Validity of response assessment criteria in neoadjuvant chemotherapy for gastric cancer (JCOG0507-A)

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Abstract

Background Neoadjuvant chemotherapy may improve outcomes in gastric cancer. Tumor responses can be evaluated with RECIST, Japanese Classification of Gastric Carcinoma (JCGC), and histological criteria. These approaches have not yet been compared.

Methods We analyzed two phase II trials of neoadjuvant chemotherapy using S-1 plus cisplatin. JCOG0210 included patients with linitis plastica and large ulcero-invasive tumors, whereas JCOG0405 comprised those with para-aortic or bulky lymph node metastases. Radiologic evaluations were conducted using RECIST in JCOG0405 and JCGC criteria in JCOG0210, because the latter included many patients without measurable lesions. A histological

responder was defined as a patient in whom one third or more of the tumor was affected. The hazard ratios (HR) for death between responders and non-responders and response rate differences between short- and long-term survivors were estimated.

Results In JCOG0210 ($n = 49$), HR was 0.54 in JCGC responders ($P = 0.059$) and 0.40 in histological responders ($P = 0.005$). The difference in response rates between short- and long-term survivors using histological criteria (34 %, $P = 0.023$) was greater than that using JCGC criteria (24 %, $P = 0.15$). In JCOG0405 ($n = 51$), HR was 0.67 in RECIST responders ($P = 0.35$) and 0.39 in histological responders ($P = 0.030$). In short- and long-term survivors, respectively, RECIST response rates were 62 and 67 % ($P = 0.77$), whereas histological response rates were 33 and 63 % ($P = 0.048$).

Conclusions Histological criteria showed higher response assessment validity than RECIST or JCGC criteria and yielded the best surrogate endpoint for overall survival.

Keywords RECIST · JCGC · JCOG

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Introduction

Gastric cancer is the second-leading cause of cancer deaths worldwide and the most common cancer in Japan and Korea [1]. Although surgery is the standard treatment for resectable gastric cancer [2, 3], the prognosis of patients with advanced tumors is poor [4]. In particular, linitis plastica (Borrmann type 4) and large ulcero-invasive-type (Borrmann type 3) tumors, as well as those with paraaortic nodal metastases or bulky lymph node metastases, have extremely poor outcomes even after curative resection [5, 6]. For these advanced tumors, neoadjuvant chemotherapy

is expected to improve long-term prognoses. The Japan Clinical Oncology Group (JCOG) has conducted two multicenter phase II trials to evaluate the efficacy and safety of S-1 plus cisplatin as a neoadjuvant regimen and has reported promising results [7, 8].

Three criteria for evaluating tumor responses to chemotherapy are currently available. The Response Evaluation Criteria in Solid Tumors (RECIST) is the gold standard in the evaluation of tumor response, but it requires the presence of a measurable lesion [9]. Because resectable gastric cancer seldom has measurable lesions, we cannot use RECIST in the neoadjuvant setting. The Japanese Classification of Gastric Carcinoma (JCGC) includes a response evaluation criterion involving barium X-ray or endoscopic examination, which is useful for tumors without measurable lesions [10]. Furthermore, we can evaluate tumor response histologically in resected specimens. As there have been no studies comparing the validities of these radiologic and histological criteria, we have conducted this correlative study (JCOG0507-A) to find the best surrogate endpoint for overall survival in neoadjuvant studies for gastric and esophageal cancers. In esophageal cancer patients, we had reported that histological response rate was the better surrogate endpoint for survival than RECIST response rate [11]. This article reports the results for gastric cancer, comparing RECIST, JCGC, and histological criteria.

Methods

Patient population

We included all eligible patients from two clinical trials (JCOG0210 and JCOG0405) that were conducted by the JCOG. These phase II trials aimed to evaluate the efficacy and safety of neoadjuvant S-1 plus cisplatin in gastric cancer patients [7, 8]. The eligibility criteria of the JCOG0210 trial included linitis plastica (Borrmann type 4) and ulcero-invasive-type (Borrmann type 3) tumors. In the case of ulcero-invasive tumors, the size of the primary tumor was required to be 8 cm or larger. Between March 2003 and December 2003, 49 eligible patients were enrolled in the JCOG0210 trial. Responses to neoadjuvant chemotherapy were evaluated using JCGC criteria. After preoperative chemotherapy, 41 patients could undergo gastrectomy, which provided tissue samples for use in assessing the histological response to preoperative chemotherapy. Six patients failed in simple laparotomy because of the presence of incurable lesions. Two patients did not undergo surgery for reasons of chemotherapy-related death in one patient and refusal of any protocol treatment in one patient.

The eligibility criteria for the JCOG0405 trial included gastric cancer with paraaortic nodal metastases or bulky lymph nodes. Between February 2005 and June 2007, 51 eligible patients were enrolled in the JCOG0405 trial. Responses to neoadjuvant chemotherapy were evaluated with RECIST. After preoperative chemotherapy, 48 patients could undergo gastrectomy, which provided material to evaluate the histological response to preoperative chemotherapy. Three patients did not undergo surgery because of progressive tumor.

All patients in the JCOG0210 and the JCOG0405 trials gave written informed consent. These trials were approved by the JCOG Clinical Trial Review Committee and the institutional review board of each institution involved. Permission for the secondary use of trial data was included in patients' informed consent for JCOG0210 and JCOG0405. The protocol of this correlative study (JCOG0507-A) was approved by the JCOG Protocol Review Committee. JCOG0405 is registered with UMIN-CTR (<http://www.umin.ac.jp/ctr/>), identification number C000000094.

Treatments

The same chemotherapy regimen was used in each of the two trials. S-1 was given orally at 80 mg/m² for the first 3 weeks of a 4-week cycle. Cisplatin was given as an intravenous infusion of 60 mg/m² on day 8 of each cycle. Patients received two 4-week cycles of neoadjuvant S-1 plus cisplatin and then underwent gastrectomy with D2 (in the JCOG0210 trial) or D2 plus paraaortic lymphadenectomy (in the JCOG0405 trial). If curative resection was considered difficult after the second course, addition of a further course of chemotherapy before surgery was permitted only in the JCOG0405 trial. After surgery, no further treatment was given until tumor recurrence.

Response evaluation

After the second course of neoadjuvant chemotherapy, tumor response was evaluated with JCGC criteria based on computed tomography (CT), barium X-ray, and endoscopic examination findings in the JCOG0210 trial, whereas response evaluation using RECIST in the JCOG0405 trial was based only on CT findings. These evaluations were performed by the central reviewers. Response evaluations based on RECIST were not conducted in the JCOG0210 trial because many patients did not have measurable lesions. We could not evaluate the JCGC response in the JCOG0405 trial because barium X-rays and endoscopic examinations were not performed after neoadjuvant chemotherapy.

With the JCGC criteria, overall tumor response depends on the combined responses of primary gastric lesions and metastatic lesions. The details of the JCGC criteria have been described elsewhere [10]. Briefly, morphological changes of gastric lesions are evaluated by X-ray or endoscopic examinations, and the overall responses are classified into four categories: complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). Measurable lesions with at least a 50 % decrease in total tumor size in two dimensions and at least a 30 % decrease in total tumor size in one dimension are classified as PR. Evaluable but nonmeasurable lesions with flattening on X-ray or endoscopic examination, or diffusely infiltrating lesions with at least 50 % enlargement of the gastric lumen in the tumor area by X-ray examination, are also classified as PR. CR or PR cases were treated as responders.

Surgical specimens were assessed histologically, and tumor response was evaluated according to the histological criteria of the JCGC [12]. Briefly, histological evaluations were classified into five categories according to the proportion of the tumor affected by degeneration or necrosis: grade 3, no viable tumor cells remain; grade 2, viable tumor cells remain in less than 1/3 of the tumorous area; grade 1b, viable tumor cells remain in more than 1/3 but less than 2/3 of the tumorous area; grade 1a, viable tumor cells occupy more than 2/3 of the tumorous area; grade 0, no evidence of treatment effect. A histological responder was defined as a patient in whom one third or more of the tumor was affected (grade 1b, 2, or 3). Because the definition of histological responder is controversial, we also evaluated the results when a histological responder was classified as grade 2 or 3. Patients who did not undergo surgery were regarded as non-responders. These evaluations were performed by the pathologists at each institution.

Statistical analysis

The data from all eligible patients were analyzed in this study. Cases in which the tumor was not resected or could not be evaluated were treated as non-responders. With the methods used in this study, a comparison of the overall survival between responders and non-responders was said to have a pitfall because early death cases were classified into the non-responder group. In our study, however, there were no early deaths during the protocol treatment, which implies that minimal bias was induced by the classification system employed in our study.

The relationship of response and overall survival was evaluated using hazard ratios (HRs). The HR for death of responders to non-responders was estimated using the Cox proportional hazard model, and survival distributions were

compared using the log-rank test. The difference in response rates between short- and long-term survivors was estimated and tested with Fisher's exact test. Statistical analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The clinicopathological characteristics of all eligible patients in the JCOG 0210 and 0405 trials are shown in Table 1. The proportion of male patients in the JCOG0405 trial was higher than that in the JCOG0210 trial. The majority of tumors were of the undifferentiated type in the JCOG0210 trial, whereas the differentiated type was more frequent in the JCOG0405 trial. Pathological node-negative (pN0) patients comprised 16 % of both the JCOG0210 (8 of 49) and JCOG0405 (8 of 51) trial populations.

Response rates

The responses to neoadjuvant S-1 plus cisplatin as evaluated by the JCGC, RECIST, and histological criteria are shown in Table 1. The response rates in the JCOG0210 trial were 57 % [95 % confidence interval (CI), 42–71 %] with the JCGC criteria and 47 % (95 % CI, 33–62 %) with histological criteria. The response rates in the JCOG0405 trial were 65 % (95 % CI, 50–78 %) with the RECIST and 51 % (95 % CI, 37–65 %) with histological criteria.

Survival curves in responders and non-responders

Overall survival curves for the JCOG0210 trial are shown in Fig. 1. The difference of the 3-year overall survival rate between responders and non-responders was 17.8 % (responders, 32.1 %; non-responders, 14.3 %) on JCGC criteria and 27.6 % (responders, 39.1 %; non-responders, 11.5 %) on histological criteria. The HR for death of histological responders to non-responders (0.40; 95 % CI, 0.20–0.77) was lower than that using JCGC criteria (0.54; 95 % CI, 0.28–1.03), and the log-rank *P* value on histological criteria (*P* = 0.005) was much smaller than that on JCGC criteria (*P* = 0.059).

Overall survival curves for the JCOG0405 trial are shown in Fig. 2. The difference in the 3-year overall survival rate between responders and non-responders was 5.0 % (responders, 60.6 %; non-responders, 55.6 %) on RECIST and 29.1 % (responders, 73.1 %; non-responders, 44.0 %) on histological criteria. The HR for death of histological responders to non-responders (0.39; 95 % CI, 0.17–0.94) was lower than that using the RECIST (0.67;

Table 1 Patient characteristics

	JCOG0210 (<i>n</i> = 49)	JCOG0405 (<i>n</i> = 51)
Age (years)		
Median	61	63
Range	32–75	42–75
Gender		
Male	28	42
Female	21	9
Borrmann macroscopic type		
0	0	2
1	0	1
2	0	15
3	20	31
4	29	0
5	0	2
Histology		
Differentiated	9	28
Undifferentiated	40	22
Unknown	0	1
Clinical T stage		
cT1	0	1
cT2	2	10
cT3	45	38
cT4	2	2
Clinical N stage		
cN0	16	0
cN1	20	0
cN2	13	25
cN3	0	26
Residual tumor		
R0	31	42
R1 or R2	10	6
Unresected	8	3
Pathological T stage		
pT0	1	2
pT1	4	7
pT2	11	23
pT3	18	15
pT4	7	1
Unresected	8	3
Pathological N stage		
pN0	8	8
pN1	10	5
pN2	16	21
pN3	7	14
Unresected	8	3
Tumor responses evaluated by the JCGC criteria		
CR	0	–
PR	28	–

Table 1 continued

	JCOG0210 (<i>n</i> = 49)	JCOG0405 (<i>n</i> = 51)
NC	13	–
PD	3	–
NE	5	–
Tumor responses evaluated by the RECIST		
CR	–	0
PR	–	33
SD	–	14
PD	–	4
Tumor responses evaluated by the histological criteria of the JCGC		
Grade 3	1	1
Grade 2	12	13
Grade 1b	10	12
Grade 1a	9	19
Grade 0	9	3
Unresected	8	3

T stage and N stage were according to the 13th edition of the Japanese Classification of Gastric Carcinoma

JCGC Japanese classification of gastric carcinoma, CR complete response, PR partial response, NC no change, SD stable disease, PD progressive disease, NE not evaluable

95 % CI, 0.29–1.56), and the log-rank *P* value on histological criteria (*P* = 0.030) was much smaller than that on RECIST (*P* = 0.35).

When a histological responder was classified as grade 2 or 3, the HRs for death of modified histological responders to non-responders were 0.57 (95 % CI, 0.26–1.25) in the JCOG0210 trial and 0.32 (95 % CI, 0.09–1.08) in the JCOG0405 trial. The log-rank *P* values on modified histological criteria were 0.15 in the JCOG0210 and 0.067 in the JCOG0405.

Response rates in short- and long-term survivors

Because the median overall survival time in all eligible patients in the JCOG0210 was 17.3 months, we divided patients into short- and long-term survivors with a cutoff for overall survival time of 18 months. The respective response rates based on JCGC and histological criteria were 46 % and 31 % in short-term survivors and 70 % and 65 % in long-term survivors (Fig. 3). The difference in response rates between short- and long-term survivors using histological criteria (Fisher's exact test, *P* = 0.023) was greater than that using JCGC criteria (Fisher's exact test, *P* = 0.15).

Although for the JCOG0405 trial the median overall survival time was not reached at the time of this analysis, the 3-year overall survival rate was 59 %. We therefore set

Fig. 1 Overall survival curves between responders and non-responders for the JCOG0210 trial: JCGC criteria (**a**), $P = 0.059$ (log-rank test); histological criteria (**b**), $P = 0.005$ (log-rank test)

the cutoff for overall survival time at 36 months. The respective response rates using RECIST and histological response rates were 62 % and 33 % in short-term survivors and 67 % and 63 % in long-term survivors (Fig. 4). The difference in response rates between short- and long-term survivors using histological criteria (Fisher's exact test, $P = 0.048$) was greater than that using RECIST (Fisher's exact test, $P = 0.77$).

Again, when a histological responder was classified as grade 2 or 3, the differences in response rates between short- and long-term survivors based on modified histological criteria were 16 % (Fisher's exact test, $P = 0.33$) in the JCOG0210 trial and 22 % (Fisher's exact test, $P = 0.11$) in the JCOG0405 trial.

Discussion

In this correlative study of two phase II trials, histological criteria, as compared to RECIST and JCGC criteria,

demonstrated a greater difference in both overall survival between responders and non-responders and in response rates between short- and long-term survivors. This result indicates that the histological response was the best surrogate endpoint for overall survival in these neoadjuvant trials for gastric cancer, and the conclusion for gastric cancer was the same as that in esophageal cancer [11], which is very important for the development of cancer treatments. If the histological response can be used as the primary endpoint in neoadjuvant settings, we can evaluate any gastric cancer population regardless of the presence of measurable lesions.

RECIST is the gold standard in the evaluation of tumor responses, but it requires the presence of a measurable lesion. In the present version of RECIST (Ver. 1.1), the criteria for measurable lesions were revised to be stricter: a lymph node must be more than 15 mm in short-axis diameter [13]. There are many unresectable gastric cancer patients without measurable metastatic lesions, because the most frequent pattern of recurrence in advanced or

Fig. 2 Overall survival curves between responders and non-responders for the JCOG0405 trial: RECIST (a), $P = 0.35$ (log-rank test); histological criteria (b), $P = 0.030$ (log-rank test)

Fig. 3 Comparison of the response rates between short-term (*short survivors*) and long-term (*long survivors*) survivors for the JCOG0210 trial: JCGC criteria (a), $P = 0.15$ (Fisher's exact test); histological criteria (b), $P = 0.023$ (Fisher's exact test)

recurrent cases is peritoneal seeding. Particularly in neo-adjuvant settings, resectable gastric tumors seldom have measurable lesions. Furthermore, the primary lesion of digestive tract is not suitable for measurable lesion in terms of reproducibility, as the RECIST guideline cautioned.

The JCGC response evaluation criteria were established to evaluate tumor responses even for tumors without measurable lesions. Although it can be used for any type of gastric cancer, evaluation using endoscopic examination is subjective. Furthermore, repetition of barium X-ray or

Fig. 4 Comparison of the response rates between short- and long-term survivors for the JCOG0405 trial: RECIST (a), $P = 0.77$ (Fisher's exact test); histological criteria (b), $P = 0.048$ (Fisher's exact test)

endoscopic examination for evaluation of tumor response is a significant burden for patients. In contrast, histological evaluation does not require any presurgical examination. If the histological response is indeed the most useful indicator in neoadjuvant settings, patients will not need to undergo invasive examinations after chemotherapy.

There are several different histological grading systems for the evaluation of tumor responses in addition to that defined by the JCGC. Becker et al. [14, 15] proposed the following system: tumors with no viable cells are assigned grade Ia; tumors with 1–10 % viable cells, grade Ib; tumors with 10–50 % viable cells, grade II; and tumors with more than 50 % viable cells, grade III. Ajani et al. [16, 17] proposed a grading scheme: cases showing either an absence of tumor cells or necrosis in more than 90 % of the resected tumor were classified as responders. In this study, we used the JCGC grading system, whereby cases showing viable tumor cells remain in less than two thirds are classified as responders, but for our sensitivity analysis we changed the cutoff point from two thirds to one third. Both the JCOG0210 and JCOG0405 trials showed similar results using this grading system.

This study had some limitations. First, histological evaluations were performed only by the pathologists at each institution, although response evaluations using RECIST and JCGC criteria were conducted by the central reviewers. Because histological evaluations are not completely objective, there may have been some issues with inter-rater reliability. However, our JCOG study group institutions are staffed with experts not only in surgery and chemotherapy, but also in pathology. We believe there was little heterogeneity in the histological evaluations performed by this experienced group. Another study is now ongoing to compare the predictive values based on the different scoring systems of histological response after central review by two reference pathologists. A second limitation is that this study enrolled only patients who had received preoperative S-1 plus cisplatin. S-1 plus cisplatin

is one of the standard regimens for metastatic gastric cancer [18, 19]. The validity of histological tumor response evaluation may vary with different chemotherapeutic regimens, and further studies are needed to investigate this point.

In conclusion, histological response rate seemed to be a better surrogate endpoint for overall survival than radiologic response rate in studies of neoadjuvant therapy for gastric cancer.

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