The Relationship Between Antitumor Effects and Relative Dose Intensity of S-1 plus Cisplatin Treatment for Metastatic Gastric Cancer

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Abstract. Background/Aim: S-1 plus cisplatin is the standard first-line chemotherapy for metastatic gastric cancer (MGC) in Japan, but the relationship between dose intensity and antitumor effects remains unclear. Patients and Methods: We retrospectively studied 64 patients who received S-1 plus cisplatin for MGC from January 2006 to December 2010 in two Japanese hospitals. Results: The median relative dose intensity (RDI) of S-1 plus cisplatin was 87% (range, 59.5%-100%). The cut-off value of RDI of S-1 plus cisplatin was identified to be 80% by a receiver operating characteristic analysis of the tumor response. In the RDI<80% (n=19) and the RDI≥80% (n=45) groups, the response rates were 20.0% and 37.5% (p=0.182), the median survival times were 394 and 376 days (p=0.915), and the median progression-free survival (PFS) was 188 and 170 days (p=0.851), respectively. Conclusion: An appropriate RDI reduction may be permitted for patients with MGC in palliative settings.

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer worldwide death (1). Although several novel chemotherapeutic agents, such as S-1, irinotecan, oxaliplatin, and taxanes, have been shown to be effective against metastatic gastric cancer (MGC), the prognosis of patients with MGC remains poor. Fluoropyrimidine plus cisplatin is generally considered as the standard chemotherapy for MGC worldwide and this combination has been used as a control arm in many phase III clinical trials (2, 3). In a phase III clinical trial for MGC conducted in Japan, S-1 plus cisplatin was recognized as the standard chemotherapy (4).

The dose response curve has been shown to be steep and generally linear in highly sensitive types of tumors, such as leukemia, lymphoma, and germ cell tumors, whereas the dose intensity may have little effect in types of relatively insensitive cancer (5). In practice, the doses of anticancer drugs are sometimes reduced for a number of reasons, including adverse events, basal disease and age. However, the appropriate dose reduction to a level that will help retain antitumor activity against MGC remains unclear.

Therefore, the present study assessed the relationship between the dose intensity and the antitumor effects of S-1 plus cisplatin chemotherapy against MGC. The results of the present study may provide novel information regarding the management of MGC by using S-1 plus cisplatin chemotherapy.

Patients and Methods

Patients. In this study, we studied patients with MGC who received S-1 plus cisplatin as first-line chemotherapy from January 2006 to December 2010 at Nagoya City University Hospital and Nagoya Daini Red Cross Hospital through a computerized database maintained at each institution. Patients who discontinued chemotherapy before completion of the first cycle were excluded from the study. Patients with renal dysfunction (creatinine levels of 1.3 mg/dl or more) and other concomitant malignant tumors were also excluded from this study. Patients who were treated by a schedule of S-1 plus cisplatin for which the efficacy has not been proven were also excluded from the study. Data were retrospectively analyzed, and informed consents were provided by all patients.

Chemotherapy schedule. S-1 was orally administered at a dose that was based on the body surface area (BSA) of the patient: BSA <1.25 m², 80 mg; 1.25 m² ≤BSA<1.5 m², 100 mg; and BSA ≥1.5 m², 120 mg. In the S-1 plus cisplatin regimen, S-1 was
orally administered at the above dosage for the first three consecutive weeks of a 5-week cycle, and 60 mg/m² of cisplatin were administered intravenously on day 8 of each cycle (4).

**Definitions.** The relative dose intensity (RDI) is the ratio of the actual dose intensity administered (DI mg/m²/week) and the planned DI, according to the following equation.

\[
RDI (%) = \frac{\text{actual DI}}{\text{planned DI}} \times 100
\]

The RDI was first calculated separately for each component of the chemotherapy regimen (RDI₅₁, and RDIₐ₃isplatin). Finally, an average RDI of S-1 and cisplatin (RDI₃₄) was derived according to the following equation.

\[
RDI₃₄ = \frac{\text{RDI₅₁} + \text{RDIₐ₃isplatin}}{2}
\]

The overall survival time was measured from the first day of chemotherapy until death or the last day of the follow-up period. The progression-free survival (PFS) was defined as the time from the first day of chemotherapy to disease progression, death, or the last day of follow-up. The response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1 (6) using computed tomography (CT) examinations. In all patients, CT evaluations were performed every two to three cycles. Performance status (PS) and toxicities were graded according to the Eastern Cooperative Oncology Group (ECOG) PS and the Common Terminology Criteria for Adverse Events (CTCAE ver. 4.0) (7), respectively.

**Statistics.** The true-positive fraction (TPF) and the false-positive fraction (FPF) for the antitumor responses were calculated for every potential RDI₃₄ cut-off level, and the cut-off level of RDI₃₄ was identified using a receiver operating characteristic (ROC) analysis. Assuming that keeping of a certain RDI can absolutely achieve antitumor response, TPF indicates the ratio of responding patients with RDI more than a certain value and all the responding patients, and FPF does the ratio of non-responding patients with RDI more than a certain value and all the non-responding patients.

Kaplan Meier curves were constructed in order to analyze survival data and PFS, and differences between the two groups were compared with a log-rank test. The other data were analyzed using Fisher’s exact probability test or a Mann Whitney U-test, as appropriate. \(p\)-values less than 0.05 were considered statistically significant. Data analyses were performed using Dr. SPSS II for Windows release 11.0.1J software (SPSS Japan, Tokyo, Japan).

**Results**

**Patients.** The exclusion details are shown in Figure 1. Out of 84 patients with MGC who received S-1 plus cisplatin as first-line chemotherapy, 20 patients were excluded for the following reasons: discontinuation before the completion of their first cycle, not adenocarcinoma, double cancer, renal dysfunction, inappropriate schedule, and due to other reasons. Although low-dose cisplatin is sometimes combined with S-1 for other cancers (8), appropriate dosage and schedule for S-1 plus cisplatin has been already determined in previous clinical trials (4, 9). Thus, 64 patients were evaluated in this study.

The characteristics of the patients included in this study are shown in Table I. The primary tumor was not resected in 49 cases, but resection was in 15 cases. Organs with metastasis most frequently included lymph nodes (40 cases), the number of metastatic sites was 1 in 38 cases, 2 in 16 cases, and ≥3 in 10 cases and there were 55 patients with target lesions and 9 without target lesions. The median RDI for S-1, cisplatin, and S-1 plus cisplatin were 88%, 89%, and 87%, respectively.
Response. Table II shows the response rate of S-1 plus cisplatin chemotherapy. Out of 55 patients with target lesions that could be evaluated according to the RECIST criteria, tumors in 18 patients (32.7%) showed partial response (PR).

As shown in Figure 2, a graph of the ROC analysis was plotted in order to investigate the cut-off levels of RDI\textsubscript{Comb} from 60% to 100% at 5% intervals. The TPF and FPF for tumor responses that were more than PR were 83.3% and 67.6%, respectively, in the setting of a RDI\textsubscript{Comb} cut-off level of 80%, which showed maximum differences between the TPF and FPF values. Hence, RDI\textsubscript{Comb} of 80% was determined as the cut-off value by the ROC analysis for tumor response, and patients were categorized into two groups on this basis: RDI\textsubscript{Comb} <80% and RDI\textsubscript{Comb} ≥80%. As a result, 19 patients were included in the RDI\textsubscript{Comb} <80% group, and 45 patients were included in the RDI\textsubscript{Comb} ≥80% group in this study.

The median RDI\textsubscript{Comb} were 72.5% (range, 59.5%-79.5%) and 91.5% (range, 80%-100%) in the RDI\textsubscript{Comb} <80% and ≥80% group, respectively. Fifteen patients out of the 40 exhibited PR in the RDI\textsubscript{Comb} ≥80% group, while three patients out of the 15 had PR in the <80% group. Although no significant differences were found, the response rate had a tendency to be higher in the RDI\textsubscript{Comb} ≥80% group than in the other group ($p=0.182$, 37.5% vs. 20.0%).

Overall survival. The overall survival times are shown in Figure 3. The median survival time (MST) for the overall population was 394 days [95% confidence interval (CI)=359-429 days; Figure 3a]. The MST was 394 days (95% CI=358-430 days) in the RDI\textsubscript{Comb} <80% group and 376 days (95% CI=319-433 days) in the ≥80% group (Figure 3b). No significant differences were noted for the overall survival between the two groups.

The median follow-up period was 313 days in the RDI\textsubscript{Comb} <80% group and 335 days in the ≥80% group, while no significant differences were found between the two groups ($p=0.808$).

Progression-free survival. The PFS is presented in Figure 4. The median PFS for the overall population was 171 days (95% CI=151-191 days; Figure 4a). The median PFS was 188 days (95% CI=150-226 days) in the RDI\textsubscript{Comb} <80% group and 170 days (95% CI=141-199 days) in the ≥80% group (Figure 4b). No significant differences were noted for the PFS between the two groups.

Adverse events. Adverse events that were greater than grade 3 are shown in Table III. Adverse events that were greater than grade 3 that occurred with a frequency ≥5% in both the RDI\textsubscript{Comb} <80% and ≥80% group were neutropenia (21.0% and 15.6%), anemia (10.5% and 15.6%), nausea (5.3% and 8.9%), and anorexia (15.8% and 8.9%). One patient developed acute coronary syndrome of grade 3, and one patient exhibited hearing impairment of grade 3 in the RDI\textsubscript{Comb} ≥80% group.

Discussion

In clinical trials for cancer, the administration schedule and the dose reductions are strictly controlled by the protocol, but appropriate dose delays and dose reductions are sometimes required, depending upon the conditions of the patients in the practical setting. Chemotherapy for MGC has been recently developed, and the effects of dose delays or reductions of chemotherapy for MGC on tumor response, disease progression and survival prognosis have not been investigated. We analyzed the impact of RDI of an S-1 plus cisplatin regimen, which is one of the standard chemotherapy treatments for MGC. The present study suggests that strict
retention of the RDI may not be important for chemotherapy for MGC. To the best of our knowledge, this study represents the first systemic analysis of the RDI of a standard chemotherapy for MGC.

The median RDI of S-1 plus cisplatin was 87% in the present study. RDI was 93.3% for S-1 plus cisplatin and 98.0% for S-1 monotherapy in the SPIRITS trial (4), whereas it was 88.9% for S-1 monotherapy and 88.1% for S-1 plus irinotecan in the GC0301/TOP-002 study (10). Despite the practical setting, the RDI of S-1 plus cisplatin found in our study was similar to the one observed in a previous phase III study for gastric cancer. Furthermore, an MST of 13.0 months and a median PFS of 6.0 months were reported in a previous phase III trial (4) and the findings in the present study were consistent with previous data (MST: 394 days, PFS: 171 days). These results suggest that the data in our study were reliable.

No data on RDI exist for S-1 plus cisplatin chemotherapy, but an RDI of 80% is generally considered acceptable (11). In fact, the cut-off value of RDI for tumor response in this study was 80%.

Although no significant differences were found in this study, probably because of the small sample size, the response rate showed a tendency to be higher in the RDIComb ≥80% group than in the <80% group in our study. However, the survival and the PFS were similar between the two groups. In the current study, chemotherapy might be well-controlled by dose reductions depending on the patient’s condition because no significant differences were noted between the two groups for side effects. An appropriate dose reduction may be permitted in chemotherapy for MGC, particularly because the roles of chemotherapy are the prolongation of life and the palliation of some symptoms and not the cure. The meaning of RDI is controversial in chemotherapy for many types of incurable solid cancer. A retrospective analysis of non-small cell lung cancer demonstrated no significant relationship between survival and RDI (12). Patients with epithelial ovarian cancer had reduced PFS with RDI <70% (13). In metastatic breast cancer, maintaining the RDI at levels of 85% or more, improved the overall survival, but this did not have an influence on disease progression and the response rate (14). Our study suggests that maintaining the RDI at levels of 80% or more may be crucial for tumor response, but the RDI for gastric cancer chemotherapy did not have a big influence on disease progression and survival time.

For relative response, PFS, and overall survival in MGC, S-1 plus cisplatin was superior to S-1 monotherapy, where the same dose of S-1 was administered for four weeks of a 6-week cycle (4). Converting the schedule of S-1 monotherapy into that of S-1 plus cisplatin, the RDIComb is calculated as 55.6% for S-1 monotherapy because the RDI of S-1 is 111%, and the RDI of cisplatin is 0%. This suggests that attaining an RDI of 55.6% or more is necessary, at least for S-1 plus cisplatin. No significant differences in response rate, PFS, and overall survival are shown in the present study because the median RDIComb was high at 72.5%, even in the RDI <80% group.

In contrast, multiple reports have demonstrated a correlation between the RDI and the survival prognosis, and that maintaining RDI is important for better outcomes in
curable malignancies, such as malignant lymphoma (15-17). Moreover, it has been reported that an RDI of 85% or more, improved the relapse-free survival and the overall survival in an adjuvant setting of early breast cancer (18). Even for incurable cancer, it is very important to obtain tumor shrinkage by chemotherapy in neoadjuvant therapy settings and critical situations. Our data demonstrate that maintaining the RDI is crucial for advanced gastric cancer in neoadjuvant settings and in critical situations that need a higher response. Triplet combination chemotherapy with paclitaxel, cisplatin and S-1 with high antitumor activity (19) may be also effective for these settings of MGC.

Figure 3. Overall survival. a: Survival curve for the overall population. B: Survival curve according to RDI for S-1 plus cisplatin (RDI_{comb}). MST: Median survival time; 95% CI: 95% confidence interval.

Figure 4. Progression-free survival. a: For the overall population, b: according to RDI for S-1 plus cisplatin (RDI_{comb}). mPFS: Median progression-free survival; 95% CI: 95% confidence interval.
The current study has potential limitations since it was a retrospective study using a small sample size. In the future, we hope to conduct an analysis of RDI and its antitumor effects in a large, prospective study for MGC.

In conclusion, maintaining the RDI at levels of 80% or more may be crucial in order to produce antitumor effects in chemotherapy of S-1 plus cisplatin against MGC. However, an appropriate RDI reduction could be permitted in the palliative settings for MGC.

References


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