment. IP was diagnosed on the basis of chest CT revealing bilateral diffuse pulmonary interstitial infiltrates, and hypoxia without hypercapnia on arterial blood gas analysis. In order to confirm the diagnosis, peripheral white blood cells (WBCs), serum lactate dehydrogenase (LDH), C-reactive protein (CRP), and Klebsvonden Lungen-6 (KL-6) were assessed in all patients who developed IP. We also monitored the serum immunoglobulin G (IgG) level in patients. As a test for infection, we measured serum β-D-glucan, antigens for *Candida*, *Aspergillus*, *Klebsiella*, and adenovirus, cytomegalovirus (CMV) antigenemia, and antibodies against *Mycoplasma*. Blood and sputum from some patients were cultured. We further analyzed the serum level of β-D-glucan in 30 patients receiving R-CHOP without any symptoms or signs suggesting IP during the same period as a control.

3 Results

Table 1 shows the characteristics of patients who receive R-CHOP and CHOP, and the incidences of IP. There were n significant differences in the baseline characteristic including the median age, sex, distribution of histolog: disease stage, or International Prognostic Index betwee patients receiving the two treatments. IP was diagnosed in 1 of 90 (14.3%) patients treated with R-CHOP and none of 1C patients receiving CHOP. As other lung complications, tw cases of bacterial pneumonia and one case of development (tuberculosis were detected in the R-CHOP group, and fiv cases of bacterial pneumonia in the CHOP group.

All IP cases during R-CHOP were diagnosed as outp; tients. Furthermore, 12 of the cases occurred between £ and 120 days after treatment initiation of (6, 1, 1, and cases were diagnosed during the third, fourth, fifth, ar sixth cycles of treatment, respectively). Chest radiograpl showed bilateral diffuse ground-glass opacity in ε patients. There was no cystic lesion, fibrotic area wi honeycombing, or consolidation in air bronchogram Patients developed severe hypoxia of 46.2–62.1 (mee 51.2) mmHg of PaO$_2$ without hypercapnia (mean PaCO 35.4 mmHg, range 33.0–40.4), but no patients underwent respiratory function test. No cases had a history of ar other lung disease, disease progression nor lung involv ment of the lymphoma at the onset of IP (Table 2).

At the onset of IP, the peripheral WBC counts we within the normal range in seven patients, elevated in tw

Table 1 The characteristics of patients treated with both R-CH(and CHOP

	R-CHOP $n = 90$ n (%)	CHOP $n = 105$ n (%)	P-val
Median age	66.5	68	0.2
Sex			
Male	46 (51)	60 (57)	0.4
Female	44 (49)	45 (43)	
Histology			
DLBCL	73 (81)	86 (82)	0.8
FL, others	17 (19)	19 (18)	
Stage			
I–II	48 (53)	56 (53)	0.9
III–IV	42 (47)	49 (47)	
IPI			
L, L-I	64 (71)	62 (59)	0.8
H, H-I	26 (29)	43 (41)	
IP	13 (14)	0	<0.0:

R-CHOP rituximab plus cyclophosphamide, doxorubicin, vincristi: and prednisone, *DLBCL* diffuse large B-cell lymphoma, *FL* follicu lymphoma, *IPI* International Prognosis Index, *L* low, *L-I* low-int mediate, *H* high, *H-I* high-intermediate, *IP* interstitial pneumonia

Table 2 Clinicopathological data in 13 patients developing interstitial pneumonia

Case	Age	Sex	Histology	Stage	Duration from start of therapy (days)	Status at onset	Symptom
1	62	F	DLBCL	I A	83	CR	No
2	75	F	DLBCL	I A	89	CR	No
3	83	F	DLBCL	II A	60	PR	Dyspnea
4	81	F	DLBCL	I B	78	PR	Dyspnea
5	67	F	DLBCL	II A	102	CR	Fever
6	60	F	DLBCL	II A	83	CR	No
7	42	M	DLBCL	IV A	158	CR	Fever
8	75	F	DLBCL	II A	78	CR	Fever
9	71	F	DLBCL	IV A	99	NC	Fever
10	64	M	FL	IV A	62	PR	Fever
11	70	M	DLBCL	I A	71	PR	Fever
12	36	F	DLBCL	I A	96	CR	Fever
13	61	M	DLBCL	I A	60	CR	Dyspnea

M male, *F* female, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *CR* complete response, *PR* partial response, *NC* no change, *ND* not done

patients, and low in four patients. In 5 of 13 patients, IP occurred within 10 days of the completion of granulocyte colony-stimulating factor (G-CSF) therapy. Serum LDH levels were above normal in 12 patients, and the KL-6 level was above normal in 6 of 10 patients examined (Table 3).

Among R-CHOP-treated patients, the serum level of β-D-glucan was above normal (~ 10 pg/ml; range 20.2–130.8 pg/ml) in 8 of 12 (75%) IP patients examined, and negative in all 30 non-IP patients assessed. All IP patients were negative for *Candida* and *Aspergillus* antigens in peripheral blood. Furthermore, 11 patients tested were negative for CMV antigenemia, adenovirus, and *Klebsiella* antigens, and *Mycoplasma* antibodies. In five patients whose sputum was examined, *P. jirovecii* DNA was detected by the polymerase chain reaction in two patients, and *Candida albicans* was detected by culture in another two patients.

In 12 patients with IP, the serum IgG level was monitored every 2 months. Prior to treatment, the median serum IgG level was 1,193 mg/dl (range 832–1,736) and within the normal range in 11 of 12 patients, and the median serum IgG level at the onset of IP was 794.5 mg/dl (range 572–1,082) and below the normal range (820–1,700 mg/dl) in 10 (83.3%) of 12 patients.

For IP treatment, we used steroids, ST, and antifungals in the majority of patients. All patients responded well to treatment, and recovered within 2–3 weeks. The changes in β-D-glucan, CRP, and LDH are shown in Table 4. After recovery from IP, five patients received R-CHOP therapy and four underwent radiotherapy while receiving antifungal and anti-PCP treatment. No patient experienced recurrence of IP.

4 Discussion

Several studies have reported an association between IP and rituximab-combined chemotherapy. However, there have been no prospective studies on this adverse event, and the etiology remains unclear. Herein, we compared the incidence of IP in patients with B-cell NHL treated by R-CHOP with that in patients treated by CHOP alone. There were no cases of IP among patients treated with CHOP, whereas 13 of 90 (14.3%) patients treated with R-CHOP developed IP, although there were no significant differences in baseline data between the two treatment groups.

Among patients treated with R-CHOP examined regarding their serum level of β-D-glucan, it was increased in 8 (cases 4, 5, 6, 7, 9, 10, 12, and 13) of 12 (75%) IP patients compared with none of 30 non-IP patients as a control. Among five IP patients undergoing sputum examination, *P. jirovecii* was positive in two by the polymerase chain reaction and *C. albicans* was positive in another two, one (case 8) of whom was β-D-glucan-negative. G-CSF was suspected to be the cause of IP in case 9 as IP developed during G-CSF administration with a sudden increase in the leukocyte count, as has been reported [10, 11]. In our study, fever and itching were noted during the first rituximab infusion in 6 of 13 patients. Two (cases 1 and 2) of them were negative for β-D-glucan, and, thus, possibly developed rituximab-induced lung injury during the succeeding rituximab infusion, because it has been reported to develop during the second or later administration in patients showing an allergic reaction on the first infusion [4, 7]. In two patients (cases 3 and 11), we did not identify the cause of the IP.

β-D-glucan has emerged as an adjunctive diagnostic measurement for PCP and invasive fungal infection, although an increase in serum β-D-glucan does not directly lead to a diagnosis of PCP or fungal infection [12–14]. In two patients with IP, PCP was diagnosed by detecting *P. jirovecii* DNA in sputum, which is known to be a less sensitive specimen than bronchoalveolar lavage or

Table 3 Clinical, biochemical data in 13 patients developing interstitial pneumonia

Case	Serum beta-D glucan (pg/ml)	Culture of sputum	LDH (U/l)	KL-6 (U/ml)	WBC count at onset (/μl)	Duration from G-CSF therapy	Infusion reaction	Treatment
1	Negative	ND	395	388	1,600	ND	Yes	mPSL 250 mg, FLCZ, ST
2	Negative	ND	445	832	5,500	14 days	Yes	mPSL 250 mg, FLCZ, ST
3	ND	ND	201	ND	1,700	ND	Yes	mPSL 250 mg, FLCZ, ST, CFPM
4	28.7	C. albicans	355	755	4,900	3 days	Yes	mPSL 250 mg, MKFG, CFPM
5	20.2	ND	367	390	2,800	4 days	No	mPSL 250 mg, CFPM
6	100.0	ND	329	ND	400	ND	No	PSL 60 mg, FLCZ, ST
7	50.6	Negative	543	335	4,800	4 days	No	MKFG, ST, CFPM, γ-globulin
8	Negative	C. albicans	378	ND	7,000	ND	No	VRCZ, CFPM
9	130.8	ND	489	500	12,800	During therapy	No	mPSL 250 mg, FLCZ, ST
10	48.5	PCP	347	421	4,200	ND	Yes	mPSL 250 mg, VRCZ, ST, CFPM
11	Negative	ND	253	686	10,700	ND	No	PSL 30 mg, ST, FLCZ
12	59.2	ND	450	531	6,500	ND	Yes	mPSL 1,000 mg, ST, FLCZ
13	65	PCP	580	748	6,500	4 days	No	mPSL 500 mg, ST, FLCZ

Infusion reaction indicates fever and itching during first rituximab administration

ND not done, *C. albicans* Candida albicans, *PCP* Pneumocystis carinii pneumonia, *WBC* white blood cell (4,000–8,000), *LDH* lactate dehydrogenase (−235), *KL-6* Klebsvonden Lungen-6 (−499), *G-CSF* granulocyte colony-stimulating factor, *PSL* prednisone, *mPSL* methylpredonisolone, *FLCZ* fluconazole, *ST* sulfamethoxazole-trimethoprim, *CFPM* cefepime dihydrochloride, *MKFG* micafungin sodium, *VRCZ* voriconazole

transbronchial lung biopsy. To clearly detect PCP, further investigations are required.

Recently, the incidences of PCP were reported to be 6 and 13% in patients treated with rituximab-combined bi-weekly CHOP with or without etoposide, respectively, while only 2 of 141 (1%) patients developed PCP following the conventional tri-weekly R-CHOP therapy. Although the authors did not clearly demonstrate the severe depletion of

Table 4 The changes in clinical, biochemical data from onset of interstitial pneumonia to post treatment

Case	β-D-glucan (pg/ml)	CRP (mg/dl)	LDH (U/l)
1	Neg	0.3→0.1	395→230
2	Neg	0.1→0.1	445→213
3	ND	6.1→0.1	201→222
4	28.7→ND	10.3→0.2	355→277
5	20.2→Neg	0.3→0.1	367→233
6	100.0→Neg	1.9→0.1	329→200
7	50.6→Neg	12.4→0.3	543→357
8	Neg	12.9→0.3	378→229
9	130.8→Neg	4.0→1.8	489→211
10	48.5→Neg	10.0→0.1	347→194
11	Neg	1.1→0.1	253→208
12	59.2→Neg	5.6→0.3	261→252
13	65→Neg	0.2→0.1	580→203

Onset→after treatment for interstitial pneumonia

Neg negative, *ND* not done *CRP* C-reactive protein (−0.5), *LDH* lactate dehydrogenase (−235)

blood T lymphocytes, they suggested that dose-intensification and the addition of rituximab to CHOP-like regimens depleted the cellular immune system through the cytostatic effects of dose-intensified steroids and anti-cancer agents on lymphocytes, resulting in the development of PCP [8, 9]. They also showed that the addition of rituximab to CHOP-like regimens, such as CHOP and CHOP-14, with or without etoposide, increased the incidence of PCP [8]. Our results also suggest that the addition of rituximab to CHOP significantly increases the incidence of IP in patients with B-cell NHL, and some cases were possibly caused by *P. jiroveci* and fungal infection.

The incidence of IP in our study was unexpectedly high. A previous report indicated that lung injury induced by rituximab alone or in combination with chemotherapy account for less than 0.03% among over 300,000 patients worldwide [2]. On the other hand, other authors reported a lung injury rate of 11% during R-CHOP therapy [1], and a study of rituximab plus bleomycin-containing chemotherapy identified an increased incidence of lung injury through adding rituximab to chemotherapy [15]. These studies did not provide details of lung injury and the incidence of IP. Onsets of IP in 12 of 13 cases in our analysis were in an outpatients setting, as for most patients included in other studies of R-CHOP. The reason for this phenomenon was not clear with these limited data, and, therefore, further investigations such as a multi-center study, or epidemiological approach will be necessary.

Another recent study also demonstrated that the rates of fungal infections were increased in patients treated with

R-CHOP compared with patients receiving CHOP alone. Since most of the infected patients were more than 80 years of age, the authors concluded that the addition of rituximab to CHOP increases the risk of fungal infection in a very elderly population [16]. However, the average age of our population was not remarkably higher than those in previous studies on R-CHOP, and the ages of populations in studies on PCP during R-CHOP-14 were similar to that in the current study [8, 9].

In conclusion, 13 of 90 (14%) patients treated with R-CHOP developed IP, compared with none of 105 patients receiving CHOP alone as a historical control. Although the etiology remains unclear, increased susceptibility to *P. jirovecii* and fungal infection is suggested. This suggests the need to administer prophylactic treatment with antifungals and ST during R-CHOP therapy. The possible increase in the incidence of IP should be kept in mind when CHOP is combined with rituximab, since the treatment outcome for IP on the use of steroids, ST, and antifungals was favorable.

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ORIGINAL ARTICLE

Predictive factors for efficacy of capecitabine in heavily pretreated patients with metastatic breast cancer

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Abstract

Purpose The purpose of the present study is to evaluate what clinical factors affect the efficacy, time to treatment failure (TTF), and overall survival (OS) of oral capecitabine monotherapy in heavily pretreated patients with metastatic breast cancer (MBC).

Methods A total of 102 consecutive patients with MBC who had been administered capecitabine monotherapy between June 2003 and August 2004 were retrospectively reviewed. Capecitabine (828 mg/m^2) was given twice daily for 3 weeks followed by a 1-week rest period; this was repeated every 4 weeks. We evaluated the potential clinical factors for TTF and OS, using univariate analysis (log-rank test) and the multivariate Cox regression model. Median follow-up was 16.9 months.

Results A total of 100 patients (98%) had been pretreated with either anthracyclines or taxanes, and 81 patients (79%) with both anthracyclines and taxanes. Response rate was 17% and clinical benefit rate was 41%. Median TTF and OS were 4.9 and 24.3 months, respectively. Multivariate analysis demonstrated that no liver metastasis ($P = 0.015$), good performance status ($P = 0.033$), longer disease-free interval ($P = 0.036$), and hormone receptor-positive tumor ($P = 0.038$) were significant for TTF. No liver metastasis ($P = 0.00012$), objective response to capecitabine ($P = 0.00084$), and good performance status ($P = 0.0011$) were significant for OS.

Conclusions Capecitabine monotherapy is effective over the long term for heavily pretreated patients with MBC who have no liver metastasis, good performance status, longer disease-free interval, or hormone receptor-positive tumor. Patients who have no liver metastasis, who respond to capecitabine, or who have good performance status are expected to survive even longer.

Keywords Capecitabine · Metastatic breast cancer · Predictive factors · Time to treatment failure · Overall survival

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Introduction

Metastatic breast cancer (MBC) is an incurable, lethal disease. The aim of systemic therapy against MBC is focused mainly on palliation and improved quality of life.

Capecitabine is an oral fluoropyrimidine carbamate, which is converted to 5-fluorouracil (5-FU) selectively in tumor throughout a cascade of three enzymes. After gastrointestinal absorption, capecitabine is first hydrolyzed in the liver by carboxylesterase to produce 5'-deoxy-5-fluorocytudine. This moiety is then deaminated on its pyrimidine ring to produce 5'-deoxy-5-fluorouridine by cytidine deaminase, an enzyme located principally in hepatic and

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neoplastic tissue. The last enzymatic step, activation of 5'-deoxy-5-fluorouridine to 5-FU, is catalyzed by thymidine phosphorylase, highly expressed in tumor tissues, thus minimizing systemic exposure to 5-FU [1].

Capecitabine achieved a high tumor control rate with low toxicity in heavily-pretreated patients with MBC. Our former study [2] and other studies [3, 4] showed the objective response (OR) rate has varied from 17 to 29%, median time to progression (or treatment failure) from 3.6 to 4.9 months, and median overall survival (OS) from 9.4 to 24.3 months.

Patients with incurable cancer have a clear preference for oral chemotherapy over intravenous chemotherapy [5–7]. Moreover, in patients with metastatic colorectal cancer, capecitabine improves their quality of life and medical resource use in terms of avoidance of hospital visits for intravenous drug administration, less expensive drug therapy, and fewer treatment-related hospitalizations for adverse drug reactions, compared to intravenous 5-FU therapy [7]. Therefore, when oral capecitabine monotherapy is effective over time for patients with MBC, patients can improve their quality of life and medical resource use. The purpose of the present study is to evaluate what clinical factors affect the efficacy, time to treatment failure (TTF) and OS of capecitabine monotherapy in patients with MBC.

Patients and methods

Patients

Consecutive patients with MBC who had been administered capecitabine monotherapy between June 2003 and August 2004 at our hospital were retrospectively reviewed. The eligibility criteria were as follows: (1) capecitabine monotherapy for at least one cycle, (2) metastatic lesion(s) measurable according to the Response Evaluation Criteria in Solid Tumors guidelines [9], and (3) performance status of three or less according to the Eastern Cooperative Oncology Group's scale. The patients of the present study were the same as our former study [2].

Treatment plan

Capecitabine was given orally 828 mg/m^2, twice daily for 3 weeks, followed by a 1-week rest period. This was repeated every 4 weeks in an outpatient setting. The dose was calculated on the basis of body surface area at baseline (Table 1).

Patients with an OR or stable disease (SD) could continue to receive the treatment until progressive disease (PD) or unacceptable toxicity developed. Treatment interruption and/or individual dose adjustment of capecitabine was considered when patients experienced any adverse events

Table 1 Determination of capecitabine dose according to body surface area

Body surface area (m^2)	Dose (mg, twice daily)
<1.31	900
1.31–1.64	1,200
≤1.64	1,500

assessed at grade 2 or more as defined by the National Cancer Institute, Common Toxicity Criteria, version 3.0.

Evaluation of efficacy

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines [9] by the investigators and the independent reviewers, with computed tomography scans at baseline and every 2 or 3 months. Complete response (CR) was defined as the disappearance of all known lesions for at least 4 weeks. Partial response (PR) was defined as a reduction by at least 30% of the sum of all measurable lesions. PD was defined as an increase of the sum of all measurable lesions by greater than 20% or as appearance of a new lesion. And SD was defined as neither CR, PR, nor PD. Long SD was defined as SD lasting for more than 24 weeks.

Objective response rate was defined as the sum of CR and PR rates. Clinical benefit (CB) rate was defined as the sum of CR, PR, and long SD rates. TTF was defined as the period from commencement of capecitabine to discontinuation of capecitabine due to PD or unacceptable toxicity. OS was defined as the period from commencement of capecitabine to the patient's death for any reason.

Selection of potential predictive factors for efficacy of capecitabine

We selected the following potential predictive factors for efficacy of capecitabine: age, disease-free interval (DFI), performance status (PS), estrogen receptor (ER), progesterone receptor (PgR), hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), the number of metastatic sites, the site of metastases, and the number and regimens of chemotherapeutic pretreatments.

Disease-free interval was defined as duration from surgery to first recurrence. When metastatic disease was diagnosed at the time of initial presentation, DFI was defined as zero. PS was scored according to the Eastern Cooperative Oncology Group's scale. ER positive or PgR positive were defined the positive cells 10% or more in immunohistochemistry in primary invasive breast cancer. HR positive was defined as ER+ and/or PgR+. HER2 positive were defined HER2 protein scored as 3+ in immunohistochemistry or HER2 gene amplified twofold or greater in fluorescence in situ hybridization in

primary invasive breast cancer. Metastatic sites included lymph node, lung, bone, liver, pleura, and chest wall. The number of chemotherapeutic pretreatments was defined as the sum of prior regimens consisting of at least two courses of anthracyclines (doxorubicin or epirubicin), taxanes (paclitaxel, docetaxel), bolus 5-FU, oral fluoropyrimidines, cyclophosphamide/methotrexate/5-FU (CMF), mitomycin, irinotecan, vinorelbine, and trastuzumab.

In addition, when we analyzed the potential predictive factors for OS, we added OR and CB of capecitabine to the above factors.

Statistical analyses

First we used univariate analysis to screen for potential predictive factors affecting TTF and OS. Next we used multivariate analysis for the significant factors from the univariate analyses. A P value of <0.05 was considered significant. Confidence intervals (CI) were set at the 95% level.

Univariate analysis

The cumulative survival rates were calculated by the Kaplan–Meier method, which was performed to analyze censored data. Univariate exploration of potential predictive factors for TTF and OS employed log-rank tests (Peto–Peto method).

In these analyses, each factor is divided into two groups. Age was grouped using age 40 as the cut point. Two years was used as the cut point for DFI. For PS, patients were grouped as ones with PS = 0–1 and ones with PS = 2–3. For ER, PgR, HR and HER2, we examined two statuses of positive and negative results. For the number of metastatic sites, we defined one group as patients having one and two sites with the other group having three or more sites. For the sites of metastases, we grouped lymph node, lung, bone, liver, pleura, and chest wall into two statuses of involved and not involved. For the number of chemotherapeutic pretreatments, we defined one group as patients who had had 1–2 regimens and the other group as having three or more regimens. And for the regimens of chemotherapeutic pretreatments, we established two groups of anthracycline-pretreated and untreated, taxane-pretreated and untreated, bolus 5-FU-pretreated and untreated, oral fluoropyrimidine-pretreated and untreated, and CMF-pretreated and untreated.

Multivariate analysis

We used multivariate Cox regression model to investigate which factors affect survival time. Initially, all significant factors selected by univariate analysis were entered into the model as binary variables. Next, non-significant variables were removed sequentially using a backward elimination strategy based on the likelihood ratio test. We then selected

a model with all factors being significant. These statistical analyses were performed with the open-source software R (http://www.r-project.org/), version 2.6.0.

Results

Patient characteristics

A total of 102 consecutive patients were assessed in the present study. Median follow-up time for patients was 16.9 months, with a range from 0.9 to 46.5 months. All patients were Japanese women. The demographic characteristics of the present study population are presented in Table 2.

The patients in the present study had advanced disease. More than half (57%) had metastasis in three or more organs. Approximately half of the patients had visceral metastasis of the lung (51%) or liver (46%). Moreover, they had been heavily pretreated. A total of 100 patients had been pretreated with either anthracyclines or taxanes (98%), and 81 patients with both anthracyclines and taxanes (79%).

Efficacy

Of the 102 patients, response was assessable in 96. Five patients achieved CR (5%) and 12 achieved PR (12%). Therefore, the OR rate for capecitabine was 17% (95% CI; 9–24%). Moreover, 32 patients achieved SD, and of these, 25 achieved long SD (25%); hence, the CB rate for capecitabine was 41% (95% CI; 32–51%) (Table 3).

Median TTF was 4.9 months, and median OS was 24.3 months (Fig. 1).

Univariate analyses

Log-rank tests showed that the following five and eight factors were statistically significant for TTF and OS, respectively. For TTF, age ($\leq$40 vs. $\leq$41 years; $P = 0.005$), DFI (0–2 (s) vs. $\leq$2 years; $P = 0.024$), PS (0–1 vs. 2–3; $P = 0.018$), HR (+ vs. −; $P = 0.023$), and liver metastasis (− vs. +; $P = 0.001$) were significant. For OS, PS (0–1 vs. 2–3; $P = 0.0005$), number of metastatic sites (1–2 vs. 3 sites $\leq$; $P = 0.004$), bone metastasis (− vs. +; $P = 0.016$), liver metastasis (− vs. +; $P = 0.0002$), number of chemotherapeutic pretreatments (1–2 vs. 3 regimens $\leq$; $P = 0.046$), pretreatment of taxanes (− vs. +; $P = 0.045$), OR (− vs. +; $P = 0.006$), and CB (− vs. +; $P = 0.0002$) were significant (Table 4).

Multivariate analyses

The following four and three factors were statistically significant for TTF and OS, respectively. For TTF, liver

Table 2 Patient characteristics ($n = 102$)

Characteristics	No.	%
Age		
Mean (range)	56.1 (29–85)	
Disease free interval (years)		
Mean (range)	3.5 (0–11.8)	
Performance status		
0–1	82	80
2–3	20	20
Estrogen receptor (ER)		
+	67	66
−	30	29
Unknown	5	5
Progesterone receptor (PgR)		
+	59	58
−	34	33
Unknown	9	9
Hormone receptor (ER and/or PgR)		
+	74	73
−	23	23
Unknown	5	5
HER2 overexpression		
+	6	6
−	87	85
Unknown	9	9
No. of metastatic sites		
Mean (range)	2.8 (1–6)	
1–2	44	43
≤3	58	57
Sites of metastases		
Lymph node	63	62
Lung	52	51
Bone	52	51
Liver	47	46
Pleura	26	25
Chest wall	25	25
No. of chemotherapeutic pretreatments		
Mean (range)	4.0 (1–8)	
1–2	15	15
≤3	87	85
Regimens of chemotherapeutic pretreatments		
Anthracyclines	91	89
Taxanes	90	88
Bolus 5-fluorouracil	86	84
Oral fluoropyrimidines	33	32
CMF	32	31

Table 3 Response to capecitabine ($n = 102$)

	No.	%
Response		
Complete response	5	5
Partial response	12	12
Stable disease	31	30
Long stable disease	25	25
Progressive disease	48	47
Not evaluable	6	6
Objective response rate	17	17
Clinical benefit rate	42	41
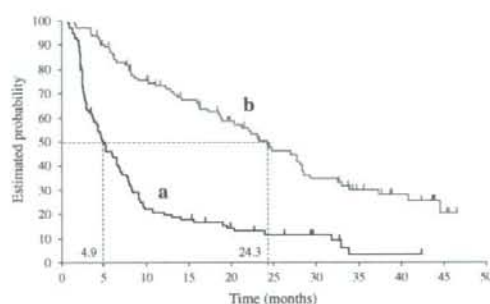
Fig. 1 Time to treatment failure (a) and overall survival (b)

liver metastasis (− vs. +; $P = 0.00012$), OR (− vs. +; $P = 0.00084$), and PS (0–1 vs. 2–3; $P = 0.00113$) were significant (Table 6).

Discussion

The present study has shown that palliative chemotherapy with oral capecitabine monotherapy can be effective over the long term for heavily pretreated patients who have no liver metastasis, good PS, longer DFI, or HR-positive tumor. The quality of life for heavily pretreated patients having one of these four factors can be expected to improve. Furthermore, in addition to response to capecitabine, two of these four factors —no liver metastasis and good PS—had also a positive influence on longer survival.

These predictive factors resulting from the present study are similar to those from earlier works. Predictive factors for efficacy and survival of cytotoxic chemotherapy have been extensively studied. But unlike the relationship between ER and tamoxifen or HER2 and trastuzumab, no predictive test for a response to cytotoxic chemotherapy has been sufficiently validated to use in a standard clinical setting. Most consistent predictive factors in the metastatic setting are nonspecific clinical features: good PS [10–14], small

metastasis (− vs. +; $P = 0.015$), PS (0–1 vs. 2–3; $P = 0.033$), DFI (0–2 vs. ≤2 years; $P = 0.036$), and HR (+ vs. −; $P = 0.038$) were significant (Table 5). For OS,

Table 4 Univariate analyses of time to treatment failure and overall survival of capecitabine

Category	No.	Time to treatment failure	Overall survival
Age			
≤40 vs. ≤41	9 vs. 93	0.005 (<0.01)	0.06 (NS)
Disease-free interval (years)			
0–2 vs. ≤2	43 vs. 59	0.024 (<0.05)	0.08 (NS)
Performance status			
0–1 vs. 2–3	82 vs. 20	0.018 (<0.05)	0.0005 (<0.001)
Hormone receptor status			
Estrogen receptor + vs. −	67 vs. 30	0.14 (NS)	0.66 (NS)
Progesterone receptor + vs. −	59 vs. 35	0.08 (NS)	0.78 (NS)
Hormone receptor + vs. −	74 vs. 23	0.023 (<0.05)	0.54 (NS)
HER2 overexpression			
+ vs. −	6 vs. 88	0.32 (NS)	0.52 (NS)
No. of metastatic sites			
1–2 vs. ≤3	44 vs. 58	0.10 (NS)	0.004 (<0.01)
Site of metastases			
Lymph node − vs. +	39 vs. 63	0.83 (NS)	0.99 (NS)
Lung − vs. +	50 vs. 52	0.17 (NS)	0.77 (NS)
Bone − vs. +	50 vs. 52	0.66 (NS)	0.016 (<0.05)
Liver − vs. +	56 vs. 46	0.001 (<0.01)	0.0002 (<0.001)
Pleura − vs. +	76 vs. 26	0.82 (NS)	0.75 (NS)
Chest wall − vs. +	77 vs. 25	0.93 (NS)	0.89 (NS)
No. of chemotherapeutic pretreatments			
1–2 vs. ≤3	15 vs. 87	0.20 (NS)	0.046 (<0.05)
Regimen of chemotherapeutic pretreatments			
Anthracyclines − vs. +	11 vs. 91	0.61 (NS)	0.41 (NS)
Taxanes − vs. +	12 vs. 90	0.14 (NS)	0.045 (<0.05)
Bolus 5-fluorouracil − vs. +	16 vs. 86	0.36 (NS)	0.54 (NS)
Oral fluoropyrimidines − vs. +	69 vs. 33	0.28 (NS)	0.53 (NS)
CMF − vs. +	70 vs. 32	0.33 (NS)	0.84 (NS)
Efficacy			
Objective response − vs. +	84 vs. 17	−	0.006 (<0.01)
Clinical benefit − vs. +	60 vs. 42	−	0.0002 (<0.001)

number of metastatic sites [10, 11, 15], no visceral metastasis [12, 13], especially no liver metastasis [12, 14–16], longer DFI [14, 16], ER positive [11, 15], no adjuvant chemotherapy [11, 15, 16], and response to chemotherapy [12, 14].

Some studies have reported the prognostic importance of initial site of metastasis [17, 18]. Patients with breast cancer developing liver metastasis since 1950s have been considered to have a poor prognosis, with median survival rates of less than 6 months [19]. Although survival in MBC patients with liver metastasis can be prolonged by introducing effective modern chemotherapy [19, 20], liver metastasis still contributed most significantly to shorter response and survival in the present study.

Several studies in vitro [21, 22] demonstrated that positive ER was associated with chemoresistance to 5-FU and other antitumor drugs. Some clinical studies showed that positive ER was a predictive factor of resistance to cytotoxic chemotherapy in the neoadjuvant [23] and metastatic setting [24]. On the other hand, the present study and other studies in the metastatic setting [11, 15] demonstrated that positive HR is a predictive factor for longer TTF. HR-positive tumors seem to grow more slowly and less aggressively than HR-negative ones, because survival from first relapse is longer in patients with HR-positive tumors than negative tumors [25, 26]. Therefore, the time to progression with chemotherapy tends to be longer in HR-positive tumors [27].

Previous studies in vitro had shown that introduction of HER2 in breast cancer cells induced resistance to 5-FU [28, 29]. In the clinical setting, patients whose tumors

Table 5 Multivariate analyses: predictive factors for time to treatment failure of capecitabine

	Coefficient	Hazard ratio	95% CI	P value
Liver metastasis	0.547	1.728	(1.114, 2.679)	0.015
Performance status	0.611	1.843	(1.049, 3.236)	0.033
Disease-free interval	−0.476	0.621	(0.398, 0.969)	0.036
Hormone receptor	−0.527	0.590	(0.359, 0.971)	0.038

CI confidence interval

Table 6 Multivariate analyses: predictive factors for overall survival of capecitabine

	Coefficient	Hazard ratio	95% CI	P value
Liver metastasis	1.058	2.880	(1.678, 4.944)	0.00012
Objective response	−1.243	0.289	(0.123, 0.676)	0.00084
Performance status	1.141	3.131	(1.675, 5.854)	0.00113

CI confidence interval

overexpress HER2 are less likely to benefit from adjuvant nondoxorubicin- and 5-FU-containing regimens, such as CMF [30] or phenylalanine mustard plus 5-FU [31], than patients whose tumors have normal HER2 expression levels. But it is unclear whether patients whose tumors overexpress HER2 are less likely to benefit from capecitabine monotherapy. The present study has a limitation with regard to HER2 status: most patients with HER2-positive breast cancer were excluded because they were administered capecitabine concomitant with trastuzumab. Combination therapy of capecitabine and trastuzumab is effective for patients with HER2-positive MBC [32–34].

The number or content of regimen of chemotherapeutic pretreatments was not important in predicting the efficacy of capecitabine in heavily pretreated patients. Therefore, it seems to be worth giving oral capecitabine to heavily pretreated patients with MBC.

In conclusion, even if patients with MBC are heavily pretreated with chemotherapy, the patients who have no liver metastasis, good PS, longer DFI, or HR-positive tumors can be expected to live longer with capecitabine monotherapy. The heavily pretreated patients who have no liver metastasis, who respond to capecitabine, or show good PS are expected to survive even longer.

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original article

Soluble interleukin-2 receptor retains prognostic value in patients with diffuse large B-cell lymphoma receiving rituximab plus CHOP (RCHOP) therapy

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Background: Soluble interleukin-2 receptor (SIL-2R) is known to be a prognostic parameter in patients with diffuse large B-cell lymphoma (DLBCL) receiving cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) therapy. However, its prognostic value has not been well known since the introduction of rituximab.

Patients and methods: We retrospectively evaluated the prognostic impact of SIL-2R in 228 DLBCL patients, comparing 141 rituximab-combined CHOP (RCHOP)-treated patients with 87 CHOP-treated patients as a historical control.

Results: Patients with high serum SIL-2R showed significantly poorer event-free survival (EFS) and overall survival (OS) than patients with low SIL-2R in both the RCHOP group (2-year EFS, 66% versus 92%, $P < 0.001$; OS, 82% versus 95%, $P = 0.005$) and the CHOP group (2-year EFS, 40% versus 82%; OS, 61% versus 90%, both $P < 0.001$). Multivariate analysis including the five parameters of International Prognostic Index (IPI) and two-categorized IPI revealed that SIL-2R was an independent prognostic factor for EFS and OS in the RCHOP group as well as in the CHOP group.

Conclusions: Our results demonstrate that SIL-2R retains its prognostic value in the rituximab era. The prognostic value of SIL-2R in DLBCL patients receiving rituximab-combined chemotherapy should be reassessed on a larger scale and by long-term follow-up.

Key words: diffuse large B-cell lymphoma, rituximab, soluble interleukin-2 receptor

introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma [1]. It takes an aggressive clinical course and comprises a heterogeneous group of lymphomas in terms of morphology, phenotype, molecular biology and clinical behavior. Up to now, the International Prognostic Index (IPI) has been the most widely used predictive model for patients with DLBCL treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) [2]. On the other hand, soluble interleukin-2 receptor (SIL-2R) has also been investigated as a prognostic factor, and several studies have demonstrated that a high level of SIL-2R before treatment is associated with both a low remission rate and poor prognosis [3–8].

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SIL-2R is the soluble form of interleukin-2 receptor (IL-2R). IL-2R is expressed on the cell membrane of lymphocytes and plays important roles in their activation and proliferation [9]. It is composed of at least three glycoprotein chains: α (55 kDa), β (75 kDa) and γ (64 kDa). Each subunit is able to bind to the ligand independently with either low (IL-2Rα) or intermediate (IL-2Rβ and γ) affinity. It is now possible to examine the expression of the soluble-type α subunit [10]. The soluble IL-2Rα chain is induced and expressed only after mononuclear cell (T cell, B cell, monocyte, and natural killer cell) activation [11, 12]. Therefore, activated T and B cells have elevated levels of SIL-2R.

Although the CHOP regimen has been the mainstay of treatment for aggressive lymphomas for several decades [13], treatment outcome has significantly improved with the introduction of rituximab (an anti-CD20 chimeric antibody) in both young and elderly patients [14–17]. Since the introduction of rituximab, several prognostic factors have been reevaluated. Sehn et al. [18] recently reevaluated five prognostic

factors and demonstrated that the IPI remained predictive; they proposed a revised IPI in which DLBCL patients are classified into very good (no IPI risk factors), good (one to two risk factors) and poor (three to five risk factors) categories. In contrast, BCL2, BCL6 and immunohistochemically defined germinal center (GC) phenotype have been reported to have no prognostic value when rituximab is added to chemotherapy [19–24]. Other clinical factors or biomarkers identified in patients receiving CHOP therefore need to be reassessed in patients treated with CHOP combined with rituximab.

Up to now, the prognostic value of SIL-2R in RCHOP has not been investigated. The aim of the present study was to retrospectively reassess the prognostic value of SIL-2R in DLBCL patients receiving RCHOP as compared with CHOP alone and to investigate whether or not this factor still influences the outcome of DLBCL.

patients and methods

patient characteristics

In the present study, we reviewed the medical records of patients with CD20-positive DLBCL who received CHOP with or without rituximab as a first-line therapy at the Cancer Institute Hospital from January 2000 to December 2006 and were followed until January 2008. The study protocol and sampling were approved by the Institutional Review Board of the Cancer Institute Hospital. Informed consent for retrospective analysis and additional immunophenotypic analysis and gene rearrangement studies was obtained.

Patients were analyzed if they were older than 18 years and had a performance status (PS) of zero to three according to the criteria of the European Cooperative Oncology Group. Patients were excluded if they had clinically relevant cardiac diseases or positivity for antibodies against HIV-1 or 2. Patients with primary mediastinal large B-cell lymphoma, primary CNS lymphoma and primary testicular lymphoma were also not included in this study.

The disease stage was evaluated according to the Ann Arbor staging system. All patients had undergone staging investigations, including physical examinations, blood and serum analysis, bone marrow aspiration and biopsy and computed tomography of the neck, chest, abdomen and pelvis. Magnetic resonance imaging was used for evaluation of involved organs in the head and neck. The following clinical and laboratory data were available at the time of diagnosis: age, sex, serum lactate dehydrogenase level, PS, presence of B symptoms, clinical stage and number of extranodal sites. This allowed the IPI scores to be determined in the studied patients. Patients were categorized into either a low-risk group (IPI score, 0–2) or a high-risk group (IPI score, 3–5). Response to initial therapy was evaluated according to the Cheson criteria [25].

treatment

In both the CHOP and RCHOP groups, CHOP chemotherapy was given triweekly at a standard dose. Patients with stages IB–IV received six cycles, and patients with stage IA three cycles, of CHOP chemotherapy followed by radiotherapy for the involved field. After incorporation of rituximab into the CHOP regimen in February 2004, patients were treated with RCHOP regimen, in which rituximab was administered at a standard dose of 375 mg/m^2 once weekly for 8 weeks concurrently with triweekly CHOP, as described previously [26].

chemical studies

The serum SIL-2R levels were determined using a sandwich enzyme-linked immunosorbent assay kit (Cell-free Interleukin-2 Receptor Test Kit, T Cell Science, Cambridge, MA) using two mAbs against distinct two different epitopes of the p55 alpha-chain of the IL-2R complex. Serum SIL-2R was considered 'high' when higher than the median and 'low' when lower than the median.

pathological studies

Biopsy samples collected before treatment were fixed in formalin, embedded in paraffin, sliced and stained with hematoxylin and eosin for morphological analysis. For diagnosis of DLBCL, immunohistochemical analysis was carried out using the dextran-polymer method (EnVision+; Dako, Glostrup, Denmark) with mAbs against CD5, CD10, CD20, Ki67, BCL2, BCL6 and MUM1 in most cases and with CyclinD1 to exclude the possibility of a pleomorphic variant of mantle cell lymphoma when the lymphoma was CD5 positive. Patients with a small-cell component implying transformation from low-grade/indolent B-cell lymphoma were excluded. All the samples were reviewed by an expert hematopathologist (KT).

statistical analysis

Basic characteristics of the CHOP group and RCHOP group were compared by Fisher's exact test. Event-free survival (EFS) was calculated from the date of diagnosis to the date of documented disease progression, relapse or death from any cause or to the stopping date. Overall survival (OS) was calculated from the date of diagnosis until death from any cause or the last follow-up. If the stopping date was not reached, the data were censored at the date of the last follow-up evaluation. Survival curves were estimated by the Kaplan–Meier method, and overall differences were compared by the log-rank test. Log-rank test was carried out according to SIL-2R, two-categorized IPI for the two treatment groups. To estimate the unbiased prognostic impacts of SIL-2R on EFS and OS, Cox proportional hazards analysis was applied. First, we conducted univariate Cox analysis for SIL-2L, all IPI factors and dichotomized IPI and then we carried out multivariate Cox analysis adjusted for SIL-2R and each of the IPI risk factors, with final adjustment for SIL-2R and dichotomized IPI. Only factors that were associated with at least a trend toward significance in the univariate analysis (unadjusted P value <0.20) were evaluated in the multivariate model. We set P <0.05 as the level of statistical significance. Data were analyzed using SPSS software version 11.0 for Windows (SPSS, Chicago, IL).

results

patient characteristics

A total of 228 patients were analyzed, of whom 87 (38.2%) were given CHOP and 141 (61.8%) were given RCHOP. The median SIL-2R was 1005.5 mg/dl (range 220–35 600), and high SIL-2R was observed in 114 (50.0%) patients: 40 of 87 (46.0%) in the CHOP group and 74 of 141 (52.5%) in the RCHOP group. There was no significant difference in the proportion of high SIL-2R patients between the two treatment groups. The characteristics of the patients are listed in Table 1. Patient and disease characteristics were well balanced between the groups.

survival analysis

With median follow-up periods of 30 months in the RCHOP group and 44 months in the CHOP group, EFS rates at 2 years were 78% and 65%, respectively ($P = 0.030$), and OS rates at 2 years were 89% and 81%, respectively ($P = 0.040$).

Table 1. Patients' characteristics according to serum SIL-2R level for CHOP and RCHOP group

Characteristics	CHOP group			RCHOP group			P
	All	Low SIL2R	High SIL-2R	All	Low SIL2R	High SIL2R	
No. of patients (%)	87(100)	47 (54)	40 (46)	141 (100)	67 (48)	74 (52)	
Sex, no. (%)							0.41
Male	50 (57)	27 (57)	23 (58)	72 (51)	27 (40)	45 (61)	
Female	37 (43)	20 (43)	17 (42)	69 (49)	40 (60)	29 (39)	
Age, no. (%)							0.52
≤60	24 (28)	13 (28)	11 (28)	45 (32)	29 (43)	16 (22)	
>60	63 (72)	34 (72)	29 (72)	96 (68)	38 (57)	58 (78)	
LDH, no. (%)							0.54
Normal	29 (32)	22 (35)	7 (17)	68 (48)	45 (67)	23 (31)	
High	58 (68)	25 (65)	33 (83)	73 (52)	22 (33)	51 (69)	
PS, no. (%)							0.81
0–1	77 (89)	44 (94)	33 (83)	127 (90)	66 (98)	61 (82)	
2–3	10 (11)	3 (6)	7 (17)	14 (10)	1 (2)	13 (18)	
Stage, no. (%)							0.73
I, II	55 (63)	40 (85)	15 (38)	93 (66)	57 (85)	36 (49)	
III, IV	32 (37)	7 (15)	25 (72)	48 (34)	10 (15)	38 (51)	
Extranodal sites, no. (%)							0.84
0, 1	67 (77)	43 (91)	24 (60)	106 (75)	63 (94)	43 (57)	
≤2	20 (23)	4 (9)	16 (40)	35 (25)	4 (6)	31 (43)	
IPI, no. (%)							0.86
L/L-I	60 (69)	40 (85)	20 (50)	100 (71)	63 (94)	37 (50)	
H/H-I	27 (31)	7 (15)	20 (50)	41 (29)	4 (6)	37 (50)	

SIL2R, soluble interleukin-2 receptor; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; RCHOP, rituximab-combined CHOP; LDH, lactate dehydrogenase; PS, performance status; IPI, International Prognostic Index; L/L-I, low or low-intermediate; H/H-I, high or high-intermediate; high SIL-2R; SIL-2R >1000 U/ml, low SIL-2R; SIL-2R ≤1000 U/ml.

For CHOP therapy, the EFS and OS rates at 2 years were 82% and 93% for low SIL-2R and 43% and 65% for high SIL-2R, respectively. The differences in both the EFS and OS rates between the two SIL-2R levels were significant (both $P < 0.001$) (Figure 1A and B). In the RCHOP group, the EFS and OS rates at 2 years were 90% and 95% for low SIL-2R and 66% and 84% for high SIL-2R, respectively. The differences in both EFS and OS rates between the two SIL-2R levels were significant (EFS, $P < 0.001$; OS $P = 0.005$) (Figure 1C and D).

To study the impact of rituximab on the predictive value, we examined the clinical outcome according to treatment in the SIL-2R low and high groups. The patients with high SIL-2R who received RCHOP therapy had a significantly better OS at 2 years than patients treated with CHOP alone (84% versus 65%, $P = 0.020$). The EFS at 2 years was estimated to be 66% for the RCHOP group and 43% for the CHOP group ($P = 0.010$). For the patients with low SIL-2R, the influence of rituximab on OS and EFS was not significant (OS, 93% versus 95%, $P = 0.310$; EFS, 82% versus 90%, $P = 0.160$) (Table 2).

For comparison with this parameter, we analyzed the survival curves according to the IPI in both treatment groups. The EFS and OS rates at 2 years were 35% and 59% for high or high-intermediate IPI and 77% and 91% for low or low-intermediate IPI, respectively, in the CHOP group. The differences in both EFS and OS rates between the two IPI groups were significant (both $P < 0.001$). Similarly, the EFS and OS rates

were 58% and 80% for high or high-intermediate IPI and 86% and 94% for low or low-intermediate IPI, respectively, in the RCHOP group. Again, the differences in the EFS and OS rates were significant ($P < 0.001$ and $P = 0.004$, respectively).

To estimate unbiased prognostic impacts, Cox univariate analysis showed that a high SIL-2R level, high PS, advanced stage, multiple extranodal sites and high or high-intermediate risk of IPI were associated with poor EFS and OS in both treatment groups (Table 3). In the second step, Cox multivariate analysis showed that only SIL-2R was significantly associated with a higher risk of event and that SIL-2R and PS were independently associated with poor OS in both treatment groups (Table 4). Finally, SIL-2R was a significant risk factor for EFS and a borderline risk factor for OS in both the CHOP and RCHOP groups ($P = 0.060$ and 0.070, respectively), whereas IPI was a significant risk factor for EFS and OS in the CHOP group and a borderline significant risk factor for EFS and OS ($P = 0.070$ and 0.080, respectively) in the RCHOP group (Table 5).

discussion

Although SIL-2R is easy to measure, its prognostic value has been underestimated due to its evaluation in smaller populations than those for other parameters, such as IPI [2]. The SIL-2R level was reported to be significantly high in highly aggressive lymphomas [6] and subsequently was recognized to reflect tumor burden and poor outcome [3–8]. However, these