RESEARCH ARTICLE

Clinical Characteristics Associated with Long-term Survival in Metastatic Gastric Cancer after Systemic Chemotherapy

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Abstract

Background: Systemic chemotherapy for patients with metastatic gastric cancer (MGC) is generally palliative, although some patients experience long-term survival after treatment. Thus, we identified clinical characteristics that are associated with long-term survival of patients with MGC after palliative chemotherapy. Materials and Methods: We retrospectively reviewed 514 MGC patients who received systemic chemotherapy at our institution from 2001 to 2008. To identify clinical predictors of survival beyond 2 years, multivariate logistic regression analyses were performed, and 5-year survival rates were estimated among MGC patients following chemotherapy. Results: Among 514 patients, 96 (19%) and 16 (3%) survived beyond 2 and 5 years, respectively, and performance status of 0 or 1 (odds ratio [OR]=3.39; p=0.01), previous gastrectomy (OR=1.86; p=0.01), single metastatic site (OR=1.80; p=0.03), and normal alkaline phosphatase levels (OR=2.81; p<0.01) were identified as independent predictors of long-term survival. Of the 16 5-year survivors, six were alive at the end of the study and showed no evidence of disease despite cessation of chemotherapy. Conclusions: The present data demonstrate distinct clinical characteristics that are associated with long-term survival of MGC patients, and indicated that palliative chemotherapy can be curative in highly selected patients.

Keywords: Advanced gastric cancer - chemotherapy - predictive factor - survival

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Introduction

Although the incidence of gastric cancer has recently declined, it remains the second leading global cause of death (Jemal et al., 2011). Similarly, gastric cancer mortality rates are decreasing in Japan, but remain the second most common cause of death, with 48,632 confirmed deaths in 2013 (Cancer Information Service, National Cancer Center, Japan, 2013). The standard of care for metastatic gastric cancer (MGC) is systemic chemotherapy, which improves survival and quality of life compared with best supportive care (Pyrhonen et al., 1995; Glimelius et al., 1997). The combination of fluoropyrimidines and platinum with or without docetaxel or epirubicin is the standard treatment option, and produces a median survival time of 8.6-13.0 months (Van Cutsem et al., 2006; Cunningham et al., 2008; Koizumi et al., 2008). However, systemic chemotherapy for MGC is generally palliative and survival beyond 2 years is rarely observed.

Several case reports and small case series have documented long-term survival (LTS) in selected patients with MGC (Saitoh et al., 2000; Tetzlaff et al., 2006; Hosokawa et al., 2007; Yamamoto et al., 2012; Kadowaki et al., 2014; Schildberg et al., 2014), and recent large phase III trials report 2-year survival rates of 9%-24% (Van Cutsem et al., 2006; Koizumi et al., 2008; Boku et al., 2009). In four phase II and 1 phase III trials for MGC conducted by the Japan Clinical Oncology Group (JCOG) from 1985 to 1997 (Yoshida et al., 2004), 39 (8%) and 11 (2%) of 497 patients survived beyond 2 and 5 years, respectively. However, these trials were conducted before the introduction of recent cytotoxic agents such as irinotecan and taxanes, and did not evaluate predictive factors for LTS. Furthermore, most recent trials of modern regimens failed to document long-term outcomes. Therefore, data showing clinical predictors of LTS and the possibility of cure for MGC patients after chemotherapy are limited. The aim of the present study was to clarify clinical characteristics that are predictive of LTS among MGC patients for whom irinotecan and taxanes treatments are available, and to estimate 5-year survival rates. The present data will be informative for evaluating changes in long-term outcomes of treatments with new agents including targeted drugs.

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Materials and Methods

Patients

Between January 2001 and July 2008, 518 consecutive patients with MGC were treated with systemic chemotherapy at the Aichi Cancer Center Hospital. Inclusion criteria were as follows: at least 5-years of follow-up, histological confirmation of adenocarcinoma at the time of initial diagnosis, and demonstrated noncurative disease in imaging or histological examinations. Data were collected for age, gender, tumor differentiated type, the Eastern Cooperative Oncology Group (ECOG) performance status (PS), history of gastrectomy, metastatic sites, number of metastatic sites, adjuvant chemotherapy, serum alkaline phosphatase (ALP) levels at baseline, serum carcinoembryonic antigen (CEA) levels at baseline, first-line chemotherapy regimens, progression-free survival (PFS) at first-line therapy, tumor response after first-line therapy, and the use of second- or third-line chemotherapy. Responses of metastatic lesions to chemotherapy were assessed according to the Revised Evaluation Criteria in Solid Tumor (RECIST) version 1.0 (Therasse et al., 2000). We defined LTS as survival beyond 2 years after the initiation of systemic chemotherapy. The cutoff date for analysis was March 31, 2014. Approval was obtained from the Ethics Committee of the Aichi Cancer Center Hospital.

Statistical analysis

The aim of this study was to identify pretreatment characteristics that are predictive of survival beyond 2 years, and to estimate the 5-year survival rate among MGC patients treated with palliative chemotherapy. All clinical factors were converted into dichotomous variables including (1) age, <60 *vs* ≥60 years; (2) male *vs* female; (3) well or moderately differentiated *vs* poorly differentiated cancers; (4) PS of 0 or 1 *vs* PS ≥2; (5) a history of gastrectomy, yes *vs* no; (6) involved metastatic sites, yes *vs* no; (7) number of metastatic sites, 1 *vs* 2 or more; (8) adjuvant chemotherapy, yes *vs* no; (9) baseline ALP within upper limit normal (ULN) *vs* baseline ALP ≥ ULN, (10) baseline CEA, <ULN *vs* ≥ULN; and (11) treatment, fluoropyrimidines plus platinum-based therapy *vs* other regimens. Univariate analyses of categorical variables were performed using chi-square or Fisher's exact probability tests, as appropriate. Because all the patients were followed until their demise or for at least 5 years, this study was primarily descriptive in nature. Therefore, multivariate logistic regression analyses using forward selection methods were performed to identify clinical variables that are associated with LTS, and to calculate corresponding odds ratio (OR). Differences with p values of <0.20 in univariate analyses were included as covariates in multivariate analyses. PFS was recorded from the date of initial chemotherapy until the time of disease progression, death, or last contact. Overall survival (OS) was recorded from the date of the initial chemotherapy until death from any cause or last contact. PFS and OS curves were estimated using the Kaplan-Meier product limit method and were compared using the log-rank test. All data analyses were conducted using Dr. SPSS II software (SPSS Japan Inc., Tokyo, Japan), and a 2-sided p value of <0.05 was considered statistically significant.

Results

Patient characteristics and chemotherapy

Of the 518 patients treated in this period, 514 (99%) were included in analyses and four were lost to follow-up prior to 5 years and were excluded from the analysis. First line chemotherapy regimens included fluoropyrimidine monotherapy in 269 patients (52%), fluoropyrimidine plus platinum-based therapy in 137 patients (27%), taxane monotherapy in 35 patients (7%), 5-fluorouracil plus methotrexate in 33 patients (6%), irinotecan plus cisplatin in 26 patients (5%), and other regimens in 14 patients (3%).

Patient characteristics and treatment outcomes are listed in Table 1. The median age was 62 years (range, 29-84). Among the 514 patients analyzed, 372 (72%) had poorly differentiated cancers and 78 (15%) had PS of two or more. Of the 246 (48%) patients who received resection of primary tumors before the start of chemotherapy, 57 (11%) received gastrectomy and had residual disease and 189 (37%) had recurrent disease after curative gastrectomy. The number of metastatic sites was only one in 273 patients (53%) and two or more in 241 (47%) patients. Abnormally high ALP and CEA levels were detected in 141 (27%) and 208 (41%) patients, respectively. A total of 376 (73%) and 192 (37%) patients received second- and third-line chemotherapy.

Survival outcomes

Median follow-up for living patients was 91 months (range, 71-119 months). Median OS was 11.7 months [95% confidence interval (CI), 10.7-12.7 months], and 1-, 2-, 3-, and 5-year survival rates were 49%, 19%, 8%, and 3%, respectively (Figure 1). A total of 96 (19%) and 16 (3%) patients survived for more than 2 and 5 years, respectively. Among 514 patients, 505 died of MGC or from unknown causes, six remained alive with no evidence of disease, and three were alive with disease at the cut-off date.

Pretreatment factors associated with LTS

As shown in Table 1, pretreatment factors that were predictive of LTS in univariate analyses included well or moderately differentiated cancer type (p=0.05), PS of 0 or 1 (p=0.003), prior gastrectomy (p<0.001), single metastatic sites (p<0.001), and normal ALP levels (p<0.001). The type of treatment was not a significant factor. In multivariate logistic regression analyses, a PS of 0 or 1 [odds ratio (OR)=3.47; p=0.01], history of gastrectomy (OR=1.85; p=0.01), single metastatic sites (OR=1.72; p=0.04), and normal ALP levels (OR=2.41; p<0.001) were significantly associated with LTS (Table 2). Of the 490 patients in which ALP levels were determined, patients with 0 (n=16), 1 (n=74), 2 (n=131), 3 (n=164), and 4 positive predictive factors (n=105) had 2-year survival rates of 0%, 5%, 12%, 20%, and 32%, respectively. Among the 342 patients with target lesions, 109 achieved

Table 1. Patient Characteristics According to LTS and non-LTS

Characteristics	Total n=514 (%)	Non-LTSa n=418 (%)	LTSa n=96 (%)	p
Age (years)				0.76
Median (range)	62.0 (29-84)	62.0 (29-84)	63.0 (29-83)	
<60	216 (42)	177 (42)	39 (41)	
≥60	299 (58)	241 (58)	57 (59)	
Gender				0.15
Male	337 (66)	268 (64)	69 (72)	
Female	177 (34)	150 (36)	27 (28)	
Differentiation				0.05
Well/moderate	140 (27)	106 (25)	34 (35)	
Poor	372 (72)	310 (74)	62 (65)	
Unknown	2 (0.4)	2 (0.5)	0 (0)	
Performance status				0.003
0-1	436 (85)	345 (82)	91 (95)	
≥2	78 (15)	73 (18)	5 (5)	
Target lesions				0.06
No	172 (33)	132 (32)	40 (42)	
Yes	342 (67)	286 (68)	56 (58)	
Previous gastrectomy				<0.001
No	268 (52)	234 (56)	34 (35)	
Yes	246 (48)	184 (44)	62 (65)	
Metastatic site				
Peritoneum	310 (60)	258 (62)	52 (54)	0.17
Lymph node	276 (54)	231 (55)	45 (47)	0.14
Liver	141 (27)	119 (29)	22 (23)	0.27
Bone	24 (5)	23 (6)	1 (1)	0.06
Number of metastatic sites				<0.001
1	273 (53)	205 (49)	68 (71)	
≥2	241 (47)	213 (51)	28 (29)	
Adjuvant chemotherapy				0.2
No	444 (86)	365 (87)	79 (82)	
Yes	70 (14)	53 (13)	17 (18)	
Baseline ALP[b]				<0.001
<ULN[c]	349 (68)	273 (65)	76 (79)	
≥UNL[c]	141 (27)	130 (31)	11 (11)	
Unknown	24 (5)	15 (4)	9 (9)	
Baseline CEA[d]				0.13
<ULN[c]	290 (56)	230 (55)	60 (63)	
≥UNL[c]	208 (41)	176 (42)	32 (33)	
Unknown	16 (3)	12 (3)	4 (4)	
First-line therapy				0.18
FU+platinum-based	137 (27)	107 (26)	31 (32)	
Others	377 (73)	311 (74)	65 (68)	
First PFS[e] (months)				<0.001
Median (range)	4.1 (0-110)	3.6 (0-19.4)	10.8 (0.5-110)	
Response†				<0.001
Responder (CRf+PR[g])	109 (32)	73 (26)	36 (64)	
Nonresponder	233 (68)	213 (74)	20 (36)	
Second-line therapy				<0.001
No	138 (27)	128 (31)	10 (10)	
Yes	376 (73)	290 (69)	86 (90)	
Third-line therapy				<0.001
No	322 (63)	289 (69)	33 (34)	
Yes	192 (37)	129 (31)	63 (66)	
Taxanes dosing history				0.001
No	174 (34)	156 (37)	18 (19)	
Yes	340 (66)	262 (63)	78 (81)	
Irinotecan dosing history				<0.001
No	333 (65)	291 (70)	42 (44)	
Yes	181 (35)	127 (30)	54 (56)	

†Included patients with target lesions; LTS[a], long-term survivors; ALP[b], alkaline phosphatase; ULN[c], upper limit of normal; CEA[d], carcinoembryonic antigen; PFS[e], progression free survival; CR[f], complete response; PR[g], partial response

complete responses (CR) or partial responses (PR), and the response rate was 32%. The response rate in the LTS group (64%, 36 of 56) was higher than that in the non-LTS group (26%, 73 of 286; p<0.001). PFS at first-line treatment was significantly longer in the LTS group compared with that in the non-LTS group (median, 10.8 *vs* 3.6 months; log-rank p<0.001). The LTS group received taxanes and irinotecan and second- and third-line therapy more frequently than the non-LTS group.

Long-term survivors beyond 5 years

Patient characteristics of the 16 5-year survivors are shown in Table 3. Among these patients, survival times ranged from 60 to 119 months. The majority of patients had PS of 0 or 1 (94%, 15 of 16), received surgical resections of primary tumors (94%, 15 of 16), had normal ALP levels (100%, 12 of 12), and only one involved site (88%, 14 of 16). However, 10 patients received curative gastrectomy and five received noncurative gastrectomy before initial chemotherapy. Metastatic sites included the peritoneum alone in eight patients and abdominal lymph nodes alone in six. Fluoropyrimidine-based therapies were the first-line therapy for most patients, and comprised oral S-1 in nine patients and fluoropyrimidine plus platinum combination therapy in five. Despite cessation of treatment, six patients survived with no evidence of disease recurrence until the last follow-up. Among these, one patient (patients 6) achieved a CR after first-line therapy, although recurrence of lung metastasis was observed and curative resection was performed. Three patients (patients seven, 10, and 12) with residual disease

Table 2. Multivariate Analysis of Clinical Factors Associated with LTS

Characteristics	Odds ratio	95%CI	p
Performance status			
0-1 *vs* ≥2	3.47	1.34-9.02	0.01
Gastrectomy			
Yes *vs* No	1.85	1.14-3.02	0.01
Number of metastatic sites			
1 *vs* ≥2	1.72	1.03-2.88	0.04
Baseline alkaline phosphatase			
<ULN[a] *vs* ≥UNL[a]	2.41	1.46-3.96	<0.001

ULN[a], upper limit of normal

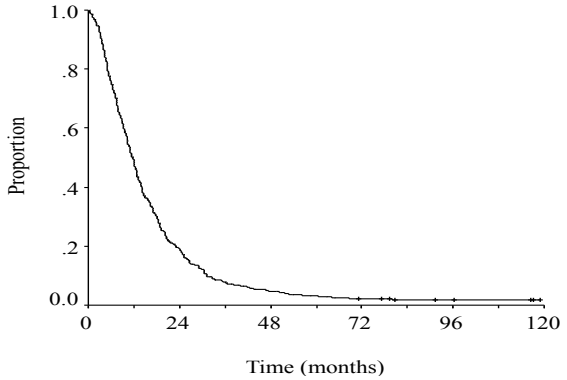

Figure 1. Kaplan-Meier Survival Curves of Overall Survival (OS). The median OS was 11.7 months (95% confidence interval, 10.7-12.7 months), and 2-, 3-, and 5-year survival rates were 19%, 8%, and 3%, respectively

Table 3. Clinical Characteristics of 5-year Survivors

No.	Age	Sex	Performance status	Histology	Previous gastrectomy	Metastatic sites	ALP[a]	Regimen	Response	Survival (months)	Status
1	63	Male	1	Poorly-differentiated	No	Peritoneum	-	SP[c]	IR/SD[g]	60	Dead
2	59	Male	1	Poorly-differentiated	Curative	A-LN[b]	Normal	S-1	SD	63	Dead
3	51	Male	0	Poorly-differentiated	Palliative	Peritoneum, A-LN[b]	Normal	XP[d]	CR	64	Dead
4	48	Female	0	Poorly-differentiated	Palliative	Peritoneum	Normal	S-1	IR/SD[g]	65	Dead
5	54	Female	1	Poorly-differentiated	Curative	Peritoneum	-	Paclitaxel	IR/SD[g]	69	Dead
6	71	Male	0	Differentiated	Curative	A-LN[b], Lung	Normal	XP[d]	CR	71	Alive
7	65	Female	0	Poorly-differentiated	Palliative	Peritoneum	Normal	Paclitaxel	IR/SD[g]	77	Alive
8	63	Male	0	Poorly-differentiated	Palliative	A-LN[b]	Normal	SOX[e]	CR	79	Alive
9	58	Male	1	Differentiated	Curative	Peritoneum	Normal	S-1	SD	80	Dead
10	56	Male	0	Differentiated	Curative	A-LN[b]	-	S-1	SD	81	Dead
11	55	Female	0	Poorly-differentiated	Palliative	Peritoneum	Normal	SP[c]	IR/SD[g]	81	Alive
12	66	Male	1	Differentiated	Curative	A-LN[b]	Normal	S-1	NE	91	Alive
13	59	Male	1	Poorly-differentiated	Curative	Peritoneum	Normal	FL[f]	IR/SD[g]	96	Alive
14	67	Male	0	Poorly-differentiated	Curative	A-LN[b]	-	5-FU	CR	117	Alive
15	32	Male	2	Poorly-differentiated	Curative	A-LN[b]	Normal	S-1	PR	117	Alive
16	64	Male	0	Poorly-differentiated	Curative	Peritoneum	Normal	S-1	IR/SD[g]	119	Alive

ALP[a], alkaline phosphatase; A-LN[b], abdominal lymph node; SP[c], S-1 plus cisplatin; XP[d], capecitabine plus cisplatin; SOX[e], S-1 plus oxaliplatin; FL[f], 5-fluorouracil plus leucovorin; IR/SD[g], incomplete response/stable disease

continued to receive systemic chemotherapy, and seven patients died of disease progression.

Discussion

To the best of our knowledge, this is the first study to evaluate LTS among patients with MGC for whom newer cytotoxic agents such as taxanes and irinotecan were available. The present study primarily focused on LTS among unselected patients and mortality data were rigorously obtained. MGC patients who achieved LTS had distinct clinical characteristics, including PS of 0 or 1, only one metastatic site, previous gastrectomy, and normal ALP levels, and a minority of patients survived beyond 5 years. Among the 514 patients analyzed, six (1.2%) were free of disease after cessation of chemotherapy, supporting curative chemotherapeutic intentions in highly selected patients.

Most previous studies fail to describe long-term outcomes or to identify factors that are predictive of LTS in MGC patients treated with palliative chemotherapy. A retrospective study of data from JCOG trials that were performed prior to marketing of taxane and irinotecan reported 2- and 5-year survival rates of 8% (39 of 497) and 2% (11 of 497) among MGC patients, respectively (Yoshida et al., 2004). This study showed that better PS, a small number of metastatic sites, and macroscopically nonscirrhous tumors are favorable prognostic factors for OS. However, in contrast with the present study, predictors of LTS were not identified. Recently, 2-year survival rates were reported from the S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer (SPIRITS trial) (Koizumi et al., 2008), and were 24% for the S-1 plus cisplatin arm and 15% for the S-1 arm. In the JCOG9912 trial (Boku et al., 2009), 2-year survival rates were 14% in the continuous fluorouracil infusion arm, 18% in the irinotecan plus cisplatin arm, and 21% in the S-1 arm. Moreover, in a phase III trial (V325) comparing docetaxel, cisplatin, and 5-fluorouracil (DCF) with cisplatin and 5-fluorouracil (CF) (Van Cutsem et al., 2006), 2-year survival rates were 18% for DCF and 9% for CF. The 2-year survival rate (19%) in the present study was higher than that observed in the early JCOG trials (8%) and was comparable with data from prospective studies of modern regimens (Van Cutsem et al., 2006; Koizumi et al., 2008; Boku et al., 2009). In the SPIRITS and JCOG9912 trials, 74% to 83% of patients received second-line chemotherapy. Similarly, in the present study 73% of patients received second-line chemotherapy. Moreover, long-term survivors received multiple-line treatments with newer cytotoxic agents, including taxanes and irinotecan, more frequently than the other patients. In agreement with previous studies (Thuss-Patience et al., 2011; Kang et al., 2012; Ford et al., 2014), the present improvement in LTS may reflect the prevalence of second- and third-line chemotherapy with taxanes and irinotecan. Although recent trials of modern regimens suggest that improved overall survival with chemotherapy can lead to LTS, the present LTS data were not associated with types of chemotherapeutic regimens. However, few patients received fluoropyrimidine plus platinum-based regimens, and further investigations are warranted to evaluate the impact of first-line therapy on LTS.

In addition, previous retrospective studies (Hosokawa et al., 2007; Lee et al., 2007a; Lee et al., 2007c; Koo et al., 2011; Inal et al., 2012; Kadowaki et al., 2014) and a large prospective randomized trial (JCOG9912) (Takahari et al., 2014) show that better PS, single metastatic sites, previous gastrectomy, and normal ALP levels are associated with improved OS; Takahari et al. (Takahari et al., 2014) constructed the JCOG index using these prognostic factors. With the exception of the cut-off value for PS, the present LTS predictive factors were identical to the prognostic factors chosen for the JCOG index. Small numbers of metastatic sites and primary tumor resection successes rates are expected to reflect lower tumor volumes in patients with MGC. Patients with MGC who underwent gastrectomy but had residual disease often had minimal disease, including intraoperative peritoneal disseminations and other metastatic lesions. Recurrent

disease is often diagnosed with low tumor burdens during early follow-up and surveillance after curative surgery. Several previous studies report elevated ALP levels as a prognostic factor that generally reflects the presence of liver disease, bone metastases, and malignant disease (Lee et al., 2007a; Koo et al., 2011; Kadowaki et al., 2014; Takahari et al., 2014). In the present study, high ALP levels were associated with poor PS, liver metastasis, bone metastasis, target lesions, and multiple metastatic sites (data not shown). Thus, this serum marker may reflect increased tumor aggressiveness and burden.

In the present study, the observed 5-year survival rate (3%, 16 of 514) was equivalent to that (2%, 11 of 497) reported in early JCOG studies. These data do not indicate whether this extraordinary survival followed chemotherapy or reflected the underlying indolent nature of cancers in selected patients. However, most patients experienced durable responses or disease stabilization after first-line treatment, and six had no evidence of disease after cessation of therapy, suggesting that chemotherapy contributed to the present 5-year survival rate. Although specific sites of metastasis were not related to LTS, eight (50%) and six (38%) of the 16 5-year survivors had incurable peritoneal and abdominal lymph node metastasis, respectively. Similarly, Hosokawa et al. (Hosokawa et al., 2007) reported that 22 patients with only peritoneal metastasis survived for a median of 24 months, and 16 of these were diagnosed during laparotomy or laparoscopy; this suggests earlier detection of peritoneal disease. Furthermore, they found that six of nine 3-year survivors had only peritoneal disease. In the present study, most patients with peritoneal metastasis were diagnosed during open surgery, computed tomography imaging, or enema examinations, and had low tumor volumes. In a retrospective study from Korea (Park et al., 2011), patients with only para-aortic lymph node metastases had a higher response rates, longer times to progression, and improved OS compared with those with the other metastatic patterns. In the present cases, abdominal lymph node metastases were not histologically confirmed, although the majority of patients had evidence of tumor shrinkage and tumor marker decline after chemotherapy. Thus, patients with only lower peritoneal disease volumes or abdominal lymph node metastases may have improved chances of LTS following chemotherapy.

The present study was limited to retrospective analyses at a single center. Although consecutive patients were included in the study, intrinsic biases may have arisen from clinical practices and the patient population. Therefore, further investigations are required in larger cohorts of patients. Moreover, metastatic sites were not confirmed using pathological analyses in most cases. Thus, over classification of imaging abnormalities as metastatic disease may have occurred, although most patients had clinically convincing disease and died of disease progression. Finally, our analysis included patients for whom targeted agents such as trastuzumab and ramucirumab were not available as standard treatment options. Thus, future analyses of these agents may show improved long-term outcomes in MGC patients.

In conclusion, we assessed clinical characteristics of MGC patients who achieved LTS after systemic chemotherapy, and identified prognostic factors that indicate curative potential in highly selected MGC patients. These data may facilitate subsequent studies of changes in survival outcomes with new therapies such as molecular targeted agent.

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