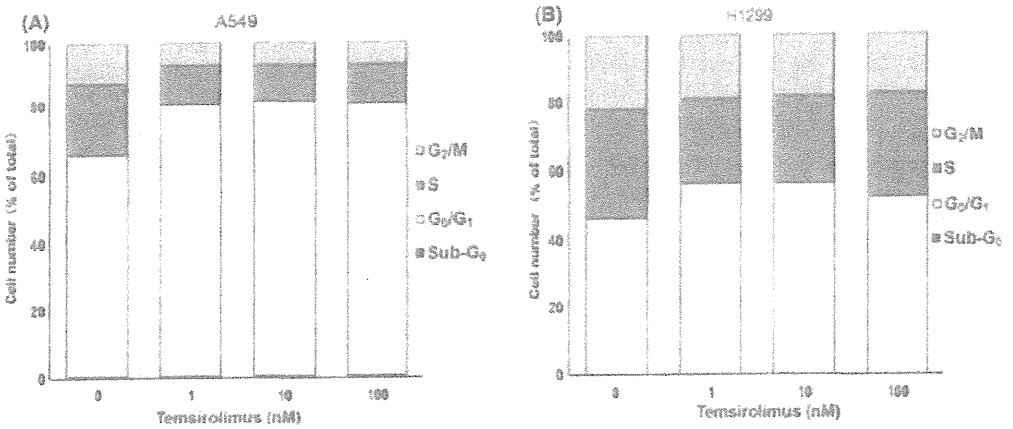

Fig. 3. Temsirolimus induces cell cycle arrest rather than cell death. A549 (A) and H1299 (B) non-small-cell lung carcinoma cells were treated with 10 nM temsirolimus for 24 h and the cell cycle distribution was analyzed by flow cytometry.

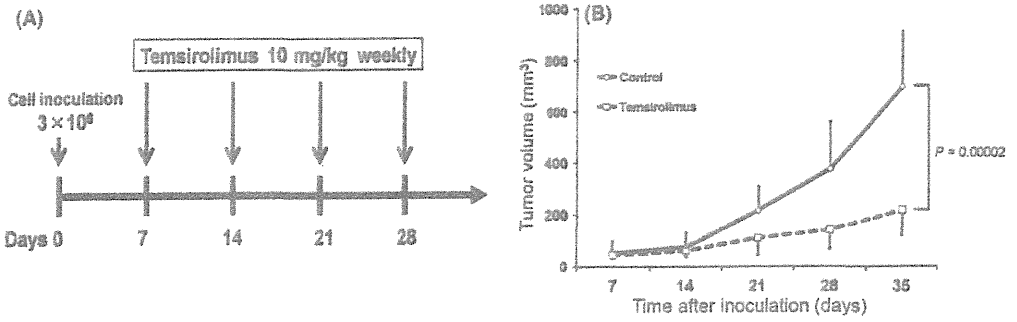

Fig. 4. Temsirolimus reduces the growth of s.c. tumors of A549 non-small-cell lung carcinoma cells. A549 cells were inoculated s.c. in the dorsum of nude mice (day 0) and i.v. injections of either temsirolimus (10 mg/kg) or saline as a vehicle were started from day 7 and continued once a week (A). Tumor volume was measured as a cube (length × width × height) and was tracked for up to 5 weeks (B). The representative data were taken from three independent experiments.

Ki-labeling index, defined in Materials and Methods) in the tissues treated with temsirolimus (temsirolimus, 0.106 ± 0.019; control, 0.191 ± 0.044; $P < 0.05$) (Fig. S2A). However, temsirolimus treatment did not increase the incidence of apoptosis in the tumor tissues, as checked by immunohistochemistry for cleaved caspase-3 (temsirolimus, 0.004 ± 0.002; control, 0.004 ± 0.002; $P > 0.05$) (Fig. S2B). These results were similar to our *in vitro* data, supporting our conclusion that the primary effect of temsirolimus is antiproliferative rather than cytotoxic. Thus, the advantage of *in vivo* temsirolimus treatment was to provide prolonged survival in advanced NSCLC tumor-bearing mice by suppressing tumor growth.

Inhibition of mTOR by temsirolimus suppresses the action of hypoxia inducible factor 1α (HIF-1α). Finally, we assessed the inhibition of mTOR by temsirolimus in NSCLC cells and tumors. Because recent reports have shown that the action of HIF-1α, a major transcriptional activator for angiogenesis and oncogenes, is regulated by the mTOR pathway,[29] and is therefore inhibited by temsirolimus *in vitro* and *in vivo*,[25,30] we also determined the effect of temsirolimus on the expression status of HIF-1α in the nuclei, where activated HIF-1α normally translocates.[31] Temsirolimus treatment suppressed the translocation of HIF-1α to the nucleus in all of NSCLC cells (Fig. S3A). As HIF-1α is known to play a critical role in cell proliferation and angiogenesis,[32] this inhibition of HIF-1α action by temsirolimus should at least partially contribute to its antiproliferative effect.

Regarding the antiangiogenic effect of temsirolimus by negatively regulating HIF-1α, we additionally determined the expression of vascular endothelial cell growth factor (VEGF), a known transcriptional target of HIF-1α. In cultured NSCLC cells, the amount of VEGF protein secreted in the culture medium was suppressed by temsirolimus treatment in a dose-dependent manner (Fig. S3B,C). Similarly, the production of VEGF mRNA expression, especially the 572-bp form of VEGF, was decreased in the pleural disseminated tumors of the mice that had temsirolimus treatment (Fig. S3D). The inhibition of HIF-1α/VEGF-mediated angiogenesis might also contribute to slowing tumor growth by temsirolimus treatment.

Discussion

Temsirolimus, an analogue of rapamycin, is a new molecular targeted agent and was first approved for the treatment of renal cell carcinoma. In terms of NSCLC, it was reported that inhibiting mTOR with rapamycin revealed a growth inhibitory effect in some NSCLC cell lines.[33] Temsirolimus was developed as an improved derivative of rapamycin,[34] and our data indicated its effectiveness by showing its potent inhibitory effect on cell proliferation of cultured NSCLC cells at a low concentration (as low as 1 nM). Concerning the antiproliferative effect of temsirolimus, our results reproduced the results of a previous report using rapamycin, which induced cell cycle arrest at the G_1 checkpoint and inhibited cell proliferation of murine NSCLC without inducing apoptosis.[23] In this study, temsirolimus suppressed the phosphorylations of p70 S6 kinase and S6 (Fig. 2). As the action of p70 S6 kinase and S6 is critical for

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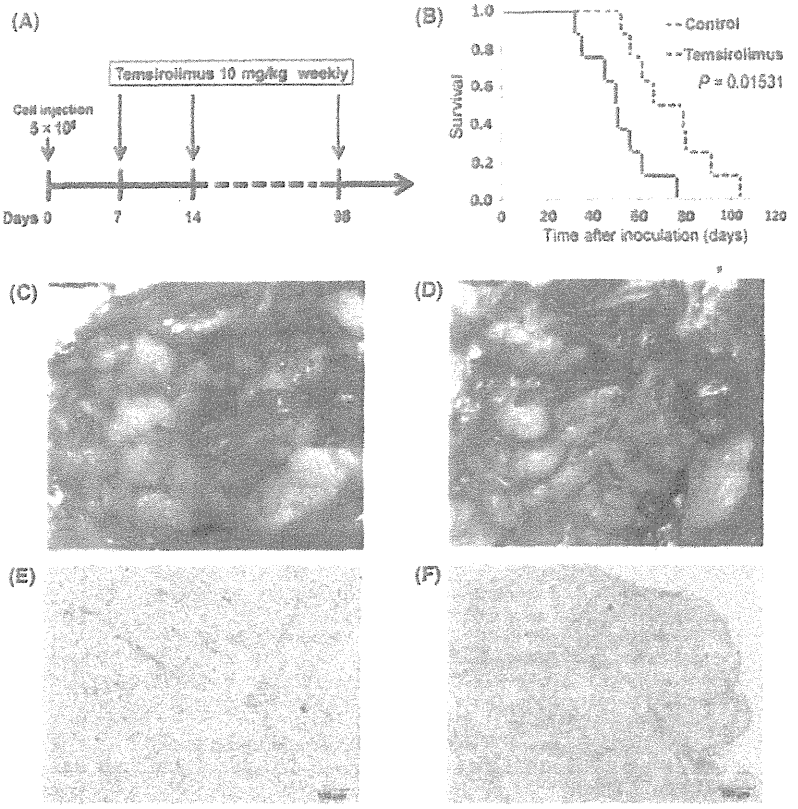

Fig. 5. Temsirolimus prolongs the survival of pleural disseminated tumor-bearing mice. A549 non-small-cell lung carcinoma cells were injected into the thoracic cavity of mice (day 0) and i.p. injections of either temsirolimus (10 mg/kg) or saline as a vehicle were started from day 7 and continued once a week (A). Cell survival periods were tracked to draw a survival curve by the Kaplan–Meier method (B). Representative images of macroscopic observation in the thoracic cavity on day 21 are shown (C, vehicle only; D, temsirolimus). Immunohistochemical examination of resected disseminated tumor tissues from the control mice (E) and temsirolimus treated mice (F) was carried out to assess the expression status of phosphorylated mTOR (day 21). Each photograph was taken at high magnification (×200). The experiment was repeated three times and the representative data are shown.

cell cycle progression,[27,35] the cytostatic effect of temsirolimus can be at least partially explained by the importance of p70 S6 kinase to cell cycle progression. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and Akt are also interesting molecules related to cell proliferation signals. A recent study using rapamycin[33] showed that the inhibition of mTOR by temsirolimus appeared to regain Akt activity (Fig. S1). According to a previous report,[36] PTEN was lost in H1299 cells by its promoter methylation, whereas it remained intact in A549 cells. Regardless of their PTEN expression, our data indicated the similar potent antiproliferative effects of temsirolimus on those cell lines (Fig. 1).

Using an animal model of pleural dissemination, a condition for human lung cancer patients with one of the worst survival rates, we observed that temsirolimus reduced the growth of both s.c. tumors and pleural disseminated tumors of NSCLC cells, and that the treatment significantly prolonged the survival of mice bearing disseminated pleural tumors (Fig. 5). It is noteworthy that the dose and schedule of temsirolimus treatment in this study followed those currently in clinical use for renal cell carcinoma, with no apparent adverse effects in the mice. Because this regimen has also been tolerated in several clinical studies for other cancers,[18–21] temsirolimus treatment might safely provide prolonged survival for advanced NSCLC patients, possibly due to its cytostatic effect.

One immunohistochemical study showed that there were differences in mTOR signaling activation depending on histological type.[14] According to that study, adenocarcinoma had more frequent ctivation of phosphorylated mTOR than squamous cell carcinoma. However, it was unclear what histological type of NSCLC temsirolimus treatment would be effective in clinical use. mTOR is frequently activated in adenocarcinoma, but the outcome differs depending on the mTOR expression.[37] In a future study, it would be intriguing to establish a more effective combination therapy with temsirolimus,[38] because mTOR activity can be modified by other effectors, such as growth factors[39] and nutrition.[40,41]

In conclusion, our data suggests that temsirolimus, with a cytostatic effect on cell proliferation, may be useful for NSCLC treatment in general and could give prolonged survival to advanced NSCLC cases with pleural dissemination specifically.

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Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Jemal A, Siegel R, Ward E *et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71–96.
2 Vital Statistics Japan (Ministry of Health, Labour and Welfare). Number of cancer deaths by age and site 2007. [Cited 21 Mar 2010.] Available from URL: http://ganjoho.ncc.go.jp/professional/index.html.
3 Suzuki S, Dobashi Y, Sakurai H, Nishikawa K, Hanawa M, Ooi A. Protein overexpression and gene amplification of epidermal growth factor receptor in nonsmall cell lung carcinomas. An immunohistochemical and fluorescence in situ hybridization study. *Cancer* 2005; **103**: 1265–73.
4 Yatabe Y, Takahashi T, Mitsudomi T. Epidermal growth factor receptor gene amplification is acquired in association with tumor progression of EGFR-mutated lung cancer. *Cancer Res* 2008; **68**: 2106–11.

5 El-Rayes BF, LoRusso PM. Targeting the epidermal growth factor receptor. *Br J Cancer* 2004; **91**: 418–24.
6 Sirotnak FM, Zakowski MF, Miller VA, Scher HI, Scher HI. Kris MG. Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res* 2000; **6**: 4885–92.
7 Herbst RS, Kies MS. ZD1839 (Iressa) in non-small cell lung cancer. *Oncologist* 2002; **7**: 9–15.
8 Okabe T, Okamoto I, Tamura K *et al.* Differential constitutive activation of the epidermal growth factor receptor in non-small cell lung cancer cells bearing EGFR gene mutation and amplification. *Cancer Res* 2007; **67**: 2046–53.
9 Asahina H, Yamazaki K, Kinoshita I. A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. *Br J Cancer* 2006; **95**: 998–1004.
10 Das AK, Sato M, Story MD *et al.* Non-small-cell lung cancers with kinase domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation. *Cancer Res* 2006; **66**: 9601–8.
11 Balak MN, Gong Y, Riely GJ *et al.* Novel D761Y and common secondary T790M mutations in epidermal growth factor receptor-mutant lung adenocarcinomas with acquired resistance to kinase inhibitors. *Clin Cancer Res* 2006; **12**: 6494–501.
12 Hay N, Sonenberg N. Upstream and downstream of mTOR. *Genes Dev* 2004; **18**: 1926–45.
13 Inoki K, Ouyang H, Li Y, Guan KL. Signaling by target of rapamycin proteins in cell growth control. *Microbiol Mol Biol Rev* 2005; **69**: 79–100.
14 Dobashi Y, Suzuki S, Matsubara H, Kimura M, Endo S, Ooi A. Critical and diverse involvement of Akt/mammalian target of rapamycin signaling in human lung carcinomas. *Cancer* 2009; **115**: 107–18.
15 Pal SK, Figlin RA, Reckamp KL. The role of targeting mammalian target of rapamycin in lung cancer. *Clin Lung Cancer* 2008; **9**: 340–5.
16 Campone M, Levy V, Bourbouloux E *et al.* Safety and pharmacokinetics of paclitaxel and the oral mTOR inhibitor everolimus in advanced solid tumours. *Br J Cancer* 2009; **100**: 315–21.
17 Wolpin BM, Hezel AF, Abrams T *et al.* Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol* 2009; **27**: 193–8.
18 Chan S, Scheulen ME, Johnston S *et al.* Phase II study of Temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. *J Clin Oncol* 2005; **23**: 5314–22.
19 Chang SM, Wen P, Cloughesy T *et al.* Phase II study of CCI-779 in patients with recurrent glioblastoma multiforme. *Invest New Drugs* 2005; **23** (4): 357–61.
20 Duran I, Kortmansky J, Singh D *et al.* A phase II clinical and pharmacodynamic study of Temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer* 2006; **95**: 1148–54.
21 Hess G, Herbrecht R, Romaguera J *et al.* Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2009; **27**: 3822–9.
22 Ohara T, Oto K, Miyoshi K *et al.* Sirolimus ameliorated post lung transplant chylothorax in lymphangioleiomyomatosis. *Ann Thorac Surg* 2008; **86**: e7–8.
23 Dudkin L, Dilling MB, Cheshire PJ *et al.* Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition. *Clin Cancer Res* 2001; **7**: 1758–64.
24 deGraffenried LA, Friedrichs WE, Russell DH *et al.* Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt Activity. *Clin Cancer Res.* 2004;**10**: 8059–67.
25 Wan X, Shen N, Mendoza A, Khanna C, Helman LJ. CCI-779 inhibits rhabdomyosarcoma xenograft growth by an antiangiogenic mechanism linked to the targeting of mTOR/Hif-1α/VEGF signaling. *Neoplasia* 2006; **8**: 394–401.
26 Shirakawa Y, Naomoto Y, Kimura M *et al.* Topological analysis of p21WAF1/CIP1 expression in esophageal squamous dysplasia. *Clin Cancer Res* 2000; **6**: 541–50.
27 Berven LA, Crouch MF. Cellular function of p70S6K: a role in regulating cell motility. *Immunol Cell Biol* 2000; **78**: 447–51.
28 Hudes G, Carducci M, Tomczak P *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356**: 2271–81.
29 Fang J, Ding M, Yang L, Liu LZ, Jiang BH. PI3K/PTEN/AKT signaling regulates prostate tumor angiogenesis. *Cell Signal* 2007; **19**: 2487–97.
30 Del Bufalo D, Ciuffreda L, Trisciuoglio D *et al.* Antiangiogenic potential of the mammalian target of rapamycin inhibitor temsirolimus. *Cancer Res* 2006; **66**: 5549–54.
31 Kallio PJ, Wilson WJ, O'Brien S, Makino Y, Poellinger L. Regulation of the Hypoxia-inducible Transcription Factor 1α by the Ubiquitin-Proteasome Pathway. *J Biol Chem* 1999; **274**: 6519–25.
32 Zhong H, De Marzo AM, Laughner E *et al.* Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases. *Cancer Res* 1999; **59**: 5830–5.
33 Sun SY, Rosenberg LM, Wang X *et al.* Activation of Akt and eIF4E survival pathways by rapamycin-mediated mammalian target of rapamycin inhibition. *Cancer Res* 2005; **65**: 7052–8.
34 Boffa DJ, Luan F, Thomas D *et al.* Rapamycin inhibits the growth and metastatic progression of non-small cell lung cancer. *Clin Cancer Res* 2004; **10**: 293–300.
35 Pullen N, Thomas G. The modular phosphorylation and activation of p70s6k. *FEBS Lett* 1997; **410**: 78–82.
36 Soria JC, Lee HY, Lee JI *et al.* Lack of PTEN expression in non-small cell lung cancer could be related to promoter methylation. *Clin Cancer Res* 2002; **8**: 1178–84.
37 Anagnostou VK, Bepler G, Syrigos KN *et al.* High expression of mammalian target of rapamycin is associated with better outcome for patients with early stage lung adenocarcinoma. *Clin Cancer Res* 2009; **15**: 4157–64.
38 Dancey J. mTOR signaling and drug development in cancer. *Nat Rev Clin Oncol* 2010;**7**:209–19.
39 Kodama Y, Baxter RC, Martin JL. Insulin-like growth factor-I inhibits cell growth in the a549 non-small lung cancer cell line. *Am J Respir Cell Mol Biol* 2002; **27**: 336–44.
40 Cohen A, Hall MN. An amino acid shuffle activates mTORC1. *Cell* 2009; **136**: 399–400.
41 Kleijn M, Proud CG. Glucose and amino acids modulate translation factor activation by growth factors in PC12 cells. *Biochem J* 2000; **347**: 399–406.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Temsirolimus induces $p21^{cip1}$ expression in none-small-cell lung carcinoma cells.

Fig. S2. Proliferation and apoptosis in tumor tissues after temsirolimus treatment in mice.

Fig. S3. Inhibition of mTOR by temsirolimus decreases the expression of proangiogenic effectors.

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Cediranib in combination with mFOLFOX6 in Japanese patients with metastatic colorectal cancer: results from the randomised phase II part of a phase I/II study

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Background: Colorectal cancer (CRC) is the second most common malignancy in Japan. Treatment with inhibitors of the vascular endothelial growth factor (VEGF) signalling pathway has proven benefit in metastatic CRC. Cediranib is an oral highly potent VEGF signalling inhibitor that inhibits all three VEGF receptors.

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Patients and methods: In this phase II, double-blind, placebo-controlled study, 172 patients with metastatic CRC were randomised to receive once-daily cediranib (20 or 30 mg) or placebo, each combined with modified FOLFOX6 (mFOLFOX6). The primary objective was comparison of progression-free survival (PFS).
Results: The comparison of cediranib 20 mg versus placebo met the primary objective of PFS prolongation [hazard ratio = 0.70 (95% confidence interval 0.44–1.11), $P = 0.167$], which met the protocol-defined criterion of $P < 0.2$. Median PFS was 10.2 versus 8.3 months, respectively. The PFS comparison for cediranib 30 mg versus placebo did not meet the criterion. The most common adverse events (AEs) in the cediranib-containing groups were diarrhoea and hypertension.
Conclusions: Cediranib 20 mg plus mFOLFOX6 met the predefined criteria in terms of improved PFS compared with placebo plus mFOLFOX6. Cediranib 20 mg was generally well tolerated and the AE profile was consistent with previous studies.
Key words: cediranib, colorectal cancer, mFOLFOX6, placebo, progression-free survival

introduction

In Japan, the incidence of colorectal cancer (CRC) has increased nearly fivefold in the last 25 years, owing primarily to changing Japanese dietary habits, which are becoming increasingly similar to those of Western countries. In 2008, there were 101 656 new cases of CRC in Japan and 43 349 deaths attributed to this disease [1]. CRC is now the second most common malignancy in Japan and is predicted to become the most common by 2015. Fluorouracil (5-FU) was one of the first chemotherapies used for the treatment of CRC, and the combination of 5-FU with leucovorin and oxaliplatin (FOLFOX) has improved outcomes. Treatment with these components (plus irinotecan in some regimens) can provide a median overall survival (OS) of up to 20 months, compared with ~6 months with best supportive care [2]. Japanese clinical guidelines recommend FOLFOX as standard treatment of metastatic colorectal cancer (mCRC) [3]. To reduce toxicity associated with the FOLFOX regimen, a number of modifications have been tried [4, 5]; the current standard is modified FOLFOX6 (mFOLFOX6).

Inhibition of the vascular endothelial growth factor (VEGF) signalling pathway with bevacizumab has demonstrated additional clinical benefit in CRC when used with 5-FU-based regimens in the first-line setting in mCRC [6, 7]. Cediranib is an oral highly potent VEGF tyrosine kinase inhibitor (TKI) that inhibits all three VEGF receptors [8, 9]. Cediranib is suitable for once-daily dosing and has demonstrated antitumour activity during early phase clinical evaluation in patients with advanced cancer [10]. Further studies demonstrated that cediranib was generally well tolerated as monotherapy [11–15] and in combination with various anticancer agents at doses ≤30 mg/day [16–21].

The efficacy of cediranib in combination with chemotherapy has been investigated in two phase III studies—HORIZON II [22] and HORIZON III [23]—in Western patients with previously untreated mCRC. Two cediranib doses were initially selected for investigation in the HORIZON programme: 20 (lowest biologically active dose) and 30 mg/day (maximum dose suitable for chronic dosing in combination with chemotherapy). The decision to investigate cediranib 20 and 30 mg/day doses in this study was taken before an end-of-phase II decision from the HORIZON programme to proceed with only the 20 mg/day dose. As such, this two-part phase I/II study, which mirrored HORIZON II, investigated cediranib, at the same doses used initially in the Western studies, plus mFOLFOX6 in Japanese patients with previously untreated mCRC (ClinicalTrials.gov identifier NCT00494221; AstraZeneca study code D8480C00039). The phase I part of this study demonstrated that both doses of cediranib were generally well tolerated in combination with mFOLFOX6 [24]. Here, we report the results of the randomised, double-blind, phase II part of this study, which assessed the efficacy of cediranib (20 or 30 mg/day) plus mFOLFOX6 compared with mFOLFOX6 alone.

patients and methods

eligibility

Eligible patients were aged ≥18 years with histological or cytological confirmation of carcinoma of the colon or rectum. Patients required chemotherapy for stage IV (metastatic) disease, had a World Health Organisation (WHO) performance status (PS) of zero or one, and one or more measurable lesions according to the RECIST (version 1.0). Any adjuvant oxaliplatin or 5-FU therapy must have been completed >12 and >6 months, respectively, before study entry. Patients with brain or meningeal metastases were considered eligible if they were clinically stable and had not required corticosteroid treatment of 10 days. Exclusion criteria included prior systemic therapy for metastatic disease and prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including bevacizumab and cediranib.

study design

This phase II, randomised, double-blind, placebo-controlled study assessed the efficacy of first-line treatment with cediranib plus mFOLFOX6 compared with mFOLFOX6 alone. Patients were randomised 1 : 1 : 1 to receive once-daily cediranib (20 or 30 mg) or placebo, each in combination with 14-day treatment cycles of mFOLFOX6 (oxaliplatin 85 mg/m^2 IV, day 1; leucovorin 200 mg/m^2 IV, day 1; 5-FU 400 mg/m^2 IV bolus, day 1 and then 2400 mg/m^2 continuous IV infusion over 46 h). Patients were stratified at randomisation according to a two-level liver function covariate [based on baseline albumin and alkaline phosphatase (ALP) levels] and WHO PS (0 versus 1). Randomised treatment was continued until objective disease progression (as defined by RECIST) or until the occurrence of toxicity, death, withdrawal of patient consent or other discontinuation criteria. RECIST measurements were made using computed tomography or magnetic resonance imaging scans; clinical assessment of these scans was conducted by the study investigators.

The primary objective was to determine the efficacy of cediranib plus mFOLFOX6 compared with mFOLFOX6 alone by assessment of progression-free survival (PFS). Secondary objectives included comparison of OS, objective response rate (ORR: complete response + partial response), duration of response, change in tumour size and assessment of the safety

and tolerability of cediranib plus mFOLFOX6. An exploratory end point was to investigate the effect of treatment on soluble markers of angiogenesis (VEGF and sVEGFR-2). VEGF and sVEGFR-2 were measured by enzyme-linked immunosorbent assay of plasma samples from patients who provided separate informed consent.

PFS and ORR were determined from objective tumour assessments (RECIST) carried out at weeks 6, 12, 18, 24 and then every 12 weeks until disease progression or death. Adverse events (AEs) were recorded and graded according to Common Terminology Criteria for Adverse Events version 3.0. The study was approved by each centre's institutional review board and was carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

statistical analysis

Assuming a median PFS of 9 months in the placebo group, an 18-month accrual period and a minimum 12-month follow-up, a total of 55 patients per group was required to have 80% power to detect a true PFS hazard ratio (HR) of 0.6 at two-sided significance level of $P < 0.2$ (one-sided $P < 0.1$), which was considered appropriate evidence of activity for a randomised phase II study [25]. The primary PFS analysis was conducted using a log-rank test stratified by WHO PS (0 or 1) and a two-level baseline liver function covariate (covariate 1 for baseline albumin < 3.5 g/l or ALP > 320 U/l; covariate 0 for all other values). PFS and OS were summarised by treatment group using the Kaplan–Meier method. The formal analysis was conducted when ~105 progression events had occurred across the three groups. No formal statistical analysis was carried out on safety data.

The results in the present study were relatively immature (65% of PFS events versus 81% in HORIZON II) and the HR was favourable compared with HORIZON II (HR = 0.84). Furthermore, there was a higher proportion of patients with a PS of zero. Therefore, further analysis of efficacy and safety outcomes was carried out when 81% of progression events had occurred.

results

patients

Between January 2008 and January 2009, 172 Japanese patients were randomised to treatment with cediranib 20 mg plus mFOLFOX6 ($n = 58$), cediranib 30 mg plus mFOLFOX6 ($n = 56$) or placebo plus mFOLFOX6 ($n = 58$) (Figure 1). Patient characteristics were representative of the patient population (Table 1). All patients were Japanese and 20%

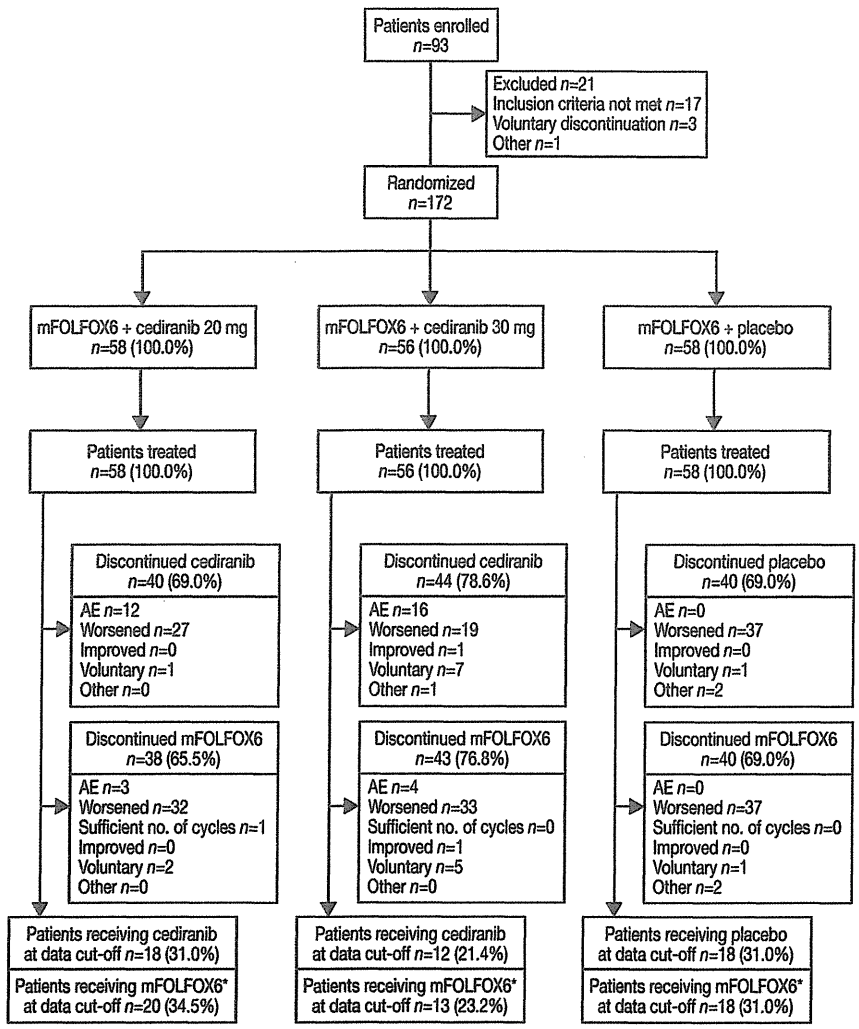

Figure 1. CONSORT diagram.

were receiving antihypertensive treatment at baseline. Baseline characteristics were generally well balanced across the groups, although there were more female patients in the cediranib 30 mg group. Imbalances were noted in metastases at baseline, time from initial diagnosis to randomisation, tumour grading, baseline ALP and baseline liver function (Table 1).

At the protocolled data cut-off (13 October 2009), 65% (112) of patients had progressed and 22% (38) had died. The most common reason for discontinuation of placebo/cediranib was worsened condition. At the second data cut-off (11 June 2010), 81% of patients had progressed and median OS follow-up was 19.0 months with 74 OS events.

efficacy

For the PFS comparison of cediranib 20 mg versus placebo, the HR was 0.70 [95% confidence interval (CI) 0.44–1.11], two-sided $P = 0.167$ (Figure 2A), which met the protocol-defined criterion for evidence of activity ($P < 0.2$). Median PFS was 10.2 and 8.3 months, respectively. For the PFS comparison of cediranib 30 mg versus placebo, the HR was 0.82 (95% CI 0.54–1.31), two-sided $P = 0.261$ (Figure 2B), which did not meet the predefined criterion. Median PFS was 8.9 months in the cediranib 30 mg arm. Predefined subgroup analysis of PFS for both dose groups did not identify a particular patient

Table 1. Patient demographics and baseline characteristics

Characteristic	Cediranib 20 mg + mFOLFOX6 ($n = 58$)	Cediranib 30 mg + mFOLFOX6 ($n = 56$)	Placebo + mFOLFOX6 ($n = 58$)
Median age (range), years	63.5 (33–79)	64.5 (40–82)	64.0 (36–80)
Sex, *n* (%)			
Male	38 (65.5)	30 (53.6)	39 (67.2)
Female	20 (34.5)	26 (46.4)	19 (32.8)
World Health Organisation performance status, *n* (%)			
0	44 (75.9)	43 (76.8)	47 (81.0)
1	14 (24.1)	13 (23.2)	11 (19.0)
Type of cancer, *n* (%)			
Colon	39 (67.2)	34 (60.7)	36 (62.1)
Rectal	19 (32.8)	22 (39.3)	22 (37.9)
Tumour grading, *n* (%)			
Well differentiated (G1)	11 (19.0)	14 (25.0)	16 (27.6)
Moderately differentiated (G2)	44 (75.9)	38 (67.9)	36 (62.1)
Poorly differentiated (G3)	2 (3.4)	3 (5.4)	4 (6.9)
Undifferentiated (G4)	1 (1.7)	1 (1.8)	1 (1.7)
Unassessable (GX)	0	0	1 (1.7)
Metastatic sites, *n* (%)			
1	32 (55.2)	29 (51.8)	28 (48.3)
>1	26 (44.8)	27 (48.2)	30 (51.7)
Metastases at baseline, *n* (%)			
Patients with liver only metastases at baseline	14 (24.1)	10 (17.9)	14 (24.1)
Patients with liver and other metastases at baseline	25 (43.1)	22 (39.3)	32 (55.2)
Patients with no liver involvement at baseline	19 (32.8)	24 (42.9)	12 (20.7)
Prior adjuvant therapy, *n* (%)			
Yes	13 (22.4)	9 (16.1)	8 (13.8)
No	45 (77.6)	47 (83.9)	50 (86.2)
Time from initial diagnosis to randomisation, *n* (%)			
<6 months	36 (62.1)	38 (67.9)	45 (77.6)
6 to <12 months	2 (3.4)	0	1 (1.7)
12 to <24 months	6 (10.3)	10 (17.9)	4 (6.9)
24 to <36 months	6 (10.3)	2 (3.6)	3 (5.2)
≥36 months	8 (13.8)	6 (10.7)	5 (8.6)
Baseline ALP, *n* (%)			
≤320 U/l	31 (53.4)	35 (62.5)	29 (50.0)
>320 U/l	27 (46.6)	21 (37.5)	29 (50.0)
Baseline liver function			
ALP > 320U/l or albumin < 35 g/l	29 (50.0)	22 (39.3)	30 (51.7)
Other	29 (50.0)	34 (60.7)	28 (48.3)
Baseline vascular endothelial growth factor			
n	36	37	38
Mean (standard deviation), pg/ml	146.5 (416.3)	74.3 (56.6)	96.9 (100.7)
Median (min, max), pg/ml	46.6 (31.2, 2520.5)	55.5 (31.2, 243.3)	54.6 (31.2, 508.1)

mFOLFOX6, modified FOLFOX6; ALP, alkaline phosphatase.

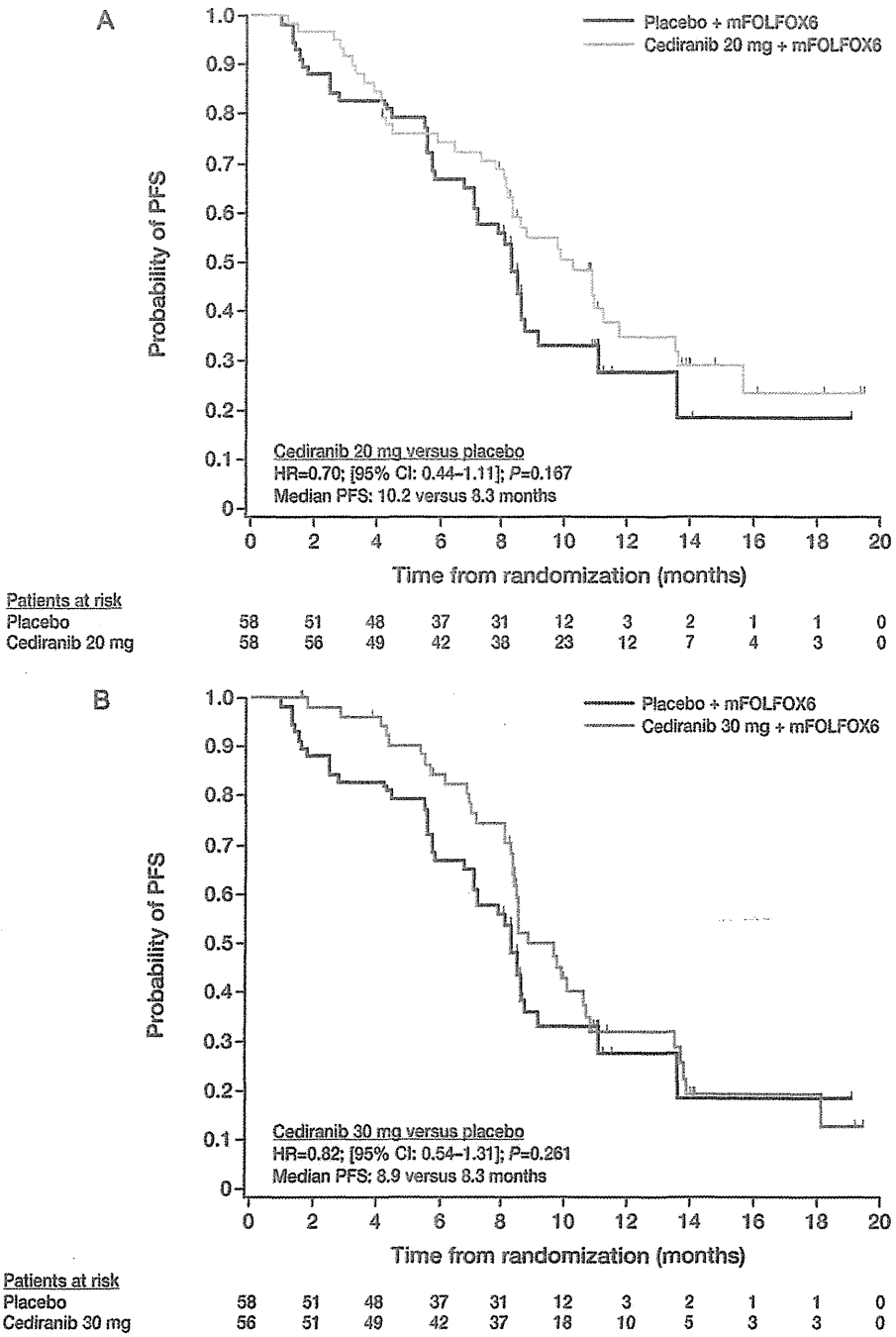

Figure 2. (A) Progression-free survival (PFS) for patients who received cediranib 20 mg + modified FOLFOX6 (mFOLFOX6) versus placebo + mFOLFOX6. (B) PFS for patients who received cediranib 30 mg + mFOLFOX6 versus placebo + mFOLFOX6.

population that derived a differential PFS benefit from cediranib versus placebo (supplemental Figure S1, available at *Annals of Oncology* online).

The ORR was 53.4%, 69.6% and 53.4% in the cediranib 20 mg, cediranib 30 mg and placebo arms, respectively; RECIST best response is summarised in Table 2. The median best percentage changes in tumour size were −37.3% (cediranib 20 mg), −43.4% (cediranib 30 mg) and −40.0% (placebo). The median duration of response was 9.2 (cediranib 20 mg), 6.7 (cediranib 30 mg) and 7.1 months (placebo) (Figure 3). At the primary analysis, there were insufficient deaths (total = 38; 15, 9 and 14 in the cediranib 20 mg, cediranib 30 mg and placebo arms, respectively) to draw conclusions on OS.

safety and tolerability

Overall, the most common AEs were diarrhoea and hypertension (Table 3); neither caused discontinuation of cediranib at the 20 mg dose. The incidence of AEs leading to discontinuation of cediranib/placebo was higher in the cediranib 30 mg group (27%) compared with the cediranib 20 mg (19%) or placebo (0%) groups; of these, only decreased

Table 2. Best RECIST response

Best response, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
CR	0	0	2 (3.4)
PR	31 (53.4)	39 (69.6)	29 (50.0)
Stable disease ≥6 weeks	24 (41.4)	14 (25.0)	20 (34.5)
Progressive disease	3 (5.2)	1 (1.8)	7 (12.1)
Non-evaluable	0	2 (3.6)	0

mFOLFOX6, modified FOLFOX6; CR, complete response; PR, partial response.

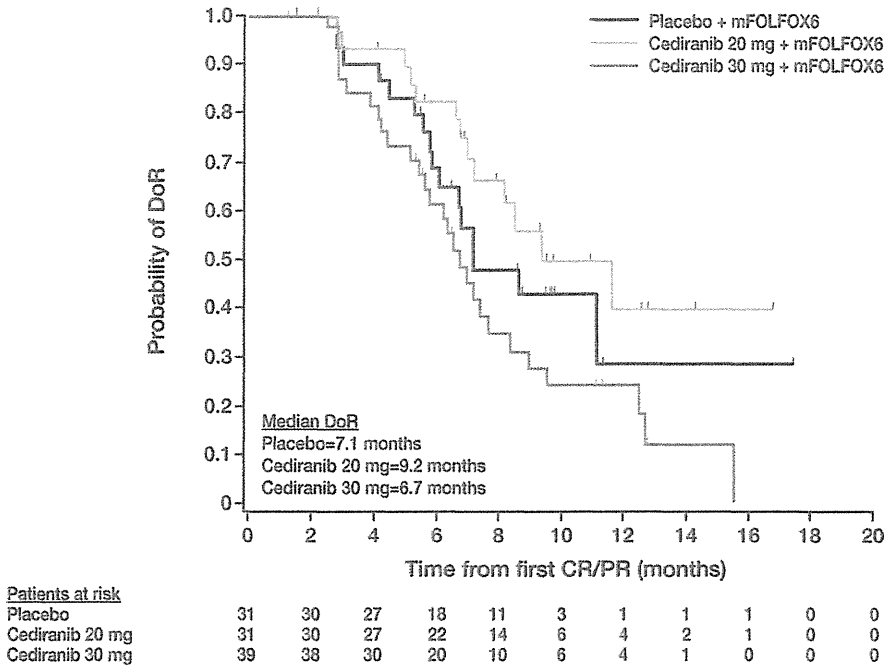

Figure 3. Duration of response for patients who received cediranib 20 mg, cediranib 30 mg or placebo, each in combination with modified FOLFOX6.

Table 3. AEs (frequency ≥30% in any group)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
Diarrhoea	53 (91.4)	49 (87.5)	22 (37.9)
Hypertension	47 (81.0)	48 (85.7)	18 (31.0)
Decreased appetite	43 (74.1)	43 (76.8)	39 (67.2)
Fatigue	39 (67.2)	40 (71.4)	36 (62.1)
Peripheral neuropathy	42 (72.4)	35 (62.5)	38 (65.5)
Nausea	39 (67.2)	37 (66.1)	37 (63.8)
PPES	31 (53.4)	34 (60.7)	8 (13.8)
Stomatitis	33 (56.9)	30 (53.6)	25 (43.1)
Vomiting	24 (41.4)	27 (48.2)	14 (24.1)
Dysphonia	24 (41.4)	16 (28.6)	2 (3.4)
Dysgeusia	18 (31.0)	17 (30.4)	18 (31.0)
Constipation	21 (36.2)	14 (25.0)	16 (27.6)
Alopecia	12 (20.7)	17 (30.4)	15 (25.9)
Epistaxis	15 (25.9)	19 (33.9)	9 (15.5)
Dysphonia	24 (41.4)	16 (28.6)	2 (3.4)

AE, adverse event; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

Table 4. CTC grade 3/4 AEs (>5% frequency in any arm)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 ($n = 58$)	Cediranib 30 mg + mFOLFOX6 ($n = 56$)	Placebo + mFOLFOX6 ($n = 58$)
Decreased appetite	11 (19.0)	10 (17.9)	1 (1.7)
PPES	8 (13.8)	12 (21.4)	0
Diarrhoea	6 (10.3)	12 (21.4)	1 (1.7)
Hypertension	4 (6.9)	6 (10.7)	1 (1.7)
Peripheral neuropathy	5 (8.6)	3 (5.4)	2 (3.4)
Peripheral sensory neuropathy	2 (3.4)	5 (8.9)	2 (3.4)
Neutropenia	3 (5.2)	0	0
Ileus	0	0	3 (5.2)

AE, adverse event; CTC, Common Terminology Criteria; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

appetite, diarrhoea and pneumonia (all $n = 2$) were reported in multiple patients.

The incidence of grade 3/4 AEs was 66%, 75% and 36% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The most common grade 3/4 AEs are summarised in Table 4. The incidence of serious adverse events (SAEs) was 39.7%, 39.3% and 19.0% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. No AEs had an outcome of death.

Clinical laboratory evaluation showed that treatment with cediranib plus mFOLFOX6 caused decreases in leucocyte, neutrophil and platelet counts and an increase in thyroid-stimulating hormone, but no new clinically important trends were observed in either cediranib group.

The median duration of exposure was 241.5, 213.0 and 223.5 days in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The proportion of patients experiencing a dose reduction/pause was highest in the cediranib 30 mg group (83.9%) versus the cediranib 20 mg (79.3%) and placebo (56.9%) groups (supplemental Figure S2, available at *Annals of Oncology* online). The dose intensity of cediranib/placebo was lower in the 30 mg group compared with the 20 mg and placebo groups; the mean daily dose of cediranib was 16.6 and 22.8 mg in the cediranib 20 and 30 mg groups, respectively. Exposure to mFOLFOX6 was similar in all arms; the median numbers of cycles of 5-FU, leucovorin and oxaliplatin were 17.0, 17.0 and 12.5, respectively, in the cediranib 20 mg group, 14.0, 14.0 and 11.0, respectively, in the cediranib 30 mg group and 15.0, 15.0 and 11.5, respectively, in the placebo group. However, more patients in the cediranib 30 mg group (33%) stopped oxaliplatin >12 weeks before progression compared with those in the cediranib 20 mg (14%) or placebo (8%) groups.

soluble biomarkers

Median VEGF levels ranged from 47 to 55 pg/ml at baseline; during treatment, levels remained similar to baseline in the placebo group but increased in cediranib-treated patients. In the cediranib 20 mg group, levels increased to 89 pg/ml by day 28 and to ~130 pg/ml thereafter. In the cediranib 30 mg group, levels increased to 160–170 pg/ml from days 28 to 84 before decreasing to 151 pg/ml by day 112.

Median sVEGFR-2 levels ranged from 9095 to 10 126 pg/ml at baseline. In the placebo group, median levels decreased to 7204 pg/ml on day 112. In the cediranib 20 mg group, median levels decreased to 7091 pg/ml on day 28 and 6403 pg/ml on day 112. The corresponding median levels in the cediranib 30 mg group were 5836 and 5789 pg/ml.

extended follow-up

At second data cut-off, PFS events had been observed in 47 (81%), 46 (82%) and 46 (79%) patients in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The PFS HR for the cediranib 20 mg group versus placebo was 0.76 (95% CI 0.51–1.15), two-sided $P = 0.0879$. Median PFS was 10.9 and 8.3 months, respectively. In the cediranib 20 mg group, 40.5% of patients were event free at 12 months compared with 28.9% in the placebo group. The PFS comparison for cediranib 30 mg versus placebo was 0.96 (95% CI 0.64–1.46), two-sided $P = 0.429$. Median PFS was 9.8 and 8.3 months, respectively, and 36.1% of patients were event free at 12 months in the cediranib 30 mg group versus 28.9% in the placebo group.

At final data cut-off, 24 (41.4%), 27 (48.2%) and 23 (39.7%) patients had died in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. For the comparison of cediranib 20 mg versus placebo, the HR was 1.09 (95% CI 0.61–1.95), two-sided $P = 0.543$; median OS was not reached in the cediranib 20 mg group. For the comparison of cediranib 30 mg versus placebo, the HR was 1.28 (95% CI 0.73–2.24), two-sided $P = 0.706$. Median OS was 22.4 and 23.3 months in the cediranib 30 mg and placebo groups, respectively.

discussion

Patients enrolled in this study were representative of the target population of Japanese patients with previously untreated mCRC and consistent with previous studies [26, 27]. Although baseline characteristics were generally well balanced across the three groups, imbalances were noted. The imbalances in ALP and albumin levels probably occurred because the data were analysed at a central laboratory, whereas stratification according to baseline liver function was carried out in individual centres.

The median PFS of patients who received mFOLFOX6 alone in this study (8.3 months) was consistent with the SWIFT-2 (8.2 months) [27] and TREE-1 (8.7 months) [28] studies, in

which patients received mFOLFOX6 as first-line treatment of mCRC. Furthermore, the median PFS of patients in this study who received cediranib 20 mg plus mFOLFOX6 (10.2 months) compares well with the time to progression (9.9 months) for patients who received bevacizumab plus mFOLFOX6 in the TREE-2 study [28]. It is worth noting that TREE-2 was conducted in non-Japanese patients and there is a lack of phase III data for bevacizumab plus FOLFOX in the first-line setting in Japanese mCRC patients. A recent phase I/II study of first-line therapy comprising capecitabine plus oxaliplatin (XELOX) and bevacizumab in 64 Japanese patients with mCRC revealed a median PFS of 11 months, although the primary end points of this study were safety and ORR [29].

Here, the higher response rate observed in patients treated with cediranib 30 mg compared with the other arms did not translate into prolonged PFS, possibly due to differences in tolerability profiles of the cediranib arms. More patients in the cediranib 30 mg group experienced AEs (in particular, grade 3/4 diarrhoea) that led to discontinuation, dose reduction or dose interruption, than in the cediranib 20 mg or placebo groups. This appeared to impact on chemotherapy delivery—patients in the 30 mg arm received a lower dose intensity of oxaliplatin, which may reflect the differences in PFS outcomes. Due to these differences in tolerability, results from this study suggest that cediranib 20 mg is more suitable than 30 mg for long-term dosing in combination with mFOLFOX6 in Japanese patients with previously untreated mCRC. Cediranib 20 mg plus mFOLFOX6 was generally well tolerated, although the incidence of SAEs was higher compared with the placebo group. The most frequently reported AEs for the combination of cediranib 20 mg and mFOLFOX6 were diarrhoea and hypertension. The >50% incidence of palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome) in patients who received cediranib is consistent with a previous phase I study of cediranib monotherapy in Japanese patients and with studies of other targeted agents in Japanese patients with advanced cancer [30, 31]. Overall, no new safety issues were identified; no fatal AEs occurred and the AE profile was consistent with previous cediranib studies [10, 15]. With the exception of hypertension, diarrhoea, proteinuria, hypothyroidism, reversible posterior leukoencephalopathy syndrome, fatigue, hepatotoxicity, haematological toxicity and thrombocytopenia (for which specific management protocols were employed), cediranib-associated AEs were managed by dose interruption of up to 14 days or, if longer, treatment discontinuation. The incidences of grade ≥3 AEs and SAEs observed in this trial following addition of a TKI to FOLFOX therapy are consistent with those reported in trials involving vatalanib and bevacizumab in combination with a FOLFOX regimen [23, 32]. Cediranib treatment has shown a less favourable AE profile compared with bevacizumab in Western patients in the HORIZON III study [23]. In a phase I/II study in Japanese mCRC patients treated with XELOX plus bevacizumab, the most common grade 3/4 AEs were neurosensory toxicity (17%) and neutropenia (16%), both of which were managed by dose reduction of XELOX components; the incidence of grade 3/4 diarrhoea was only 3% [29]. It is not clear why the toxicity profiles of cediranib and bevacizumab differ, but it is probably related to differences in mechanism of action; cediranib is a potent inhibitor of the three VEGF receptor tyrosine kinases, whereas the activity of bevacizumab is dependent on preventing VEGF from binding to VEGF receptors, rather than blocking the receptors directly. In addition, the potential contribution of cediranib activity versus non-VEGFR kinases, e.g. c-Kit inhibition [33], cannot be excluded. Furthermore, cediranib undergoes extensive metabolism, so it is possible that one or more metabolites may add to the toxicity profile.

An assessment of the levels of the soluble biomarkers VEGF and sVEGFR-2 was conducted as an exploratory objective. Owing to the limited data, caution should be taken when drawing conclusions from these findings; however, the observed increase in VEGF levels and decrease in sVEGFR-2 levels in cediranib-treated patients are consistent with previous cediranib trials [10, 21]. The increased VEGF levels may represent an acute stress response to inhibition of VEGF signalling by cediranib, whereas changes in sVEGFR-2 levels could be a surrogate marker for biological activity.

Analysis with an additional 8 months of follow-up data revealed similar findings to the pre-specified protocol analysis in both efficacy and safety outcomes. This additional analysis confirmed that PFS in this study (HR = 0.76) is consistent with the HORIZON II study (HR = 0.84), in which significantly improved PFS was observed with the addition of cediranib 20 mg to standard chemotherapy (FOLFOX/XELOX) [22].

This study met its primary end point for improved PFS with cediranib 20 mg plus mFOLFOX6 compared with placebo plus mFOLFOX6. The outcomes from this study, and from HORIZON II [22] and HORIZON III [23], provide some understanding of the potential role of VEGFR TKIs in the management of previously untreated mCRC. In unselected patient populations, cediranib provided marginal clinical benefit when added to standard oxaliplatin-based chemotherapy. These data did not support further development of cediranib in CRC; however, further investigation may reveal a particular benefit in a more selective patient population.

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funding

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disclosure

KY has received speaker fees (Merk Serono and Chugai Pharmaceutical). XS and KF are employees of AstraZeneca and own stock. All other authors have no conflicts of interest to declare.

references

1. GLOBOCAN Database. Japan: Summary Statistics. Lyon, France: International Agency for Research on Cancer 2010; Available at: GLOBOCAN 2008.
2. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005; 352: 476–487.

3. Japanese Society for Cancer of the Colon and Rectum. Clinical Practice Guidelines for the Treatment of Colorectal Cancer (For Physicians). Tokyo, Japan: Kanehara & Co Ltd 2005; 30–33.
4. Goldberg RM. Current approaches to first-line treatment of advanced colorectal cancer. Clin Colorectal Cancer 2004; 4: S9–S15.
5. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000; 18: 2938–2947.
6. Cunningham D, Atkin W, Lenz H-J et al. Colorectal cancer. Lancet 2010; 375: 1030–1047.
7. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335–2342.
8. Heckman CA, Holopainen T, Wirzenius M et al. The tyrosine kinase inhibitor cediranib blocks ligand-induced vascular endothelial growth factor receptor-3 activity and lymphangiogenesis. Cancer Res 2008; 68: 4754–4762.
9. Wedge SR, Kendrew J, Hennequin LF et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res 2005; 65: 4389–4400.
10. Drevs J, Siegert P, Medinger M et al. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007; 25: 3045–3054.
11. Batchelor TT, Sorensen AG, di Tomaso E et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007; 11: 83–95.
12. Fiedler W, Mesters R, Heuser M et al. An open-label, Phase I study of cediranib (RECENTIN) in patients with acute myeloid leukemia. Leuk Res 2010; 34: 196–202.
13. Langenberg M, van Herpen CM, de Bono JS et al. Optimal management of emergent hypertension during treatment with a VEGF signaling inhibitor: a randomized phase II study of cediranib. J Clin Oncol 2008; 26 (15S): (Abstr 3555).
14. Matulonis UA, Berlin S, Ivy P et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009; 27: 5601–5606.
15. Yamamoto N, Tamura T, Yamamoto N et al. Phase I, dose escalation and pharmacokinetic study of cediranib (RECENTIN), a highly potent and selective VEGFR signaling inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2009; 64: 1165–1172.
16. Laurie SA, Gauthier I, Arnold A et al. Phase I and pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small-cell lung cancer: the National Cancer Institute of Canada clinical trials group. J Clin Oncol 2008; 26: 1871–1878.
17. Chen E, Jonker D, Gauthier I et al. Phase I study of cediranib in combination with oxaliplatin and infusional 5-fluorouracil in patients with advanced colorectal cancer. Clin Cancer Res 2009; 15: 1481–1486.
18. Goss G, Shepherd FA, Laurie S et al. A phase I and pharmacokinetic study of daily oral cediranib, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer: a study of the National Cancer Institute of Canada Clinical Trials Group. Eur J Cancer 2009; 45: 782–788.
19. Goss GD, Arnold A, Shepherd FA et al. Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. J Clin Oncol 2010; 28: 49–55.
20. LoRusso P, Shields AF, Gadgeel S et al. Cediranib in combination with various anticancer regimens: results of a Phase I multi-cohort study. Invest New Drugs 2010 [epub ahead of print], doi:10.1007/s10637-010-9484-5.
21. van Cruijsen H, Voest EE, Punt CJ et al. Phase I evaluation of cediranib, a selective VEGFR signalling inhibitor, in combination with gefitinib in patients with advanced tumours. Eur J Cancer 2010; 46: 901–911.
22. Hoff PM, Hocchaus A, Pestalozzi BC et al. Cediranib + FOLFOX/XELOX versus placebo + FOLFOX/XELOX in patients (pts) with previously untreated metastatic colorectal cancer (mCRC): a randomized, double-blind, phase III study (HORIZON II). Ann Oncol 2010; 21 (Suppl 8): viii9. (Abstr LBA19).
23. Schmoll H-J, Cunningham D, Sobrero A et al. mFOLFOX6 + cediranib vs mFOLFOX6 + bevacizumab in previously untreated metastatic colorectal cancer (mCRC): a randomized, double-blind, phase II/III study (HORIZON III). Ann Oncol 2010; 21 (Suppl 8): viii188 (Abstr 5800).
24. Satoh T, Yamaguchi K, Boku N et al. Phase I results from a two-part Phase I/II study of cediranib in combination with mFOLFOX6 in Japanese patients with metastatic colorectal cancer. Invest New Drugs 2011 May 25 [epub ahead of print], doi:10.1007/s10637-011-9693-6.
25. Rubinstein LV, Korn EL, Freidlin B et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol 2005; 23: 7199–7206.
26. Saltz LB, Clarke S, Diaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008; 26: 2013–2019.
27. Nagata N, Kondo K, Kato T et al. Multicenter phase II study of FOLFOX for metastatic colorectal cancer (mCRC) in Japan; SWIFT-1 and 2 study. Hepatogastroenterology 2009; 56: 1346–1353.
28. Hochster HS, Hart LL, Ramanathan RK et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. J Clin Oncol 2008; 26: 3523–3529.
29. Doi T, Boku N, Kato K et al. Phase I/II study of capecitabine plus oxaliplatin (XELOX) plus bevacizumab as first-line therapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol 2010; 40: 913–920.
30. Akaza H, Tsukamoto T, Murai M et al. Phase II study to investigate the efficacy, safety, and pharmacokinetics of sorafenib in Japanese patients with advanced renal cell carcinoma. Jpn J Clin Oncol 2007; 37: 755–762.
31. Uemura H, Shinohara N, Yuasa T et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into the treatment, efficacy and safety. Jpn J Clin Oncol 2010; 40: 194–202.
32. Hecht JR, Trarbach T, Hainsworth JD et al. Randomized, placebo-controlled, Phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol 2011; 29: 1997–2003.
33. Brave SR, Ratcliffe K, Wilson Z et al. Assessing the activity of cediranib, a VEGFR-2/-3 tyrosine kinase inhibitor, against VEGFR-1 and members of the structurally related PDGFR-family. Mol Cancer Ther 2011; 10: 861–873.

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ORIGINAL ARTICLE – PANCREATIC TUMORS

Perioperative Intra-Arterial and Systemic Chemotherapy for Pancreatic Cancer

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ABSTRACT

Background. Even after curative resection of pancreatic cancer, there is a high probability of systemic recurrence. This indicates that subclinical metastases are already present at the time of operation. The purpose of this study was to assess the feasibility and outcomes of patients who received a novel multimodality therapy combining pancreatic resection and intraoperative radiation therapy (IORT) with pre- and postoperative chemotherapy for pancreatic cancer.

Methods. For eligible patients with pancreatic cancer, 5-FU was administered at a dose of 125 mg/m^2/day on days 1–5 every week as a continuous pancreatic and hepatic arterial infusion, and gemcitabine was infused intravenously at a dose of 800 mg/m^2 per day once per week for 2 weeks for preoperative chemotherapy. Pancreatic resection combined with IORT was performed 1 week after preoperative chemotherapy. Postoperative chemotherapy was performed in the same way as preoperative chemotherapy. We performed an intention-to-treat analysis for all enrolled patients.

Results. This study enrolled 44 patients. The most common toxicities were hematological and gastrointestinal events. Grade 3/4 hematological toxicities were observed during preoperative chemotherapy, although there were no grade 3/4 nonhematological events. Postoperative chemotherapy-related toxicities were more critical and frequent than preoperative ones. There were no pre- or postoperative chemotherapy-associated deaths. Median overall survival was 36.5 months with 30.5% overall 5-year survival.

Conclusions. This multimodality therapy is feasible and promises to contribute to survival. It should be evaluated in a phase III setting.

Pancreatic adenocarcinoma remains a lethal disease, with an overall 5-year survival rate ranging from 0.4 to 5%.[1,2] Even after curative resection of pancreatic cancer, there is a high probability of systemic and/or local recurrence.[3–5] This indicates that subclinical metastases are already present in most patients at the time of operation, even if preoperative radiological imaging or intraoperative examination revealed no metastatic lesions. Therefore, a multimodality strategy, including not only local control but also treatment of micrometastases, is required for patients with pancreatic cancer. For local control, beginning in 1984 we introduced extended radical pancreatectomy combined with intraoperative radiation therapy (IORT).[6] This approach provided the best control of local recurrence, but there was no survival benefit because of blood-borne metastases.[5] To treat unresectable pancreatic cancer, we introduced a combination of chemotherapy using 5-fluorouracil (5-FU) pancreatic and hepatic arterial continuous infusion and systemic gemcitabine administration; this combined therapy was well tolerated, with a 1-year survival rate of 50.9%.[7]

We studied a novel multimodality therapy combining pancreatic resection and IORT with pre- and postoperative chemotherapy using 5-FU intra-arterial continuous infusion and systemic gemcitabine administration in patients with potentially resectable pancreatic cancer. The purpose of this study was to evaluate the feasibility and outcomes of this multimodality therapy.

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PATIENTS AND METHODS

Patients

All patients were advised of the investigational nature of the study and gave their written, informed consent to participate before the beginning of the study. All patients underwent a standard pretreatment evaluation that included a physical examination, a thin-section, contrast-enhanced, multiphase spiral computed tomography (CT) of the abdomen, and ultrasonography. The absence of liver metastasis was confirmed by CT during arterial portography combined with CT-assisted hepatic arteriography (CTAP + CTHA), as described previously.[8] The absence of lung metastasis was confirmed by chest CT. The protocol required patients with potentially resectable disease as assessed by a physical examination and the following objective radiographic criteria: (1) no evidence of remote metastases; (2) no evidence of tumor extension to the celiac axis or the superior mesenteric artery. We included only patients in whom it was technically possible to resect and reconstruct the superior mesenteric vein (SMV) or the portal vein (PV), if the tumor involved SMV or PV. We excluded cases in which the tumor was 1 cm or smaller in diameter, because of the very low possibility of systemic spreading of the disease. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 2.

Perioperative Chemotherapy

The treatment schema is shown in Fig. 1. The pre- and postoperative chemotherapy consisted of the combination of 5-FU arterial continuous infusion and systemic gemcitabine administration. In all cases, the catheter for arterial infusion was introduced from the femoral artery under local anesthesia. After the closure of the distal tip of the catheter, a side hole was made at an appropriate site in the celiac axis to allow the distribution of 5-FU to both the pancreatic tumor and the liver preoperatively, and in the hepatic artery to distribute the drug to the whole liver postoperatively. An arterial port was implanted in the subcutaneous tissue. 5-FU was administered at a dose of 125 mg/m^2 per day on days 1–5 each week as continuous infusion through the arterial port for 2 weeks during preoperative chemotherapy and for 8 weeks during postoperative chemotherapy. Gemcitabine was infused intravenously for 30 min at a dose of 800 mg/m^2 once weekly for a total of 2 doses preoperatively and for a total of 18 doses postoperatively. The doses of these drugs were based on our preliminary results for the combination chemotherapy using 5-FU intra-arterial infusion and systemic gemcitabine for unresectable pancreatic cancer.[7]

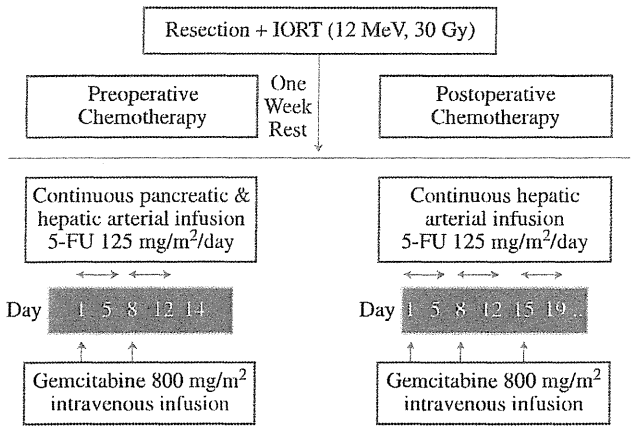

FIG. 1 Treatment schema. 5-FU was administered on days 1–5 every week as a continuous arterial infusion combined with gemcitabine infused once weekly for 2 weeks followed by pancreatic resection combined with IORT. Postoperative chemotherapy was performed in the same way as preoperative chemotherapy

In cases of grade 3 or higher toxicity according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0, drug infusion was interrupted until recovery. History, physical examination, and complete blood counts (CBCs) were repeated weekly before infusion of the drugs. Chemistry profiles were performed every 2 weeks. The catheter and port for arterial infusion were removed after the completion of intra-arterial infusion of 5-FU.

Surgery

Patients with cancer of the head of the pancreas underwent a substomach-preserving pancreaticoduodenectomy (SSPPD), a pylorus-preserving pancreaticoduodenectomy (PPPD), or a Kausch-Whipple resection: the last of these was performed if a tumor directly invaded the duodenum or antrum of the stomach, or if a distal gastrectomy had been performed before. Patients with cancer of the body or tail of the pancreas underwent a distal pancreatectomy. Patients underwent resection with reconstruction of SMV or PV if a tumor was thought during surgery to involve these vessels. For IORT, a dose of 30 Gy with a 12 MeV of electron beam was delivered to the operative field using a special pentagon applicator following dissection, as described previously.[6]

Hospital death was defined as death during hospitalization. Major surgical complications included any occurrence of anastomotic leak, postoperative intra-abdominal or gastrointestinal hemorrhage or fistula, intra-abdominal abscess, pneumonia, catheter-related sepsis, thromboembolic events, and reoperation. Pancreatic fistula was assessed according to an international study group (ISGPF) definition.[9]

Toxicity and Outcome Evaluation

Toxicities were graded according to NCI-CTC version 3.0. Survival was calculated from the day of surgery and estimated by the Kaplan–Meier method. The first site of disease recurrence was documented for outcome analysis.

All patients were evaluated every 3–4 months by physical examination as well as by chest and abdominal CT after surgery. For those without any recurrence after 2 years, follow-up was at 6-month intervals. Cytologic or histologic confirmation of disease recurrence was not required.

RESULTS

Patient Characteristics

From May 2001 through September 2008, 44 patients were enrolled in this study. The patients' characteristics are outlined in Table 1. The primary pancreatic lesion was located in the head in 33 patients, in the body in 9, and in the tail in 2. All patients underwent pancreatic resection. Pancreatic ductal adenocarcinoma was confirmed in all patients histologically. R0 resection was performed in 37 patients, R1 resection in 5 (11.4%), and R2 resection in 2 (4.5%). The median tumor size was 3 (range, 1.3–8.7) cm. Lymph node metastases were identified in 30 patients (68.2%), including para-aortic lymph node metastases in 3 patients. Resection and reconstruction of SMV or PV were necessary in 22 patients (50%), although 13 (29.5%) were proven to have histological portal invasion. Thirty-four patients received IORT after resection. All of the patients began postoperative chemotherapy after recovery from surgery, although 20 patients (45.5%) were completely treated according to the postoperative schedule. The mean pre- and postoperative doses of total 5-FU administered per patient were 2.8 and 5.2 g. The mean pre- and postoperative doses of total gemcitabine were 5.2 and 14.3 g.

TABLE 1 Patient characteristics

Characteristics	No. of patients	%
Total no. of patients	44	
Median age (yr)	65 (37–79)	
Male/female	26/18	
Site of primary lesion		
Head	33	75
Body	9	20.5
Tail	2	4.5
Pancreatectomy		
PPPD	16	36.4
SSPPD	13	29.5
PD	4	9.1
DP	11	25
Stage		
Ia	3	6.8
Ib	1	2.3
IIa	10	22.7
IIb	26	59.1
III	1	2.3
IV	3	6.8
Histologic differentiation		
Well	16	36.4
Moderately	22	50
Poorly	5	11.4
Adenosquamous	1	2.3
Tumor size (cm)		
1.0–2.0	6	13.6
2.1–4.0	33	75
>4.1	5	11.4
Nodal involvement		
Present	30	68.2
Absent	14	31.8
Portal vein invasion		
Present	13	29.5
Absent	31	70.5
Residual tumor		
R0	37	84.1
R1	5	11.4
R2	2	4.5

PPPD pylorus-preserving pancreaticoduodenectomy; *SSPPD* substomach-preserving pancreaticoduodenectomy; *PD* pancreaticoduodenectomy; *DP* distal pancreatectomy

Toxicities of Pre- and Postchemotherapy and Surgery

All 44 patients were included in the toxicity analysis. The overall toxicity profiles related to pre- and postoperative chemotherapy are outlined in Table 2. The most common toxicities were hematological and gastrointestinal events.

Nineteen patients (43.2%) experienced grade 3/4 neutropenia during preoperative chemotherapy. All preoperative chemotherapy-related toxicities abated after discontinuation of drug infusion. Forty-three patients underwent surgery 1 week after the completion of preoperative chemotherapy. Only one patient experienced a delay in surgery because of grade 4 neutropenia. Five major complications occurred in five patients after surgery, including grade C pancreatic fistula in two patients, intra-abdominal abscess in one, and cerebral infarction in one. Three patients recovered from complications by means of conservative therapies. One patient underwent reoperation for grade C pancreatic fistula. Hospital death was observed in one patient because of liver failure after intra-abdominal bleeding caused by pancreatic fistula.

TABLE 2 Pre- and postoperative chemotherapy-related grade 3/4 toxicities

	Preoperative	Postoperative
Hematological		
Anemia	0	4 (9.1)
Leukopenia	8 (18.2)	14 (31.8)
Neutropenia	19 (43.2)	24 (54.5)
Thrombocytopenia	2 (4.5)	3 (6.8)
Others		
Perforation of small intestine	0	1 (2.3)
Liver abscess	0	3 (6.8)
Cardiac ischemia/infarction	0	2 (4.5)
Renal dysfunction	0	1 (2.3)
Cholangitis	0	3 (6.8)
Appetite loss	0	1 (2.3)

Percentages are shown in parentheses

Toxicities are defined by NCI-CTC for Adverse Events v3.0

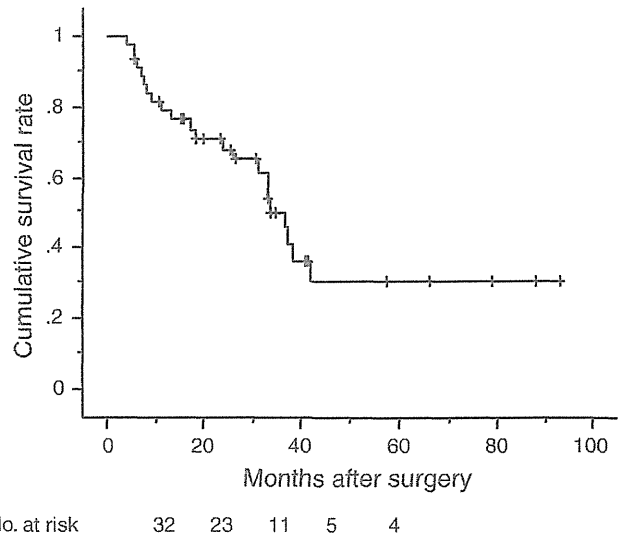

FIG. 2 Overall survival curve for all patients

Postoperative chemotherapy was initiated between 3 and 12 weeks after surgery. Twenty-four patients (54.5%) experienced grade 3/4 neutropenia during postoperative chemotherapy, although these toxicities abated after drug infusion was interrupted. Perforation of the small intestine in one patient occurred 1 year after pancreatic resection. This patient underwent emergency surgery and recovered. Grade 3/4 cardiac ischemia occurred in two patients and liver abscess in three patients (6.8%) during postoperative chemotherapy. No intra-arterial catheter-related toxicity occurred in any of the patients. Neither pre- nor postoperative chemotherapy-associated death was observed.

Survival and Outcome

The median follow-up period was 28.2 (range, 5.5–93.3) months. The 1, 3, and 5-year actuarial overall survival rates in all the patients were 78.8, 50.3, and 30.5%, respectively (Fig. 2). The median survival time was 36.5 months.

At last follow-up, 22 of the 44 patients (50%) had died. Seventeen (38.6%) had died as a result of recurrence. There were five (11.4%) non-cancer-related deaths, including one hospital death. Twenty-two patients (50%) remained alive. The median time of tumor recurrence was 24.0 months from the day of surgery. Liver metastases were observed in four patients (9.1%), peritoneal dissemination in six (13.6%), lung metastases in one (2.3%), pleural dissemination in one, bone metastases in one, and local recurrence in four (Table 3). Eight patients survived more than 32.3 months. The two patients with R2 resection died of peritoneal dissemination within 12 months.

TABLE 3 Outcomes after this multimodality therapy for patients with pancreatic cancer

	No.
Cancer deaths	17
Liver metastases	4
Lung metastases	1
Pleural dissemination	1
Peritoneal dissemination	6
Local recurrence	4
Bone metastases	1
Non-cancer-related deaths	5
Alive	22
Total	44

DISCUSSION

To our knowledge, this is the first report of perioperative intra-arterial and systemic chemotherapy for pancreatic cancer. This treatment was clearly operator-dependent. Grade 3/4 neutropenia was relatively frequent during perioperative chemotherapy, although the toxicities abated after interruption of drug infusion. Grade 3/4 nonhematological toxicities were observed during postoperative chemotherapy. Liver abscess occurred in three patients. This was thought to be influenced by regurgitated cholangitis, because all of the patients underwent hepaticojejunostomy after PD. Perforation of the small intestine occurred in one patient 3 months after completion of postoperative chemotherapy. Cardiac ischemia required hospitalization for two patients. However, the relationship between these events and chemotherapy was unclear. Toxicities were more critical and frequent during postoperative chemotherapy than during preoperative. Intra-arterial infusion was acceptable

for perioperative chemotherapy, because no catheter-related toxicity was observed.

Practical and theoretical advantages of preoperative treatment of pancreatic cancer were proposed as an early treatment for micrometastases and optimized patient selection for surgery.[10–12] Circulating tumor cells in the blood proved to be present in 28% of patients with pancreatic cancer, and the prevalence increased with tumor stages.[13] Moreover, complications, which occurred after 30–45% of major pancreatic resections, delayed the initiation of postoperative chemotherapy.[14,15] These are supported to introduce preoperative chemotherapy for pancreatic cancer.

The rationale for intra-arterial infusion of chemotherapeutic agents appears to be promising from the point of view of the drug-concentration response, because most liver metastases (>3 mm) have an arterial blood supply.[16,17] Locoregional adjuvant chemotherapy has been reported to have 3-year survival rates ranging from 48 to 54%, and lower recurrence rates of liver metastases ranging from 8 to 17% for pancreatic cancer compared with no-adjuvant studies.[3,4,18,19] This study also showed that liver metastases diminished to 9.1%, indicating that intra-arterial chemotherapy might be effective to prevent liver metastases.

We adopted pancreatic resection combined with IORT for local control in this series. Local recurrence was observed in only four patients (9.1%). Single-institution experiences suggest that local failure rates were lower in radiation groups (10–26%) than in no-radiation groups (50–80%).[20–24] This indicated that resection combined with IORT could provide good control of local recurrence.

Recently, a phase III randomized trial (CONCO 001 study) demonstrated that adjuvant gemcitabine significantly delayed the development of recurrence after resection of pancreatic cancer, with a median survival time of 22.1 months.[25] Evans et al. reported on a phase II trial of neoadjuvant gemcitabine-based chemoradiation for stage I/II pancreatic cancer.[26] The median survival time of 36.5 months in our study is similar to the 34 months in the Evans group trial despite a greater proportion of patients with node-positive (68.2%) and R2 resection (4.5%) in our study than in the Evans group trial. Because our perioperative chemotherapy is complicated, it will be necessary to clarify which adjuvant treatment is most effective for pancreatic cancer to simplify treatment.

In conclusion, this perioperative chemotherapy for pancreatic cancer is feasible and promises to contribute to survival. It should be evaluated in a phase III setting.

REFERENCES

1. Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP. Treatment and survival in 13560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. *Br J Surg*. 1995;82:111–5.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71–96.
3. Griffin JF, Smalley SR, Jewell W, Paradelo JC, Reymond RD, Hassanein RE, Evans RG. Patterns of failure after curative resection of pancreatic carcinoma. *Cancer*. 1990;66:56–61.
4. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. *World J Surg*. 1997;21:195–200.
5. Takamori H, Hiraoka T, Kanemitsu K, Tsuji T. Pancreatic liver metastases after curative resection combined with intraoperative radiation for pancreatic cancer. *Hepato-Gastroenterol*. 2004;51:1500–3.
6. Hiraoka T, Uchino R, Kanemitsu K, et al. Combination of intraoperative radiation with resection of cancer of the pancreas. *Int J Pancreatol*. 1990;7:201–7.
7. Takamori H, Kanemitsu K, Tsuji T, et al. 5-Fluorouracil intra-arterial infusion combined with systemic gemcitabine for unresectable pancreatic cancer. *Pancreas*. 2005;30:223–6.
8. Takamori H, Ikeda O, Kanemitsu K, et al. Preoperative detection of liver metastases secondary to pancreatic cancer. Utility of combined helical computed tomography during arterial portography with biphasic computed tomography-assisted hepatic arteriography. *Pancreas*. 2004;29:188–92.
9. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
10. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg*. 1992;127:1335–9.
11. Wayne JD, Abdalla EK, Wolff RA, Crane CH, Pisters PW, Evans DB. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. *Oncologist*. 2002;7:34–45.
12. Pisters PW, Wolff RA, Janjan NA, et al. Preoperative paclitaxel and concurrent rapid fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol*. 2002;20:2537–44.
13. Z'graggen K, Centeno BA, Fernandez-del Castillo C, Jimenez RE, Werner J, Warshaw AL. Biological implications of tumor cells in blood and bone marrow of pancreatic cancer patients. *Surgery*. 2001;129:537–46.
14. Sohn TA, Yeo CJ, Cameron JT, et al. Resected adenocarcinoma of the pancreas–616 patients: results, outcomes, and prognosis indicators. *J Gastrointest Surg*. 2000;4:567–79.
15. Frederick WAI, Wolff RA, Crane CH. Preoperative (neoadjuvant) therapy for resectable adenocarcinoma of the pancreas. In: Evans DB, Pisters PWT, Abbruzzese JL, Pollock RE, editors. MD Anderson Solid Tumor Oncology Series. New York: Springer; 2001. p. 243–54.
16. Archer SG, Gray BN. Vascularization of small liver metastases. *Br J Surg*. 1989;76:545–8.
17. Ackermann NB. The blood supply of experimental liver metastases. IV. Changes in vascularity with increasing tumor growth. *Surgery*. 1974;75:589–96.
18. Ishikawa O, Ohigashi H, Sasaki Y, et al. Liver perfusion chemotherapy via both the hepatic artery and portal vein to prevent hepatic metastasis after extended pancreatectomy for adenocarcinoma of the pancreas. *Am J Surg*. 1994;168:361–4.
19. Beger HG, Gansauge F, Büchler MW, Link KH. Intraarterial adjuvant chemotherapy after pancreaticoduodenectomy for pancreatic cancer: significant reduction in occurrence of liver metastasis. *World J Surg*. 1999; 23:946–949.
20. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. *Ann Surg Oncol*. 2001;8:123–32.
21. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with

pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol.* 1997;15:928–37.
22. Tepper JE, Nardi G, Suit H. Carcinoma of the pancreas: review of MGH experience from 1963–1973. Analysis of surgical failure and implications for radiation therapy. *Cancer.* 1976;37:1519–25.
23. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. *Cancer.* 1993;72:2118–23.
24. Whittington R, Bryer MP, Haller DG, Solin LJ, Rosato EF. Adjuvant therapy of resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys.* 1991;21:1137–43.
25. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer. A randomized controlled trial. *JAMA.* 2007;297:267–77.
26. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreas. *J Clin Oncol.* 2008;26: 3496–502.

Review

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Induction Chemotherapy with Docetaxel/Cisplatin/5-Fluorouracil for Patients with Node-Positive Esophageal Cancer

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Key Words
Cisplatin · Docetaxel · Esophageal cancer · 5-Fluorouracil · Induction chemotherapy · Neoadjuvant chemotherapy · Node-positive esophageal cancer

Abstract
Background: Despite improvements in the surgical management of esophageal cancer, the prognosis of patients with lymph node metastases is still unsatisfactory. Recently, survival benefit of neoadjuvant or induction chemotherapy for patients with esophageal cancer has been highlighted. ***Methods:*** Efficacy and toxicity of induction chemotherapy for esophageal cancer were reviewed. In addition, our experience on modified docetaxel/cisplatin/5-FU (DCF) as induction chemotherapy was also demonstrated. The modified DCF consisted of 60 mg/m^2 of docetaxel on day 1, and 350 mg/m^2 of 5-FU and 6 mg/m^2 of cisplatin on days 1–5. Two courses have been administered as induction chemotherapy in 51 patients with node-positive esophageal cancer. Response was evaluated by RECIST v1.0 and changes in standardized uptake value by ^{18}F-fluorodeoxyglucose positron emission tomography. ***Results:*** Induction chemotherapy may be beneficial for node-positive esophageal cancer, although the consensus has not yet been established. A regimen of induction chemotherapy should have a high response rate and cisplatin/5-FU may be underpowered as an induction setting. DCF can be a candidate for the regimen of induction chemotherapy for esophageal cancer, although severe adverse events have been reported. Several modified regimens to reduce the toxicity have been reported. The response rate of our series was 61% and a significant decrease in standardized uptake values was observed after the induction chemotherapy. Although high-grade neutropenia was still observed with this regimen, neither treatment-related death nor delay in the following treatment was observed. ***Conclusions:*** Modified DCF can be a regimen of induction chemotherapy for node-positive esophageal cancer because of its high efficacy, although an adequate care for severe neutropenia is needed.

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Introduction

Long-term survival of patients with esophageal cancer has been improved during several decades, mainly owing to progress in surgical treatment. Squamous cell carcinoma of the esophagus often spreads through the lymphatic vessels and widespread lymph node metastases are frequently observed from the early stage of this disease. Therefore, an extended radical lymph node dissection, the so-called three-field dissection, has been established in Japan [1, 2]. The prognosis of patients with esophageal cancer has been improved according to the spread of such a radical surgery, although there has been no randomized study that demonstrated the superiority of three-field dissection compared to limited lymphadenectomy.

In spite of improved surgical techniques, the prognosis of patients with lymph node metastases is still unsatisfactory even when a curative resection was performed, especially in cases with three-field lymph node metastases or numerous node metastases. A recent randomized control trial has revealed that adjuvant chemotherapy improved disease-free survival of patients with node-positive esophageal cancer [3]. Thereafter, the other studies demonstrated that the prognosis of patients who were treated with neoadjuvant chemotherapy followed by surgery was superior to that of patients who underwent esophagectomy followed by chemotherapy [4] or treated with surgery alone [5]. According to these findings, recently, chemotherapy followed by esophagectomy has become one of the standard cares for patients with resectable esophageal cancer.

Induction chemotherapy is defined as chemotherapy as the initial treatment for cancer, especially as part of a combined modality therapy. In this meaning, neoadjuvant chemotherapy is included in this entity. However, there is another definition of induction chemotherapy that is defined as the use of drug therapy as the initial treatment for patients presenting with advanced cancer that cannot be treated by other means. According to this definition, neoadjuvant chemotherapy is apparently different from induction chemotherapy. In this article, efficacy and toxicity of induction chemotherapy as the former definition, including neoadjuvant chemotherapy, has been reviewed.

Indication for Induction Chemotherapy

Consensus of who should be treated with chemotherapy prior to surgery or the other definitive treatments has not yet been developed. It is well known that lymph node metastasis is one of the major prognostic factors of patients who underwent curative esophagectomy. The nationwide registry of esophageal cancer in Japan has revealed that the number of lymph node metastasis correlated with the prognosis [6]. In the report the survival rate of patients with 1–3 metastatic nodes was significantly lower than that of patients without nodal involvement. The 5-year survival rate of patients with 4–7 metastatic nodes was as low as 20% and that of patients with more than 8 metastatic nodes was miserable. These results indicate that node-positive cases are candidates for induction chemotherapy.

The Japanese Clinical Oncology Group (JCOG) has targeted patients with clinical stage II/III by TNM classification for their randomized trials concerning adjuvant chemotherapy, mentioned above. In JCOG 9204, adjuvant chemotherapy prolonged disease-free survival of patients with node-positive tumors, but no survival benefit was evident in patients without nodal involvement [3]. The result suggests that patients with node-positive tumors should be treated with adjuvant chemotherapy. On the other hand, in JCOG 9907, which compared preoperative chemotherapy with postoperative chemotherapy, survival benefit of preoperative chemotherapy was observed only in clinical stage II patients but not in stage III patients [4]. Nodal status did not affect the survival benefit of preoperative chemotherapy in this particular study.

Regimens Used for Neoadjuvant or Induction Chemotherapy

An optimal regimen of induction chemotherapy for esophageal cancer has not yet been established. Patients who are targeted by induction chemotherapy include cases with potentially curable tumors by surgery alone and thus they may lose the chance to be cured if tumor progression occurred during the chemotherapy. Therefore, a high response rate, or at least a high disease control rate is required for the regimen. On the other hand, as esophagectomy is a surgery with great surgical stress, a regimen which does not cause organ dysfunction or does not worsen patients' physical condition is desirable. Especially patients with squamous cell carcinoma of the esophagus are frequently accompanied by several organ disorders, because they are usually of high age and tend to have a long-term history of smoking and alcoholic use.

The combination of cisplatin and 5-fluorouracil (FP) has been a standard regimen for advanced or metastatic