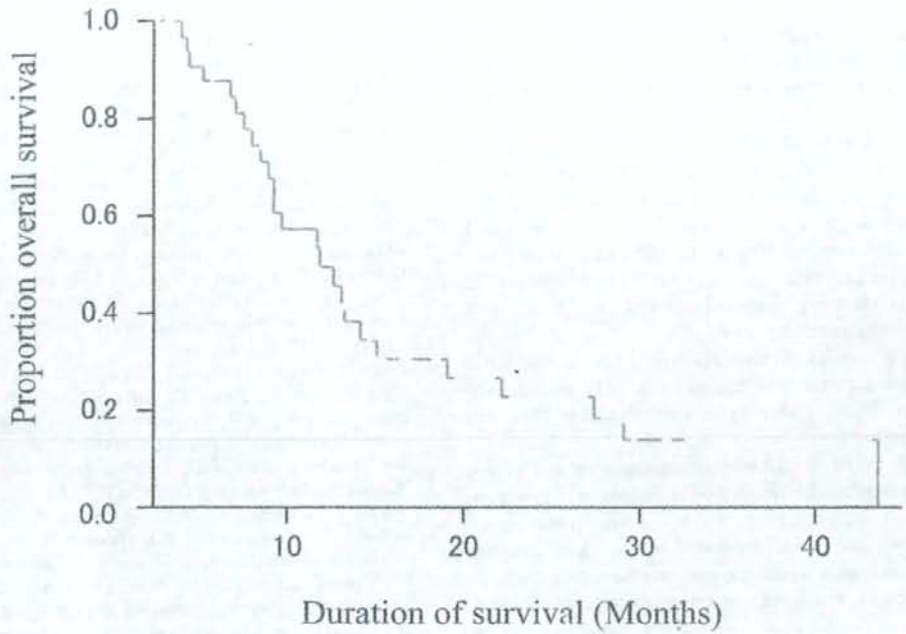

Figure 1. *Overall survival of patients following S-1/low-dose P therapy.*

followed by a one week drug-free period, and cisplatin is administered on day 1 and day 8 at a dose level of 20 mg/m^2; they reported a response rate of 61.1% with this regimen. Iwase *et al.*, in an attempt to reduce nausea and vomiting caused by cisplatin, also developed a regimen including 24-hour continuous infusion of this agent, but reported a response rate of 50% with a 10% incidence of grade 3 or greater nausea and vomiting (18).

The combined regimen of S-1 daily and low-dose twice-weekly cisplatin in the present study enabled highly effective and safe therapy that is suitable for use in outpatient clinics. Although phase I and II clinical studies of S-1 combined with taxane (19) or CPT-11 (20) have also been conducted, their results were no better than those yielded by S-1 plus cisplatin therapy. The favorable results of S-1 combined with cisplatin seem to be explained by the synergistic activity between 5-FU and cisplatin based on the theory of biochemical modulation (21, 22). The antitumor activity of 5-FU has been reported to be reinforced particularly markedly when combined with frequent low-dose cisplatin (23). This may explain the fact that the response rate in the previously treated cases was comparable to that in the cases that had never been treated. Furthermore, based on the results of a study comparing the pharmacokinetics of 5-FU in S-1 therapy (80 mg/m^2/day) and continuous intravenous infusion of 5-FU (250 mg/m^2/day) it was reported that the $AUC_{0\text{-}10h}$ for oral S-1 was 1.9 times higher than that of 5-FU administered by intravenous infusion (9). This may explain why S-1/low-dose P therapy had much greater antitumor activity than low-dose FP therapy. This greater antitumor activity may have contributed to the present high response rate in the previously treated cases.

Koizumi *et al.* (16) reported finding that grade 3 or greater adverse events following S-1 combined with high-dose cisplatin therapy consisted of hematological adverse reactions in 16.0% of all patients, anorexia in 26.0% and nausea in 16.0%. Comparison of the results reported by Koizumi *et al.* and the results of the present study shows that the toxicological profile of high-dose cisplatin therapy seems to differ slightly from that of S-1/low-dose P therapy because gastrointestinal toxicities were observed less frequently in our study.

The problems associated with outpatient chemotherapy with oral anticancer agents include variable patient compliance with the dosing instructions, the development of adverse events, and frequent difficulty in completing therapy as scheduled. Outpatient drug therapy was possible in 31 (96.9%) of the 32 patients in the present study and it was possible to complete therapy without the development of any adverse events in all but one patient. In this last

patient, the serum creatinine level increased to 1.4 mg/dl, suggesting mild compromise of renal function immediately prior to the start of the 5th cycle of treatment, and was accompanied by grade 4 thrombocytopenia and grade 3 renal and hepatic dysfunction. Combined S-1 and cisplatin therapy seems to be associated with a rise in the blood 5-FU level and an elevated risk of 5-FU toxicity for the following reasons: (i) cisplatin is a nephrotoxic drug; (ii) CDHP, a component of S-1, is excreted by the kidneys; and (iii) the serum concentration of CDHP (a DPD inhibitor) may increase. In this light, greater caution should be exercised when using combined S-1 and cisplatin therapy in renally compromised patients.

Reflecting recent phase III results in unresectable advanced and recurrent gastric cancer (24, 25), the standard regimen in Japan is shifting toward combined S-1 and cisplatin therapy.

In the S-1 and cisplatin regimen used in this study, cisplatin was administered in divided doses at a low dose level. When administered in this way, hydration is unnecessary, and even if renal function does become compromised during treatment, it is easy to reduce the dose level of cisplatin or discontinue it altogether. In this respect, this regimen is more favorable from the viewpoint of preventing adverse events than regimens involving the administration of high dose levels of cisplatin.

Conclusion

In conclusion, based on the high response rate, possibility of administration on an outpatient basis and the high quality of life of the patients, combined S-1/low-dose P therapy is considered to offer promise for the treatment of advanced and recurrent gastric cancer. The therapy deserves further evaluation, including its usefulness as second-line therapy for gastric cancer patients.

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