non-participant 'controls' were chosen from differently pooled database, which could include baseline imbalances between groups and hindsight bias (Davis *et al*, 1985; Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In this study, we compared the characteristics and outcomes of those who met the eligibility criteria but declined to participate in randomised trials, and instead chose to receive standard therapy. We thus aimed at excluding confounding factors as much as possible.

On the other hand, physician triage is pointed out to be one of the barriers to cancer clinical trial accrual (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006; Ho *et al*, 2006). We excluded the barrier by making it a rule to offer clinical trials to every patient with advanced NSCLC who satisfied the eligibility criteria.

The response rate, MST, 1-year and 2-year survival rates were all similar in both groups. We have to admit that response evaluation might not be as strict in off-protocol therapy. However, the hazard ratio for the OS was very close to 1. Although the confidence interval of 0.73 to 1.28 could not rule out the existence of clinically important difference in the treatment effect, it could not by any means be taken as a clinically relevant prognostic factor. We thus believe this confidence interval of the adjusted hazard ratio, 0.73–1.28, was narrow enough to justify the conclusion that the clinical outcomes of trial participants and non-participants were not different in our study. The differences in the number of cycles of chemotherapy given to participants and non-participants may suggest the so-called protocol effect (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), in which explicit careful description of treatment regimens could lead to improvement of outcomes. On the other hand, there clearly existed no 'care effect' representing the differences in incidental aspects of treatment or care between participants and non-participants, which the protocol may require, such as extra follow-up or extra nursing care (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004). In our cases, the same treatment teams took charge of and followed both groups of patients in the same manner, and found no differences in the post-treatment characteristics or follow-up periods. Thus, our first finding was that the clinical trials themselves seemed to have no influence on the outcomes or pattern of care of the patients.

The second finding was that we could not find any demographic characteristics to influence the patients' willingness to participate in clinical trials. Taken together with the first finding, both the characteristics and outcomes of the non-participants were very similar to the participants. This would imply that the participants ably represented the whole patient population of the disease status who met the eligibility criteria, and that conclusions from the clinical trials could be generalised.

Our study, however, could only show the similarity in the prognosis of the participants and non-participants, and, unlike an earlier report (Link *et al*, 1986), not that of the treatment effect itself. This could not be evaluated because there were no significant differences in the clinical effect between the arms in both Trial 1 and Trial 2. If newer, much more effective experimental treatment were presented in the trials, the outcome could be better in trial participants, which was the case in the adjuvant chemotherapy trial for osteosarcoma (Link *et al*, 1986). In that report, eligible patients who declined randomisation, but were given adjuvant chemotherapy, also had better outcomes. Therefore, a very effective treatment could lead to a better outcome both on and off trial. Ideally, strict comparison of the effects of the study participation itself would require randomised design of the trial participation (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004), which is almost impossible to conduct.

Thirdly, the declining rate seemed to be influenced by the trial design. Trial 1 was the comparison of four similar platinum-doublet regimens. On the other hand, Trial 2 was the comparison of two arms with sequentially different types of chemotherapy. In general, people might have the impression that injection therapy would be more effective, and less convenient, than oral administration. It is easy to understand that more patients felt difficulty in accepting the randomisation of different types of therapy, such as Trial 2 (Schmoor *et al*, 1996; Jenkins and Fallowfield, 2000).

The declining rate also seemed to be greatly affected by the attending physician. The attending physician with longer experience as a thoracic oncologist tended to have lower rate of declination. Even though we do not have records on who actually informed the participants regarding the trial, residents or trainees under Physician A seemed to have had more chance to lead the consultation, which might have affected the rate of declination. Trust in the doctor is one of the most important reasons for agreeing to enter an RCT, whereas it has also been cited as the main reason for declining to participate (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Stryker *et al*, 2006). Patients prefer the doctor to make the treatment decisions rather than to be randomised. A recent report emphasises the influence of physicians' clinical communication on patients' decision-making on participation in clinical trials (Albrecht *et al*, 2008). Improving communication and more interventions by clinical research coordinators and other medical staff members in all eligible patients may improve the accrual rate (Fallowfield *et al*, 1998; Wright *et al*, 2004; Stryker *et al*, 2006).

Finally, it was interesting to find that 8% of those who declined the RCTs participated in early-phase trials during follow-up. It is possible that the lack of effective therapies had changed their recognition of clinical trials. However, it might support the psychological states of patients as reported in earlier studies (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Wright *et al*, 2004); patients expect experimental therapies to give them improved effectiveness but with fear of uncertainty. They are reported to have negative opinions regarding the principle of randomisation. Better understanding of the patients' decision-making process and the factors influencing their psychological states may lead to improvement in RCT accrual.

Our study has several limitations. One is that it was conducted at a single academic institution; the situation might well have been different in others or when the research was performed on a multi-institution basis. The second is that we analysed data from only two trials and could not definitely conclude that a trial design would affect the patient accrual. Third, we have no data on the reasons for patient participation. That information would be definitely useful for analysing factors for consent or declining to participate, and would help to improve the accrual rate. Further research is required.

In conclusion, there was no evidence of any difference in the response rates and survival times between participants and non-participants. The declining rate of clinical trials was influenced by the referring physicians and trial designs. Further analysis of the decision-making process of those offered trials is warranted, for it may improve patient accrual to RCTs.

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Original article

Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer

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Background: **Locally advanced gastric cancer with extensive lymph node metastasis is usually considered unresectable and so treated by chemotherapy. This trial explored the safety and efficacy of preoperative chemotherapy followed by extended surgery in the management of locally advanced gastric adenocarcinoma.**

Methods: **Patients with gastric cancer with extensive lymph node metastasis received two or three 28-day cycles of induction chemotherapy with irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent gastrectomy with curative intent with D2 plus para-aortic lymphadenectomy. Primary endpoints were 3-year overall survival and incidence of treatment-related death.**

Results: **The study was terminated because of three treatment-related deaths when 55 patients had been enrolled (mortality rate above 5 per cent). Two deaths were due to myelosuppression and one to postoperative complications. Clinical response and R0 resection rates were 55 and 65 per cent respectively. The pathological response rate was 15 per cent. Median overall survival was 14·6 months and the 3-year survival rate 27 per cent.**

Conclusion: **This multimodal treatment of locally advanced gastric cancer provides reasonable 3-year survival compared with historical data, but at a considerable cost in terms of morbidity and mortality.**

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Introduction

Macroscopically complete tumour removal is a prerequisite to cure gastric cancer[1,2]. Japanese surgeons have explored the benefits and disadvantages of para-aortic nodal dissection for locally advanced tumours with nodal metastases[3–6]. The Japanese Gastric Cancer Association (JGCA) defines para-aortic lymph nodes as being regional lymph node stations (JGCA-N3)[7]. Tumours with bulky nodal metastases surrounding the coeliac artery and its branches (JGCA-bulky N2) are usually considered unresectable. The prognosis of patients with JGCA-N3 or JGCA-bulky N2 is extremely poor even when the entire tumour and lymph nodes can be resected with curative intent. Further, complete resection of these tumours often requires combined organ resection, such as distal pancreatectomy, resulting in major surgical complications[8]. Even after this surgery with curative intent, most tumours recur, suggesting that distant micrometastases were already present.

In contrast to the Japanese staging system, the tumour node metastasis (TNM) staging of the International Union Against Cancer (UICC) defines para-aortic metastases as

The Editors are satisfied that all authors have contributed significantly to this publication

distant metastases[9]. In Western countries, tumours with JGCA-N3 or JGCA-bulky N2 are therefore regarded as unresectable disease that warrants palliative chemotherapy. These patients rarely survive for more than 3 years when they receive chemotherapy alone or when surgery is followed by postoperative chemotherapy. To improve this dismal prognosis, a different strategy should be developed.

Preoperative chemotherapy has some theoretical benefits in these patients in comparison with postoperative chemotherapy. First, extended surgery can be performed easily and safely because the chemotherapy usually leads to shrinkage of lymph nodes, increasing the likelihood of R0 resection. Second, more intensive chemotherapy is possible with high compliance. Third, distant micrometastases can be treated early, before local therapy has begun. Recently, the effectiveness of a regimen of preoperative and postoperative epirubicin, cisplatin and infused fluorouracil for less advanced disease was suggested[10]. Combined chemotherapy using irinotecan hydrochloride plus cisplatin is also an attractive regimen for preoperative chemotherapy. In a phase II trial using this regimen in patients with metastatic gastric cancer, a response rate of 48 per cent and acceptable toxicity were reported[11].

The present study was conducted to evaluate the efficacy and safety of preoperative chemotherapy with irinotecan plus cisplatin followed by gastrectomy with D2 plus para-aortic nodal dissection for locally advanced gastric cancer with extensive lymph node metastases.

Methods

The study was conducted as a prospective multi-institutional phase II trial between 2000 and 2003 involving the 21 institutions of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with locally advanced gastric cancer presenting at their institution were considered for participation in the study. The absence of peritoneal dissemination was confirmed by laparoscopy before entry into the study.

Eligibility criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; para-aortic nodal metastases and/or bulky N2 cancers confirmed by contrast-enhanced computed tomography (CT) (definitions in *Fig. 1*); no metastases outside the para-aortic region, as confirmed by contrast-enhanced CT; no peritoneal or pleural effusion; no

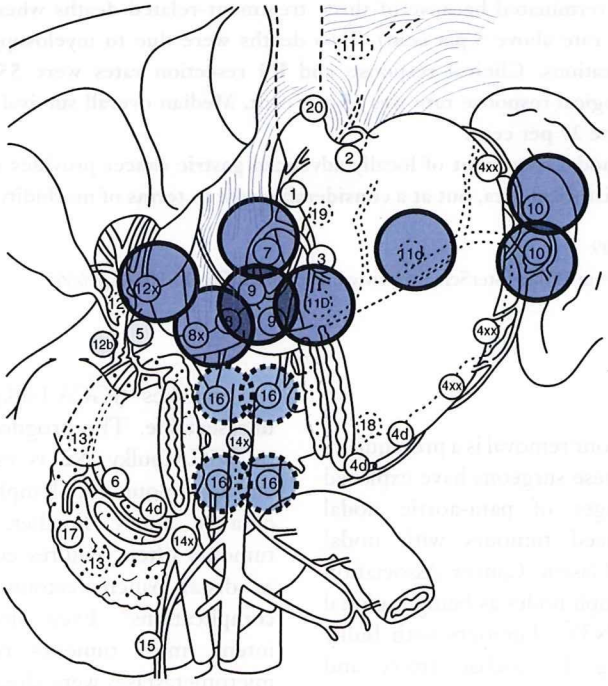

Fig. 1 Definitions of bulky N2 and para-aortic nodal metastases. Bulky N2 (in solid circles): at least one node of 3 cm or more in diameter, or at least three consecutive nodes each of diameter 1·5 cm or more, along the coeliac, splenic, common or proper hepatic arteries. Para-aortic nodes (in dashed circles): at least one node of 1 cm or more in diameter around the abdominal aorta

clinically apparent brain or bone metastases; no peritoneal metastases and negative cytology at laparoscopy; non-scirrhous type macroscopically; 20–70 years of age; Eastern Cooperative Oncology Group performance status 0 or 1; no previous chemotherapy or radiotherapy. In addition, patients had to have no signs of organ failure, as assessed by a white blood cell (WBC) count minimum of 4000/mm^3 and maximum of 12 000/mm^3, platelet count of 100 000/mm^3 or above, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than three times the upper limit of normal, total bilirubin 1·5 mg/dl or less, creatinine 1·2 mg/dl or less and creatinine clearance 60 ml/min or above, and haemoglobin 9·0 g/dl or more. There had to be no ischaemic change or ventricular arrhythmia on exercise electrocardiography, a forced expiratory volume in 1 s of 50 per cent or more, arterial partial pressure of oxygen (PaO_2) of 70 mmHg or above, and indocyanine green test in 15 min of 10 per cent or less in cases of liver dysfunction, negative serology for viral hepatitis and no past history of hepatitis. All patients gave written informed consent.

Exclusion criteria included: active gastrointestinal bleeding, infection, watery diarrhoea, synchronous or metachronous (within 10 years) malignancy other than carcinoma *in situ*, pregnancy or lactation, treatment with a major tranquillizer, lung fibrosis or interstitial pneumonitis, and bowel obstruction. Patients with allergic reactions to iodine were excluded because contrast-enhanced CT could not be performed. All patients were registered centrally at the JCOG Data Centre, where data management, central monitoring and statistical analysis were conducted. For quality assurance, a site visit audit was performed by the JCOG Audit Committee.

Preoperative chemotherapy

Irinotecan 70 mg/m^2 was administered on days 1 and 15 and cisplatin 80 mg/m^2 was given on day 1 as one course, repeated every 4 weeks[11]. If the patient had a WBC of 4000/mm^3 or less, platelet count of 10 000/mm^3 or lower, diarrhoea of grade 1 or above (increase of four or more stools per day over pretreatment), an episode of infection or abnormal serum creatinine concentration, administration of irinotecan and/or cisplatin was postponed until recovery. If recovery did not occur within 2 weeks, chemotherapy was stopped. On day 15 of each course, if the patient had an adverse event the second administration of irinotecan was postponed, and was not given if the adverse event was still observed on day 22. If the patient had haematological adverse events of grade 4 (haemoglobin level less than 6·5 g/dl, leucocyte count below 1000/mm^3, neutrophil count less than 500/mm^3, or platelet count below 25 000/mm^3), diarrhoea of grade 3 or higher (increase of more than seven stools per day or incontinence, or need for parenteral support for dehydration), or if the second administration of irinotecan was not given in the last course, the next dose of irinotecan was reduced to 60 mg/m^2. If the patient had a serum creatinine level of 1·2–1·5 mg/dl, the next dose of cisplatin was reduced to 60 mg/m^2. If serum creatinine was 1·5 mg/dl or above, initiation of the next course was delayed.

Some 7–13 days after the second administration of irinotecan in each course, resectability was evaluated based on CT findings by the Response Evaluation Criteria in Solid Tumours (RECIST)[12]. If curative resection was considered possible after the second course, the patient had surgery immediately. If curative resection was considered difficult, a further course of chemotherapy was added before surgery.

Surgery

Resection criteria included: R0 resection deemed possible by gastrectomy with D2 plus para-aortic nodal dissection, and no evidence of organ failure as assessed by a WBC count greater than 3000/mm^3 and less than 12 000/mm^3, platelet count above 100 000/mm^3, AST and ALT levels less than three times the upper limit of normal, total bilirubin less than 1·5 mg/dl, creatinine below 1·5 mg/dl and creatinine clearance above 50 ml/min, and PaO_2 greater than 70 mmHg. Eligible patients were operated on 3–6 weeks after chemotherapy.

After laparotomy, resectability was again evaluated and, if intraperitoneal wash cytology was negative, R0 resection was attempted by gastrectomy with D2 plus para-aortic nodal dissection, as described previously[13]. If necessary, D2 plus para-aortic nodal dissection was combined with splenectomy and/or distal pancreatectomy.

The treatment protocol was completed when a patient had received two or three courses of preoperative chemotherapy and had undergone R0 resection by gastrectomy with D2 plus para-aortic nodal dissection (*Fig. 2*). After completion of the protocol, no further treatment was given until tumour recurrence.

Quality control of surgery

During the recruitment period, participating surgeons and data centre representatives met three times per year to monitor the study. At each meeting, videos of various surgical procedures, including nodal dissection, were presented by several participating institutions,

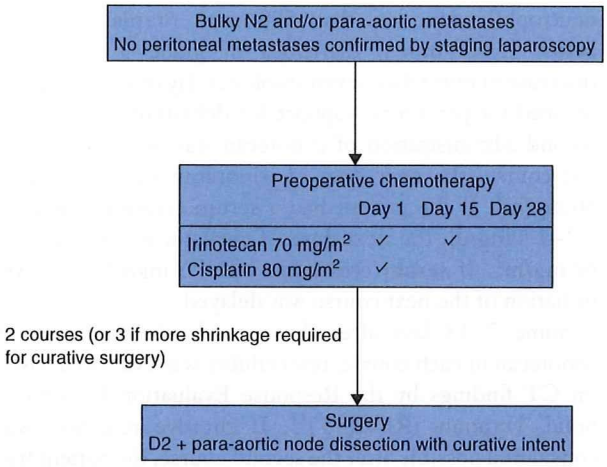

Fig. 2 Study outline

and technical details were discussed for critique. To assess compliance with lymphadenectomy, the number of dissected nodes was recorded.

Objectives and evaluation

Primary endpoints were overall survival and incidence of treatment-related death. Secondary endpoints were number of R0 resections, response to chemotherapy, chemotherapy-related toxicity and surgical complications. Clinical response was evaluated by RECIST[12], based on CT with a central review. Surgical specimens were evaluated pathologically and graded according to the proportion of tumour affected by degeneration or necrosis[14]: grade 0, no part of tumour affected; grade 1a, less than one-third affected; grade 1b, between one-third and two-thirds affected; grade 2, between two-thirds and entire tumour affected; and grade 3, no residual tumour. A pathological response was defined as one-third or more of the tumour affected (grade 1b, 2 or 3). Adverse events during chemotherapy were evaluated by the National Cancer Institute – Common Toxicity Criteria version 2.0[15].

Statistical analysis

For sample size calculation, treatment was considered effective if the lower limit of the 95 per cent confidence interval (c.i.) for 3-year survival exceeded 15 per cent. In terms of feasibility and efficiency, sample size was determined as 60 with a 3-year entry and 3-year follow-up period. In this setting, the exact binomial lower confidence limit for a 3-year overall survival rate of 30 per cent (18 of 60) was 18·9 per cent and that for 25 per cent (15 of 60) was 14·8 per cent. This was considered sufficiently precise to make inferences based on 3-year survival. Hence, the sample size was calculated as 60.

The survival curve was estimated using the Kaplan–Meier method; 95 per cent c.i. were calculated with the Greenwood formula[16]. Treatment was considered safe if point estimates of treatment-related death did not exceed 5 per cent. The stopping rule for safety was prespecified so that the study would be terminated when treatment-related death had been observed in three patients (treatment-related death exceeding 5 per cent). Statistical analysis was performed with SAS® version 8.2 (SAS Institute, Cary, North Carolina, USA). This phase II trial was approved by the JCOG Protocol Review Committee and institutional review board of each institution involved.

Results

Between August 2000 and May 2003, 55 patients were entered into the study and underwent preoperative chemotherapy. All patients were followed for more than 3 years after registration. When 55 patients had been registered, three were judged as treatment-related deaths by the JCOG data and safety monitoring committee, and the study was terminated according to the stopping rules. Thus, the treatment-related death rate was 5 (95 per cent c.i. 1 to 15) per cent. *Table 1* shows patient demographics and tumour characteristics. A flow diagram from chemotherapy to surgery is shown in *Fig. 3*. The clinical response rate for all eligible patients was 55 (95 per cent c.i. 41 to 68) per cent (30 of 55 patients) (*Fig. 3*).

Table 1 Demographics and tumour characteristics in 55 eligible patients

Median (range) age (years)	63 (46–70)
Sex ratio (M : F)	42 : 13
ECOG performance status	
0	47
1	8
Histology	
Differentiated	30
Undifferentiated	25
Nodal status	
Para-aortic nodes and bulky N2	19
Only para-aortic nodes	11
Only bulky N2	25

ECOG, Eastern Cooperative Oncology Group.

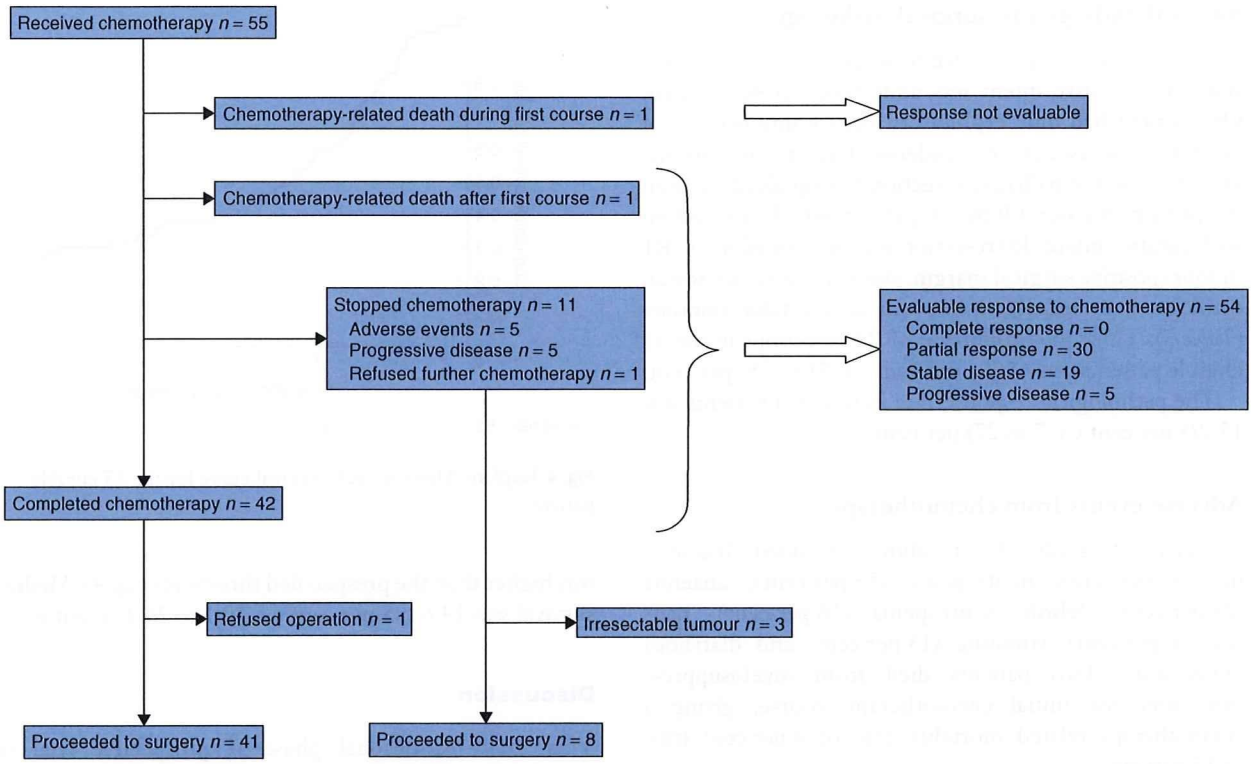

Fig. 3 Flow diagram from chemotherapy to surgery in 55 eligible patients

Table 2 Details of 49 patients who underwent surgery

	No. of patients
Peritoneal cytology	
Negative	45
Positive	4
Type of resection	
Total gastrectomy	32
Distal gastrectomy	15
Bypass	1
Exploratory laparotomy	1
Dissection of nodes along splenic artery	
With splenectomy and distal pancreatectomy	14
With splenectomy	16
Without splenectomy	13
No nodal dissection	6†
Operating time (min)*	370 (40–930)
Blood loss (ml)*	1050 (0–5650)
Blood transfusion	34
No. of para-aortic nodes dissected*	26 (0–86)
No. of nodes dissected*	87 (45–179)

*Values are median (range). †Exploratory laparotomy in one patient, bypass in one, palliative resection in one and non-curative resection in three patients.

Table 3 Pathological findings in resected patients

	No. of patients (n = 47)
Depth of tumour invasion	
T1	3
T2	18
T3	19
T4	6
Unknown	1*
JGCA, nodal status	
N0	1
N1	7
N2	9
N3	30
JGCA, pathological response	
Grade 0	6
Grade 1a	33
Grade 1b	2
Grade 2	5
Grade 3	1

*Not evaluable as no residual cancer cells. JGCA, Japanese Gastric Cancer Association.

Surgical findings and surgical pathology

Forty-nine patients proceeded to surgery (*Table 2*). Resection with curative intent was undertaken in 46 patients. One patient had only exploratory laparotomy because of peritoneal metastases, one underwent gastrojejunostomy, and one required palliative resection to stop bleeding from the primary tumour. Of the 46 patients who had resection with curative intent, R0 resection was performed in 36, R1 in four (positive surgical margin, three; positive peritoneal cytology, one) and R2 in six with unresectable tumours (*Table 3*). Thus, the proportion of R0 resections in the 55 eligible patients was 65 (95 per cent c.i. 51 to 78) per cent.

The pathological response rate in resected patients was 15 (95 per cent c.i. 7 to 27) per cent.

Adverse events from chemotherapy

Toxicity of grade 3 or above included leucopenia (31 per cent), neutropenia (55 per cent), anaemia (24 per cent), febrile neutropenia (16 per cent), nausea (36 per cent), vomiting (13 per cent) and diarrhoea (5 per cent). Two patients died from myelosuppression after the initial chemotherapy course, giving a chemotherapy-related mortality rate of 4 per cent (two of 55 patients).

Surgical complications

Surgical complications are shown in *Table 4*. One (2 per cent) of 49 patients died from multiple organ failure 3 days after thoracoabdominal surgery for oesophageal invasion in addition to a total gastrectomy with pancreaticosplenectomy.

Overall survival

The 3-year survival rate was 27 (95 per cent c.i. 15 to 39) per cent, and thus the lower limit of the 95 per cent c.i. was higher than the prespecified threshold (*Fig. 4*). Median survival was 14·6 (95 per cent c.i. 10·1 to 24·1) months.

Table 4 Surgical complications in the 49 operated patients

	No. of patients
Leakage	1 (2)
Pancreatic fistula	6 (12)
Abdominal abscess	2 (4)
Pneumonia	2 (4)
Ileus	0 (0)
Wound infection	2 (4)
Stenosis of anastomosis	1 (2)
Cardiac failure	1 (2)
Renal dysfunction	1 (2)
Other	6 (12)

Values in parentheses are percentages.

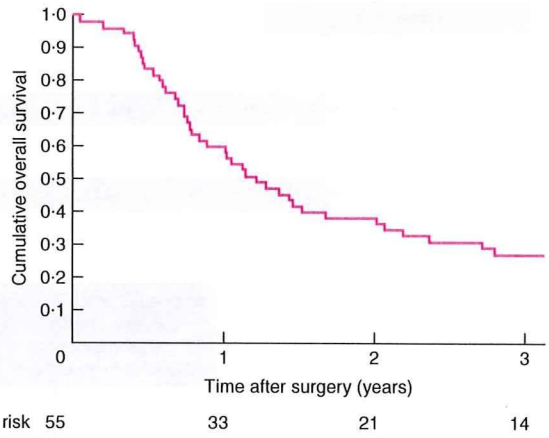

Fig. 4 Kaplan–Meier overall survival curve for the 55 eligible patients

Discussion

This multi-institutional phase II prospective trial of neoadjuvant chemotherapy in locally advanced gastric cancer with extensive lymph node metastases showed that multimodality treatment can achieve a high 3-year survival rate of 27 per cent. Usually these patients rarely survive for more than 3 years when treated by chemotherapy alone or by surgery followed by postoperative chemotherapy. Thus, the protocol treatment was effective for these patients, but was achieved at the cost of considerable morbidity and mortality, and the study had to be stopped prematurely because of treatment-related deaths.

The combination chemotherapy of irinotecan plus cisplatin was chosen because it had achieved a high response rate of 59 per cent in a previous phase II study of chemotherapy-naive patients with metastatic gastric cancer[11]. At the start of the present study in 2000, this was considered to be the most effective and promising regimen for gastric cancer. In Japan, based on these data, a phase III trial was initiated to determine the superiority of irinotecan plus cisplatin compared with 5-fluorouracil (5-FU) alone for metastatic gastric cancer[17]. In the present study, the clinical response to preoperative chemotherapy was 55 per cent, comparable with previous results using this regimen in patients with metastatic gastric cancer[11]. Although the above-mentioned Japanese phase III trial (JCOG 9912) did not demonstrate superiority for this regimen compared with 5-FU alone, a subset analysis for tumours with target lesion defined by RECIST

showed that combination chemotherapy of irinotecan plus cisplatin gave a median survival of 12·1 months, which was significantly longer than for 5-FU alone[17]. This suggested that irinotecan plus cisplatin was especially active against tumours forming bulky masses[17]. In contrast to the impressive clinical response of metastatic nodes, the pathological response in the primary tumours was relatively low in the present study. In gastric cancer, the pathological response rate is usually less than 20 per cent for any chemotherapeutic regimen, suggesting the importance of appropriate local control by surgery. The relatively good overall survival at 3 years in the present study appears to be due to the effects of neoadjuvant chemotherapy in two ways: downstaging of lymph node metastases, which enabled R0 resection in 65 per cent of patients, and good control of micrometastases.

Treatment-related death was observed in 5 per cent of patients in this study, indicating that this treatment protocol is hazardous. Of three patients, two died from chemotherapy-induced myelosuppression. Neutropenia and diarrhoea were the major toxicities of this regimen, as reported previously[11,17]. Compared with these trials, toxicity in the present study was relatively low, but the mortality rate was high. In two treatment-related deaths from chemotherapy, severe myelosuppression appeared immediately after the first administration of irinotecan plus cisplatin. Boku and colleagues[17] observed severe diarrhoea only during the first course of the same regimen in patients with unresectable gastric cancer. Noda and co-workers[18] reported on the efficacy of combination therapy with irinotecan plus cisplatin for small cell lung cancer, using a different schedule and dosage than those in the present study. They observed treatment-related deaths in three patients (4 per cent) during the first or second cycle of chemotherapy. Taken together, all of these results indicate that severe haematological toxicity and diarrhoea should be managed carefully, especially during the initial cycles of chemotherapy.

Recently, genetic polymorphism of UTG1A1, which is involved in glucuronidation of SN-38 or is an active metabolite of irinotecan, has been reported to be associated with irinotecan toxicity[19,20]. Polymorphisms of UGT have also recently been suggested as a risk factor for irinotecan-induced neutropenia[21]. These factors might have been involved in the treatment-related deaths observed in the present study, although genetic analysis was not performed. Patient risk may be reduced not only by careful management of myelosuppression, but possibly also by patient selection based on genetic analysis. However, further studies are needed to confirm this. Because the combination chemotherapy regimen employed in this study is difficult to manage in terms of toxicity, a new phase II study has been initiated to evaluate a preoperative S-1 (oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine and potassium oxonate) plus cisplatin regimen, which is considered less toxic for patients with extensive nodal metastases. S-1 and cisplatin showed a high response rate of over 50 per cent with mild toxicity in recent trials of patients with metastatic gastric cancer[22,23].

The operative mortality rate in this study was 2 per cent. In the JCOG 9501 trial, which compared D2 with D2 plus para-aortic nodal dissection, the mortality rate was 0·8 per cent for D2 plus para-aortic nodal dissection[13], whereas in the JCOG 9502 trial, which compared an abdominal approach with a left thoracoabdominal approach for gastric tumours invading the oesophagus, mortality rates were 0 and 4 per cent respectively[24]. Thus, the thoracoabdominal approach was the more hazardous of the two procedures. Because the influence of preoperative chemotherapy on surgery is unclear, patients who require such an extensive thoracoabdominal operation should probably be excluded from future studies.

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Transarterial chemotherapy alone versus transarterial chemoembolization for hepatocellular carcinoma: A randomized phase III trial☆

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See Editorial, pages x–y

***Background/Aims*: Transcatheter arterial chemoembolization (TACE) is a combination of transarterial infusion chemotherapy (TAI) and embolization, and has been widely used to treat patients with hepatocellular carcinoma (HCC). However, since the impact of adding embolization on the survival of patients treated with TAI had never been evaluated in a phase III study, we conducted a multi-center, open-label trial comparing TACE and TAI to assess the effect of adding embolization on survival.**

***Methods*: Patients with newly diagnosed unresectable HCC were randomly assigned to either a TACE group or a TAI group. Zinostatin stimalamer was injected into the hepatic artery, together with gelatin sponge in the TACE group and without gelatin sponge in the TAI group. Treatment was repeated when follow-up computed tomography showed the appearance of new lesions in the liver or re-growth of previously treated tumors.**

***Results*: Seventy-nine patients were assigned to the TACE group, and 82 were assigned to the TAI group. The two groups were comparable with respect to their baseline characteristics. At the time of the analysis, 51 patients in the TACE group and 58 in the TAI group had died. The median overall survival time was 646 days in the TACE group and 679 days in the TAI group ($p = 0.383$).**

***Conclusions*: The results of this study suggest that treatment intensification by adding embolization did not increase survival over TAI with zinostatin stimalamer alone in patients with HCC.**

***Keywords*: Zinostatin stimalamer; Survival benefit; Overall survival; Lipiodol emulsion; Gelatin sponge**

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Abbreviations: HCC, hepatocellular carcinoma; AFP, α-fetoprotein; TACE, transarterial chemoembolization; TAI, transarterial infusion chemotherapy; SMANCS, zinostatin stimalamer; CT, computed tomography; TE, therapeutic effect; SMA, styrene maleic acid; NCS, neocarzinostatin.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and a major cause of cancer mortality [1]. Although the screening of populations with a high risk of HCC using ultrasonography and serum α-fetoprotein (AFP) measurements have recently increased the number of candidates for effective local treatments such as hepatic resection and local ablation therapy, many patients exhibit HCCs that are unsuitable for local treatments at the time of the initial diagnosis or at the time of recurrence after local treatment. In these patients, transcatheter arterial chemoembolization (TACE) has been widely used, because TACE induces a marked antitumor effect in HCC.

Several randomized controlled studies have been conducted to assess the survival benefit of TACE compared with conservative therapy [2–9], and an improvement in survival with TACE has been shown in two recent phase III studies [7,8], in both of which TACE was compared with no treatment, and in two meta-analyses [10,11]. However, the impact of adding embolization on the overall survival of patients treated with transarterial infusion chemotherapy (TAI) has never been evaluated in a randomized controlled phase III study. We conducted a multi-centre, open-label trial to compare the effects of TACE and TAI alone to clarify the possible benefits of treatment intensification using embolization in addition to infusion chemotherapy. In this study, zinostatin stimalamer (SMANCS) was selected as the chemotherapeutic agent for use with both TACE and TAI. SMANCS is a lipophilic anti-cancer agent that dissolves in lipiodol to form a stable solution, retaining selectively in HCC. TAI with SMANCS has been widely used in clinical practice to treat patients with advanced HCC in Japan, because it has been reported to have fewer deleterious effects than TACE, especially on liver function, and to have an antitumor effect superior to TAI with other water-soluble agents in non-randomized studies [12,13].

2. Methods

Consecutive new patients with HCC were eligible if they had no indications for resection and/or local ablation therapy. The diagnosis was confirmed histologically and/or clinically using angiography and computed tomography (CT). Each patient was required to meet the following criteria: intrahepatic lesions that showed tumor staining by angiography and those in which the total size was less than 50% of the entire liver; adequate hematological function (white blood cells $\geqslant 3000/mm^3$, platelets $\geqslant 50{,}000/mm^3$, and hemoglobin $\geqslant 9.0$ g/dL), adequate hepatic function (serum total bilirubin $\leqslant 2.0$ mg/dL, serum albumin $\geqslant 3.0$ g/dL, serum AST [aspartate aminotransferase] $\leqslant 5$ times the upper limit of normal, serum ALT [alanine aminotransferase] $\leqslant 5$ times the upper limit of normal); adequate renal function (serum creatinine < the upper limit of normal, and serum blood urea nitrogen < the upper limit of normal); an Eastern Cooperative Oncology Group performance status of 0–1; an age of between 20 and 74 years of age; technically eligible for intra-arterial therapy; and written informed consent. Patients were excluded if they met any of the following criteria: a history of allergy to iodine-containing agents and/or contrast material; concomitant malignancy; a history of anti-cancer treatment for HCC; extrahepatic metastasis or tumor thrombus in the portal vein and/or the hepatic vein; intrahepatic arteriovenous shunting; ascites and/or pleural effusion not controlled by diuretics; pregnant or lactating woman and fertile patients not using effective contraception; myocardial infarction within the previous 6 months; or any serious physical and/or mental conditions. The study was performed in accordance with the Declaration of Helsinki, and approved by the ethics committee of each participating center. The study was investigator-designed and investigator-driven, and it received no support from any pharmaceutical companies.

Patients who met the eligibility criteria were provisionally registered before undergoing angiography. After confirmation of technical eligibility and reconfirmation of indications for the protocol intra-arterial treatments in regard to tumor status, including the number of tumors, their vascularity, and vascular invasion based on the angiographic findings, confirmatory registration was completed by each participating investigator. Central randomization to either a TACE group or TAI group was performed by using a telephone randomization system with stratification according to AFP level and treatment center. First, participants were stratified according to AFP level into a group with levels less than 400 ng/mL and a group with levels of 400 ng/mL or more. The group with AFP levels less than 400 ng/mL was further stratified according to treatment center. Randomization was achieved using a computer-generated allocation by permutation of blocks in equal proportions.

The treatments were performed by the participating investigators at 10 Japanese centers. Zinostatin stimalamer (SMANCS; Astellas Pharm Inc., Tokyo, Japan)/lipiodol emulsion (1 mg/mL) was injected slowly under fluoroscopic monitoring into the artery feeding the HCC using a catheter in a superselective manner in both the TACE and the TAI groups. The emulsion was prepared by suspending the SMANCS in lipiodol and shaking just before injection. The volume of the emulsion, up to a maximum of 6 mL (containing 6 mg of SMANCS), was adjusted according to the tumor size and tumor distribution. In the patients in the TACE group, gelatin sponge particles were utilized after the injection of the SMANCS-lipiodol emulsion. Treatment was repeated when a follow-up CT examination showed new lesions in the liver or re-growth of previously treated tumors. Treatment was discontinued if the size of the tumor treated had increased by more than 25% one month after the previous treatment; if there were any vascular contraindications, any exclusion criteria, or any severe adverse effects (defined as grade 4 leucopenia, grade 4 neutropenia, or grade 3 febrile leucopenia/neutropenia, a serum total bilirubin elevation of more than or equal to 5.0 mg/dL, a serum creatinine elevation of more than or equal to 1.5 times the upper normal limit, or grade 3 or greater non-hematological toxicity excluding nausea, vomiting, anorexia, pain, fever, hyperglycemia, fatigue, and serum transaminase elevation), or if the patient so requested.

The primary outcome measure was survival calculated from the date of randomization. Secondary outcome measures were tumor response and toxicity. Antitumor effect was evaluated by CT performed 1 month after the completion of treatment and every 3–4 months thereafter according to the response evaluation criteria proposed by the panel of experts of the Liver Cancer Study Group of Japan [14], which resemble the criteria proposed by the European Association for the Study of the Liver (EASL) Panel of Experts on HCC [15]. Tumor size was measured using the sum of the products of the perpendicular longest diameters of all measurable lesions. In the response evaluation criteria, lipiodol accumulation in the tumors is regarded as an indication of necrosis because significant positive correlations have been reported between lipiodol accumulation observed on CT images and the necrotic regions in resected tumors examined pathologically after TACE and after TAI with SMANCS [13,16,17]. Therapeutic effect V (TE V) is defined as the disappearance or 100% necrosis of all tumors, TE IV as a more than a 50% reduction in tumor size and/or more than 50% necrosis, and TE III as a more than 25% reduction and/or more than 25% necrosis. TE I is defined as a more than 25% increase in tumor size. TE II is defined as disease not qualifying for classification as TE V, IV, III, or I. The serum AFP level of each patient was also measured 1 month after treatment and every 3–4 months thereafter. Toxicity was assessed according to the criteria of the Japan Society for Cancer

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Therapy [18], whose criteria are essentially the same as the WHO criteria [19]. The follow-up period was defined in the protocol as 2 years after the enrollment of the last patient.

2.1. Statistical analysis

Based on our previous phase II studies, in which we reported a 2-year survival rate of 80% in patients treated with TACE and of 60% in patients treated with TAI, 70 patients were required in each group to achieve a 90% power to detect superior survival in the TACE group by using a two-sided alpha level of 5% [13,20]. After sensitivity analyses of combinations of survival parameters, we targeted the recruitment of 80 patients in each group. All analyses were conducted based on the intention-to-treatment principle. Survival curves were calculated from the day of randomization using the Kaplan–Meier method and compared using the log-rank test. Comparisons between groups were made using the Wilcoxon test for continuous variables and Fisher's exact test for categorical variables. Analyses were conducted using SAS ver. 8.

3. Results

Between October 1999 and June 2003, 222 patients were provisionally enrolled in the study at 10 Japanese centers (Fig 1). Sixty-one of the 222 patients were excluded because of ineligibility for intra-arterial treatment based on the angiographic findings or withdrawal of consent; too few or too many definitive tumors that required reconsideration of the treatment strategy (46), tumor thrombus in the portal vein (3), tumors without sufficient tumor staining (3), intrahepatic arteriovenous shunting (2), allergy to contrast material (1), and withdrawal of consent (6). The most common reason for exclusion was having too few definitive tumors (37/61). The patients who were excluded because of having too few definitive tumors had been considered eligible based on the detection of several small hypervascular nodules on pre-treatment CT imaging that were diagnosed as HCC, but treatment had been switched to local ablation therapy or monitoring based on angiographic findings suggesting that the nodules represented dysplastic nodules. All of the patients who withdrew consent requested TACE for their treatments. The remaining 161 patients were allocated randomly to the TACE group (79 patients) or the TAI group (82 patients). Follow-up was continued through to June 17, 2005, two years after the enrollment of the last patient. Although the baseline data of some eligible patients did not meet the eligibility criteria after they were enrolled, the study protocol permitted initiation of treatment when according to the judgment of the investigator, treatment could be performed safely. Two patients had a pre-treatment serum albumin level that was below the eligibility criterion, but there were no statistically significant differences in baseline characteristics between the two groups (Table 1).

3.1. Treatment

The total number of treatment courses was 170 with a mean of 2.2 courses per patient (range, 1–9 courses) in the TACE group and 193 with a mean of 2.4 courses (range, 1–6 courses) in the TAI group. Eight patients in the TACE group and two patients in the TAI group were scheduled for the continuation of protocol treatment as of the date of the last follow-up. The remaining 71 patients in the TACE group and 80 patients in the TAI group had discontinued treatment. The reasons for treatment discontinuation were similar in both groups (Table 2).

3.2. Survival

At the time of the final analysis, 51 patients in the TACE group and 58 patients in the TAI group had died. Seven patients in the TACE group and eight in the TAI group were lost to follow-up after the cessation of protocol treatment. The median overall survival time was 646 days in the TACE group and 679 days in the TAI group. The estimated 2-year survival rate was 48.2% for the TACE group and 49.6% for the TAI group. No significant difference in survival was seen between the two groups ($p = 0.383$, Fig. 2).

3.3. Antitumor effect

The tumor response on CT was determined in 156 patients (77 in the TACE group and 79 in the TAI group). In the TACE group, there were 8 TE V, 29 TE IV, 31 TE III, 7 TE II, and 2 TE I responses. In the TAI group, there were 5 TE V, 22 TE IV, 30 TE III, 21 TE II, and 1 TE I response. The proportion of patients with TE V or IV among the measurable patients was not significantly different between the TACE group and the TAI group (48.1% vs. 34.2%; $p = 0.11$). There was no significant difference between the two groups in the proportion of patients with a pre-treatment AFP level > 200 ng/mL whose AFP level decreased by more than half (16.5% vs. 13.4%; $p = 0.66$).

3.4. Toxicity

Hematological toxicity was relatively mild and transient in both groups, although 2 patients (2.6%) in the TACE group and 3 (3.7%) in the TAI group developed grade 4 thrombocytopenia (Table 3). Major non-hematological toxicities were hyperbilirubinemia, elevations in serum liver enzymes, fever and abdominal pain in both groups. The grade of elevated ALT levels was significantly higher in the TACE group than in the TAI group, although there were no significant differences in any other toxicities between the two groups. No treatment-related death was observed in either group. Two patients in the TACE group and six in the TAI group manifested a grade 1–2 allergic reaction immediately after injection of the SMANCS-lipiodol emulsion. Shivering in the form of trembling of the whole body lasting

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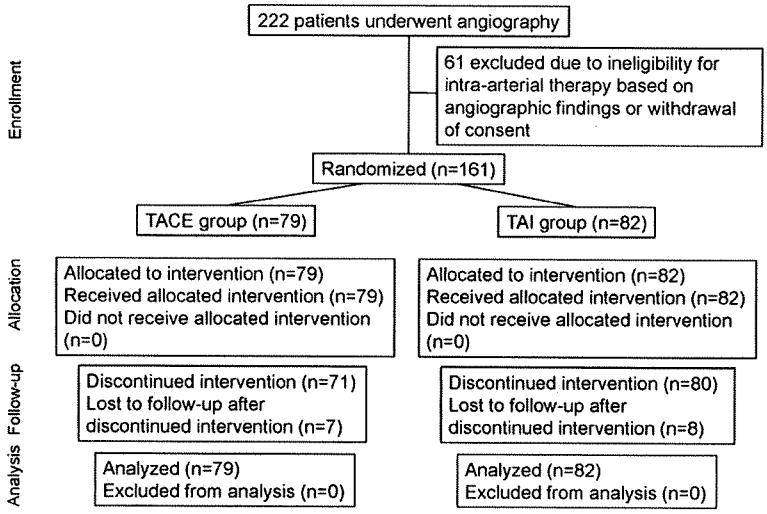

Fig. 1. Study flow diagram.

several minutes after the injection was noted in 12 patients in the TACE group and 14 patients in the TAI group, and it was thought to have been caused by SMANCS.

4. Discussion

We initiated this randomized study in 1999 because the impact of adding embolization on overall survival

Table 1
Baseline characteristics.

No. of patients		79	82
Age, year	Median (range)	65.0 (42–74)	67.0 (44–74)
Gender	Male	61 (77.2%)	70 (85.4%)
Performance status	0	76 (96.2%)	77 (93.9%)
	1	3 (3.8%)	5 (6.1%)
HBsAg	+	11 (13.9%)	7 (8.5%)
HCVAb	+	57 (72.2%)	60 (73.2%)
Alcohol abuse	+	33 (41.8%)	28 (34.1%)
Albumin, g/dL	Median (range)	3.6 (2.8–4.6)	3.6 (3.0–4.6)
Total bilirubin, mg/dL	Median (range)	1.0 (0.4–2.0)	0.9 (0.3–2.0)
AST, IU/L	Median (range)	63 (16–243)	69 (18–232)
ALT, IU/L	Median (range)	60 (12–184)	60 (10–213)
Prothrombin time, %	Median (range)	80 (41–129)	78.5 (43–111)
Platelet count, $\times 10^9$/L	Median (range)	110 (48–280)	120 (44–290)
	$<100 \times 10^9$/L	29 (36.7%)	28 (34.1%)
Ascites	+	3 (3.8%)	3 (3.7%)
Stage*	I	2 (2.5%)	4 (4.9%)
	II	18 (22.8%)	17 (20.7%)
	III	28 (35.4%)	25 (30.5%)
	IV-A	31 (39.2%)	36 (43.9%)
Tumor distribution	Unilateral	40 (50.6%)	36 (43.9%)
	Bilateral	39 (49.4%)	46 (56.1%)
Maximum tumor diameter, mm	Median (range)	35 (10–330)	35 (12–350)
Number or tumors	1	13 (16.5%)	11 (13.4%)
	2–5	43 (54.4%)	52 (63.4%)
	6	23 (29.1%)	19 (23.2%)
AFP, ng/ml	Median (range)	68.3 (2.8–79170)	93.8 (3.1–40,000)
	≥400 ng/ml	26 (32.9%)	27 (32.9%)
Serum creatinine, mg/dL	Median (range)	0.7 (0.4–1.3)	0.8 (0.5–1.1)

Abbreviations: AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.
Alcohol abuse was defined as ethanol intake ≥80 g/day for ≥5 years.
* According to the staging system of the Liver Cancer Study Group of Japan.

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Table 2
Reasons for treatment discontinuation.

	TACE group		TAI group	
Ineffectiveness of protocol treatment	10	13%	10	12%
Adverse event caused by protocol treatment				
Elevation of serum creatinine level	1	1%	1	1%
Elevation of alkaline phosphatase level	2	3%	2	2%
Dyspnea	0	0%	1	1%
Hypotension	1	1%	1	1%
Shivers	0	0%	1	1%
Abdominal pain	0	0%	2	2%
Ascites	1	1%	0	0%
Deterioration before subsequent protocol treatment				
Extrahepatic metastasis	4	5%	7	9%
Portal vein thrombosis	6	8%	3	4%
Tumor rupture	2	3%	0	0%
Ascites	9	11%	11	13%
Liver dysfunction	9	11%	11	13%
Poor general condition	2	3%	2	2%
Other disease	1	1%	6	7%
Technical problem preventing subsequent protocol treatment	13	16%	9	11%
Patient's request	10	13%	11	13%
Indication for tumor ablation	1	1%	2	2%
Protocol treatment ongoing	7	9%	2	2%
Total	79		82	

for patients with advanced HCC treated with TAI had not been fully evaluated and because the efficacy of TACE was still being debated at that time in various countries. Moreover, several differences in TACE methods had been noted between clinical practice in East Asian countries, including Japan, and randomized studies conducted in Europe, including differences in the selection of embolization materials, anti-cancer agents and their doses, in treatment intervals, and in patient characteristics such as tumor stage and liver function. In this study, in which our TACE method was introduced, we selected SMANCS as a chemotherapeutic agent for both TACE and TAI. SMANCS is an anti-cancer drug that has been approved by the Japanese government for administration with lipiodol into the artery feeding HCC, and TAI with SMANCS has been widely used instead of TACE in many hospitals because of its favorable antitumor effect and mild toxicity profile.

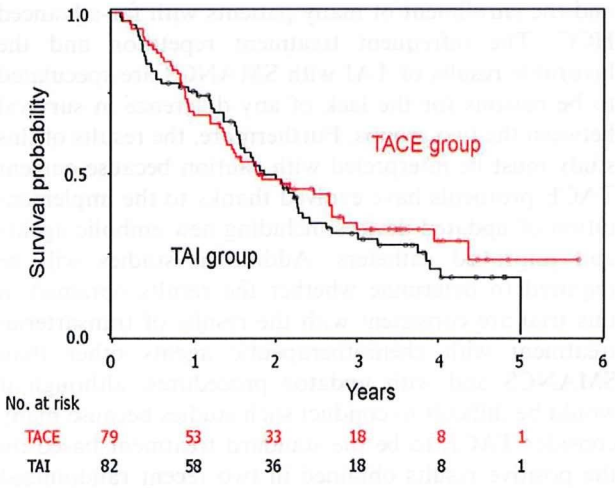

Fig. 2. Survival curves in the TACE group and in the TAI group.

This study did not confirm any significant survival advantage of TACE over TAI. A German group also reported that adding transient occlusion using degradable starch microspheres improved neither tumor response nor survival for patients treated with TAI using cisplatin and doxorubicin in a randomized phase II trial [21]. Llovet and Bruix showed that survival benefits were identified with TACE (doxorubicin or cisplatin) but not with embolization alone in their meta-analysis [11]. The survival benefit of TACE can be ascribed to the combination of embolization and chemotherapy.

It could be argued that the absence of a significant difference in survival rates between the TACE group and TAI group in this study is attributable to our methodological strategy for selecting SMANCS as the anti-cancer agent, because the agent may have produced favorable results in the TAI group. SMANCS is a high molecular weight chemical conjugate of a synthetic copolymer of styrene maleic acid (SMA) and the anti-cancer antibiotic protein, neocarzinostatin (NCS) [22,23]. SMANCS is lipophilic and dissolves in lipiodol to form a stable emulsion (SMANCS-lipiodol), which prevents rapid washout of SMANCS into plasma from trapped lipiodol. Furthermore, because of the enhanced permeability of the tumor vasculature and/or poor lym-

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Table 3
Adverse events.

	TACE group						TAI group					
	Grade 3		Grade 4		Grade 1–4		Grade 3		Grade 4		Grade 1–4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematological toxicity												
Leukocytes	1	1	0	0	27	34	0	0	0	0	26	32
Neutrophils	1	0	0	0	14	18	0	0	0	0	15	18
Hemoglobin	1	1	–		25	32	0	0	–		23	28
Platelets	10	13	2	3	54	68	10	12	3	4	57	70
Non-hematological toxicity												
Total bilirubin	21	27	0	0	60	76	15	18	0	0	62	76
Alkaline phosphatase	2	3	0	0	53	67	2	2	0	0	63	77
Aspartate aminotransferase	33	42	0	0	77	97	23	28	0	0	79	96
Alanine aminotransferase	28	35	0	0	73	92	16	20	0	0	77	94
Creatinine	0	0	0	0	13	16	0	0	0	0	16	20
Abdominal pain	0	0	0	0	55	70	2	2	0	0	50	61
Nausea/vomiting	1	1	–		43	54	0	0	–		39	48
Diarrhea	0	0	0	0	2	3	0	0	0	0	4	5
Fever	2	3	0	0	69	87	1	1	0	0	66	80
Shivers	0	0	0	0	12	15	1	1	0	0	14	17
Allergy	0	0	0	0	2	3	0	0	0	0	6	7
Ascites	1	1	–		3	4	0	0	–		0	0
Dyspnea	0	0	0	0	0	0	0	0	1	1	1	1
Hypotension	1	1	0	0	1	1	1	1	0	0	1	1

A 'dash' (–) indicates the grade was not available.

phatic drainage from the tumor interstitium, macromolecular agents like SMANCS are retained more selectively within tumors [24,25]. In fact, experimental studies have shown that tumor-systemic drug concentration ratios as high as 1000 can be achieved using TAI with SMANCS-lipiodol. Thus, the selective delivery of a long-lasting or slow-release anti-cancer agent may have had a sufficient antitumor effect and survival-prolonging efficacy in the TAI group even if embolization had not been used in combination.

The infrequent protocol treatment repetition in this study is another possible reason for the lack of any difference in survival between the two groups, because the average number of protocol treatments was only 2.2 courses in the TACE group and 2.4 in the TAI group, and thus the maximum anti-cancer potential may not have been achieved. We speculated that the choice of SMANCS was partly responsible for the infrequent repetition because hepatic vascular complications, such as the obstruction of the hepatic artery and the arterio-portal shunt, have been reported as adverse reactions specific to SMANCS [26]. These complications are often followed by liver dysfunction, ascites, and technical problems with regard to subsequent protocol treatment, which were the major reasons for treatment discontinuation in this study. The enrollment of many patients with far-advanced HCC in the present phase III study may have been another reason for the small number of treatment repetitions and the subsequent poor survival: the proportion of patients with a pre-treatment AFP level >200 ng/mL was 40% in the phase III study and 24% in the phase II study. Both the antitumor response and the overall survival of the TACE group were poorer than our expectations: the 2-year survival rate in the TACE group was 48.2% in the present study, as opposed to 79% in the phase II study of TACE with SMANCS.

In conclusion, the results of this study suggest that treatment intensification by adding embolization did not increase the survival of HCC patients over SMANCS transarterial chemotherapy alone. The results of this study also showed no significant differences in toxicity, except for an ALP elevation, between the two groups treated with SMANCS. It should be emphasized that the negative results in this study may be attributable to our methodological strategy for selecting SMANCS and the enrollment of many patients with far-advanced HCC. The infrequent treatment repetition and the favorable results of TAI with SMANCS are speculated to be reasons for the lack of any difference in survival between the two groups. Furthermore, the results of this study must be interpreted with caution because current TACE protocols have evolved thanks to the implementation of updated devices including new embolic agents and improved catheters. Additional studies will be required to determine whether the results obtained in this trial are consistent with the results of transarterial treatment with chemotherapeutic agents other than SMANCS and with updated procedures, although it would be difficult to conduct such studies because many consider TACE to be the standard treatment based on the positive results obtained in two recent randomized studies in which doxorubicin or cisplatin was used

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[7,8]. There is a more pressing need for the establishment of new and more active treatment strategies that are superior to conventional TACE to improve the dismal prognosis of this disease.

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ORIGINAL ARTICLE

Prognostic analysis and a new risk model for Hodgkin lymphoma in Japan

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Abstract The Japan Clinical Oncology Group conducted two multicenter phase II trials in 200 patients with advanced Hodgkin lymphoma (HL) in the 1990s. Among 181 patients whose histopathological specimens were available and reviewed by 6 hematopathologists, 167 (92.3%) were diagnosed with HL. Five-year overall survival (OS) among these 167 patients was 88.3%, including 89.2% among nodular sclerosis and 82.2% among mixed cellularity cases. International prognostic score was not closely associated with OS. Seven unfavorable prognostic factors for OS on univariate analysis were male, B symptoms, clinical stage of III

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or IV, elevated serum LDH, elevated alkaline phosphatase, elevated β2-microglobulin, and pathological subtype (mixed cellularity and lymphocyte depletion). On multivariate analysis, male [HR 3.30 (95% CI 1.15–9.52, $p = 0.027$)] and elevated serum LDH [HR 2.41 (95% CI 1.07–5.43, $p = 0.034$)] were independent factors for OS. Based on these prognostic factors, the 5-year OS was 95.7% in the low-risk group (no adverse factor), 87.9% in the intermediate-risk group (1 adverse factor) and 73.3% in the high-risk group (2 adverse factors). This simple prognostic model for HL warrants further validation studies.

Keywords International prognostic score · Multicenter phase II trial · Prognostic factor · Overall survival · Male gender · LDH

1 Introduction

Most of the patients with advanced Hodgkin lymphoma (HL) could be induced into complete remission (CR) with state-of-the-art combination chemotherapy or chemo-radiotherapy, and in patients with advanced HL who relapsed after achieving CR, there are some therapeutic options for curing the disease, including conventional salvage chemotherapy and high-dose chemotherapy followed by autologous stem-cell transplantation [1]. However, the excellent outcomes in the initial treatments for HL do not necessarily result in excellent survival, because 20–30% of patients with advanced HL are not cured of their disease, and moreover, the treatments are associated with increased risks of late toxicities such as secondary malignancies, cardiopulmonary toxicities, and cerebrovascular diseases [2–5]. It still seems to be necessary to identify the high-risk group of the minority of patients with fatal outcome.

Many prognostic factors for failure-free survival have been described in patients with advanced HL. These included age, sex, clinical stage, B symptoms, number of nodal sites, laboratory data such as serum albumin, hemoglobin, white cell count, lymphocyte count, etc. [6]. The international prognostic score (IPS) [7] was widely accepted as the prognostic index in advanced HL. However, only 7% of the patients had the worst adverse score of 5 or higher of IPS which represents a very high risk, and was associated with 56% of the overall survival (OS) at 5 years. Thus, it was concluded that a distinct group of patients at very high risk could not be identified by the IPS [7].

Considering the various effective treatment options and their late toxicities, it is important to identify the prognostic factors for OS in patients with advanced HL. In particular, this is relevant to the question of whether early high-dose chemotherapy with autologous stem-cell transplantation should be used as a consolidation therapy in patients with responses to induction therapy, who are nevertheless considered to remain at high risk for relapse. To address the ability to predict the prognosis of patients with advanced HL, we analyzed patients with advanced HL enrolled in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG–LSG) trials. The aims of this study were to validate the IPS in terms of OS, to evaluate the OS according to several prognostic factors including histological subtypes of HL, and to find a better prognostic model for patients with advanced HL, who were enrolled in JCOG–LSG trials with state-of-the-art combination chemotherapy or chemo-radiotherapy.

2 Patients and methods

2.1 Patients and treatments

The JCOG–LSG conducted two multicenter phase II trials for advanced HL in the 1990s that tested the efficacy of the ABVd regimen (JCOG9305) [8] and ABV regimen followed by involved-field radiotherapy (IF-RT) (JCOG9705) [9]. Major eligibility criteria were age between 15 and 69 years, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 in the two trials, and clinical stage of II, III or IV in JCOG9305 and clinical stage of IB, IIB, III, or IV or any stage with bulky lesion in JCOG9705. Bulky lesion was defined as a mass of at least 10 cm (largest diameter) and a bulky mediastinum (ratio of the mediastinum to the thorax of at least one-third at the level of the largest diameter while the patient was standing). A total of 128 patients from 35 participating institutes were enrolled in JCOG9305 between 1993 and 1997 to assess the efficacy of the ABVd regimen, which consisted of doxorubicin, bleomycin, vinblastine and a reduced dose of dacarbazine of two-thirds (250 mg/m^2) of that in the original ABVD regimen. The reasons for modification of

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the original ABVD regimen in both JCOG studies were that dacarbazine was highly emetic and it was not approved for the treatment of HL in Japan at that time. In JCOG9705, a total of 72 patients from 25 participating institutes were enrolled between 1998 and 2000 to assess the efficacy of the ABV regimen, in which the dose of doxorubicin was increased to 120% of that in the original ABVD regimen and dacarbazine was not utilized. Patients were evaluated for response after 4 cycles of chemotherapy. All patients received 2 additional cycles of chemotherapy. For those with CR after 4 cycles, chemotherapy was finished after a total of 6 cycles. Patients who were in CR or uncertain CR (CRu) after 6 cycles were given 2 additional cycles of chemotherapy. In patients with bulky lesions, IF-RT with 30–40 Gy was added if patients entered into CR or CRu after 4 or 6 cycles. Regardless of whether the lesion was bulky or non-bulky, IF-RT was added if patients entered into partial remission (PR) in JCOG9705.

CR was defined as the disappearance of all measurable or assessable diseases and all signs and symptoms of the disease lasting for at least 4 weeks. PR was defined as a reduction of 50% or greater in the sum of the perpendicular diameters of all measurable lesions and the appearance of no new lesions for at least 4 weeks. CRu was defined as the maintenance of PR for at least 3 months without any treatment. Progressive disease was defined as an increase of 25% in the size of any lesion or development of any new lesions. Relapse was defined as an increase of 25% in the size of any lesion or development of any new lesions in CR or CRu patients. The details of the results of each clinical study will be published elsewhere.

All of the protocols described above including the informed consent document were approved by both the JCOG Protocol Review Committee and the institutional review board of each institution. The protocol of JCOG0108A, an ancillary study with secondary use of the data acquired by the above-mentioned JCOG studies, was also approved by the JCOG Protocol Review Committee.

2.2 Consensus diagnosis

The procedure of reaching a consensus diagnosis of HL according to the WHO classification has been described [10]. Briefly, 6 hematopathologists consisting of 4 panelist pathologists and 2 consulting pathologists reviewed the histopathological specimens independently. Immunohistochemical studies were conducted on paraffin sections by means of the avidin–biotin–peroxidase complex technique and a panel of monoclonal antibodies including antibodies against CD20 (L26; DakoCytomation, Glostrup, Denmark), CD3 (PS-1; Novocastra, Newcastle, UK), CD15 (MMA; Becton Dickinson, San Jose, CA, USA) and CD30 (BerH2; DakoCytomation, Glostrup, Denmark). All 6 hematopathologists and 1 hematologist performed the central pathologic review, in which the case report forms of the patients were available for reference of clinical information. A consensus diagnosis was established when agreement was reached by three-fourths or greater majority of the 4 panelist pathologists with no opposition from the 2 consulting pathologists and the hematologist. The cases with discordant pathological diagnosis were re-evaluated until agreement by two-thirds or greater majority was reached among the 6 pathologists by means of reconciliation. Then, a consensus diagnosis was made. The present study included patients in two multicenter phase II trials for advanced HL who were diagnosed with HL by central pathological review.

2.3 Statistical analysis

All statistical analyses were performed by a statistician (K.Y.) at the JCOG Data Center. Patients with lymphocyte depletion had been reported as having a worse prognosis than those with other subtypes [11], but this subgroup contained only 7 patients in this study. Therefore, patients with lymphocyte depletion were grouped together with patients with mixed cellularity who had also been shown to have a worse prognosis [12]. OS was the endpoint of all statistical analyses. OS was calculated from the date of enrollment in respective study to the date of death from any cause or to the date of last follow-up in living patients. OS was estimated by the Kaplan–Meier method. The log-rank test was used to assess the significance of unadjusted differences in OS for each prognostic factor. Multivariate analysis was performed by the Cox proportional hazards model to identify subsets of prognostic factors for OS. All p values were two-sided and p values less than 0.05 were considered significant. There is no widely agreed approach to building a multivariate prognostic model from a set of candidate predictors [13, 14] and, in consideration of the limitation of events in our study, the data were analyzed from points of significancy and parsimony. A prognostic model was established by fitting all variables that significantly influenced OS in multivariate analysis, and the risk groups were identified according to the established model. For comparing OS between the risk groups, the overfitting-corrected p values were derived by fivefold cross-validation. All statistical analyses were performed using SAS release 9.1.3 (SAS Institute, Inc., Cary, NC).

3 Results

3.1 Histopathological distribution

Among the 200 patients from 41 participating institutes in Japan who were enrolled in two multicenter phase II trials