Gemcitabine and mitomycin C in advanced pancreatic cancer: a single-institution experience

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Despite chemotherapy, median survival of patients with advanced pancreatic cancer (APC) remains poor. Gemcitabine (GEM) remains standard treatment. Numerous phase II studies have suggested that combination therapies may improve response rates. Mitomycin C (MMC) when used as a single agent may have response rates comparable to other cytotoxic drugs. Therefore, MMC could be an interesting drug to be combined with GEM. This study aimed to assess the feasibility, toxicity and efficacy of GEM combined with MMC in patients with APC. Between April 1997 and January 2002, 55 consecutive patients were treated with GEM 800 mg/m^2 i.v., days 1, 8 and 15, and MMC 8 mg/m^2 i.v., day 1, every 4 weeks in an outpatient setting. Patient characteristics included: M/F 34/21, median age of 58 years, ECOG PS 0–2. A median of 3 cycles was administered. The most frequent toxicity was thrombocytopenia grade III/IV in 54% of patients. Ten patients experienced dyspnea ± X-ray-proven pneumonitis ($n = 2$). One of these patients developed a hemolytic uremic syndrome after the sixth application of MMC. There was one early death as a consequence of a stroke. The objective response rate was 29% (95% confidence interval: 17–43). Eighteen patients had stable disease resulting in an overall tumor growth control of 62%. Time to progression was 4.7 months and median overall survival was 7.25 months. We conclude that, except for thrombocytopenia, the combination of GEM and MMC is well tolerated. These results compare favorably to single-agent chemotherapy with GEM or the combination of 5-fluorouracil plus MMC. Furthermore, this regimen is cost-effective and, since it can be given on an outpatient basis, contributes to the quality of life. *Anti-Cancer Drugs* 15:575–579 © 2004 Lippincott Williams & Wilkins.

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Introduction

Patients with advanced or metastatic pancreatic carcinoma have a dismal prognosis. The median survival ranges from 3 to 6 months. At the time of diagnosis most patients suffer from severe pain, nausea, emesis and weight loss. Chemotherapy is widely used in order to improve both quality of life and survival. Traditionally, 5-fluorouracil (5-FU) has been used since the 1950s. The reported response rates vary widely between 0 and 67%. In contrast to these findings, in more recent trials from the 1990s response rates are below 15%.

5-FU-containing combinations provided objective response rates ranging from 15 to 40% in several phase II studies [1,2]. However, phase III studies failed to demonstrate a survival advantage for the combination regimens when compared to 5-FU alone [3,4].

Gemcitabine (GEM) is a nucleoside analog with structural similarities to cytarabine. Burries *et al.* [5] emphasized gemcitabine's superiority as far as clinical benefit is concerned. Clinical benefit was defined as an improvement in pain, performance status or weight without deterioration in any other respect. In a pivotal trial they randomized 126 patients either to receive GEM or 5-FU. Twenty-four percent of patients randomized to GEM experienced 'clinical benefit' as compared to 5% of patients randomized to 5-FU. There were no confirmed objective responses in either group of patients. At 1 year, 18% of the GEM patients and 2% of the 5-FU patients were alive. Due to the superior 'clinical benefit' and survival for GEM, it was approved by the US Food and Drug Administration for use as first-line therapy in pancreatic cancer and has been considered standard since then. However, many attempts have been made to increase the overall response rate and survival of patients with advanced pancreatic cancer (APC). For this reason, GEM has been combined in the last several years with other cytotoxic agents including 5-FU, cisplatin, docetaxel and irinotecan.

Initial reports of phase II studies of GEM combined with docetaxel or cisplatin have been encouraging [6–9].

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Similarly, combinations of GEM with newer agents like irinotecan, alimta, UFT and capecitabine seem to have a better activity than GEM alone [10–13]. Objective response rates range from 9 to 36% and overall survival ranges from 6.5 to 11 months. Some of these regimen are currently being evaluated in phase III trials.

Previous data have suggested that mitomycin C (MMC) used as a single agent may have a comparable response rate. Carter and Comis [14] reported a 27% response rate of MMC in pancreatic cancer based on results from four small series performed in a total of 44 patients [15–17].

This phase II study was designed to evaluate toxicity and efficacy of GEM combined with MMC in the treatment of APC. Since MMC has to be given only once every 4 weeks and thus did not pose an additional burden on the patient, the combination of MMC and GEM also seemed to be attractive when considering quality of life.

Methods

Eligibility criteria

Patients were enrolled into the study if they had histologically or cytologically proven, surgically unresectable, locally advanced or metastatic adenocarcinoma of the pancreas that was not amenable to radiotherapy and bidimensionally measurable disease according to standard WHO criteria. Furthermore, patients had to meet the following eligibility criteria: age 18–70, adequate bone marrow reserve (platelets >100/nl and leucocytes >3.5/nl), adequate renal (serum creatinine <1.5 mg/dl) and hepatic (total bilirubin <2.0 mg/dl) function, a performance status of 0–2 and a life expectancy of >12 weeks. Patients with brain metastases or those who had been treated for a prior malignancy during the previous 5 years were not eligible. The ethics committee of our institution had approved the protocol. Prior to treatment, written informed consent was obtained from all patients according institutional regulations.

Statistical analysis

The primary endpoint was response. Toxicity, time to progression (TTP) and overall survival were secondary endpoints. The univariate Kaplan–Meier product-limit analysis was computer generated and employed to evaluate time to progression and overall survival. According to the protocol, an interim analysis was performed after inclusion of 16 patients. Under the premise that more than one patient had had an objective response, another 16 patients were to be included. After we had analyzed 32 patients, the patient number was extended to a total of 55.

Treatment plan

GEM was given on days 1, 8 and 15 at a fixed dose of 800 mg/m^2 i.v. over 30 min. MMC was administered on day 1 of each cycle at a fixed dose of 8 mg/m^2 i.v. over 30 min. The cycle was repeated on day 29. A total of at least 6 cycles was planned for each responding or stable patient. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). If multiple toxicities were observed, then the dose administered was based on the most severe toxicity experienced. If leucocytes were >3.5/nl and platelets >100/nl, the full dose was administered. Treatment was delayed if leucocytes were <1/nl or platelets <50/nl.

Response assessment

To be eligible for response patients had to have bidimensionally measurable disease and had to have received at least one treatment cycle, except in case of early clinical disease progression. Response was evaluated every 2 cycles by computed tomography (CT) scans. Following WHO criteria, complete response was defined as disappearance of all detectable disease. Partial response was defined as a 50% or greater decrease in tumor size without the appearance of new disease or increase in any lesion of more than 25%. Stable disease represented no significant change in measurable or assessable malignant disease without appearance of new lesions. This included a less than 50% decrease in tumor size and a less than 25% increase in any tumor site.

Results

Patient characteristics

Between April 1997 and January 2002, 55 consecutive patients were included into this trial, 34 (62%) male and 21 (38%) female with a mean age of 58 years (Table 1). Median Karnofsky performance scale was 90 (range 70–100). Eleven (20%) patients had recurrent disease after radical surgery, two had received prior chemotherapy (2 courses of 5-FU, 3 courses of glufosfamide); 80% of patients had multiple sites of disease that included mainly the primary pancreatic tumor, lymph node disease and liver metastases.

Table 1 Patient characteristics

Characteristic	$N=55$
Phase II	31
Extended	24
Gender	
male	34
female	21
Age (years) [median (range)]	58 (41–76)
Karnofsky PS [median (range)]	90 (70–100)
Stage	
II	1 (2%)
III	10 (18%)
IV	44 (80%)
Sites of disease	
Locally advanced	12
Metastatic disease	43
liver	90%
other	10%

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Table 2 Toxicity per patient and per cycle (maximum grade) evaluated for 197 cycles given to 52 patients

Side-effects	Grade I/II [*n* (%)]		Grade III [*n* (%)]		Grade IV [*n* (%)]	
	Patient	Cycle	Patient	Cycle	Patient	Cycle
Hematological						
leukopenia	28 (54)	108 (55)	13 (25)	14 (7)	–	
thrombocytopenia	13 (25)	61 (31)	13 (25)	35 (25)	15 (29)	22 (11)
anemia	38 (73)	104 (55)	7 (13)	10 (5)	1 (2)	1 (0,5)
Gastrointestinal						
nausea	34 (65)	70 (35)	–	–	–	
diarrhea	11 (21)	13 (6)	–	–	–	
Alopecia	7 (13)	8 (4)	–	–	–	
Weight loss	27 (52)	38 (19)	–	–	–	
Rash	6 (11)	9 (4)	–	–	–	
Fatigue syndrome	27 (52)	57 (27)	–	–	–	
Dyspnea	10 (19)	22 (11)	–	–	–	
Pneumonitis	2 (4)	3 (1,5)	–	–	–	
Pneumonia	1 (2)	1 (0.5)	–	–	–	
FUO	7 (13)	10 (5)	–	–	–	
Thrombophlebitis	3 (6)	3 (1.5)	–	–	–	
HUS	–	–	–		1 (2)	1 (0.5)

A median of 3 cycles (range 1–8) was administered; 75% of patients received less than 6 cycles. The most common reason was tumor progression or worsening of the patients' clinical condition. Hematological side-effects necessitated delay of therapy in 65%. However, in no case did this result in bleeding or infectious complications.

In total, 52 patients were evaluable for toxicity and 54 patients were evaluable for response.

Toxicity

Treatment was generally well tolerated. The maximum toxicities (NCI-CTC grade III/IV) encountered during any cycle of therapy are given in Table 2. The most frequent toxicities were anemia grade I + II (73%) and thrombocytopenia grade III + IV, which were encountered in approximately half of the patients (54%). Nevertheless, apart from one occasion of epistaxis, no bleeding complications were observed. Grade III leukopenia was observed in 25% of patients. Seven patients suffered from fever of unknown origin, which might have been related to the application of GEM. Ten patients experienced dyspnea, two of them with X-ray-proven pneumonitis, which resolved after steroid medication or cessation of treatment. One of these patients developed an additional hemolytic uremic syndrome (HUS) after having received the sixth application of MMC, causing his death. To avoid this MMC-related side-effect, steroids were added to the protocol on day 1 of each cycle. Other symptoms, such as nausea, weight loss and fatigue, were caused by the underlying disease rather than by chemotherapy.

Clinical benefit

The evaluation of criteria defining clinical benefit was not among the objectives of this study. Yet, for 28 patients, an improvement of physical status, appetite or an alleviation of pain has been documented by the treating physician.

Table 3 Objective response rate, TTP and overall survival: GEM + MMC

Variable	*n* (%)
Objective response	
NE	1 (2)
CR	0 (0)
PR	16 (29)
SD	18 (33)
PD	20 (36)
Total	55 (100)
TTP (months)	4.7 (range 0.7–14)
Overall survival (months)	7.25 (range 0.7–27)

NE: not evaluable; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

Objective response, TTP and overall survival

Objective response rate was 29% (16 of 55), 18 patients pts had stable disease resulting in an overall tumor growth control of 62% (Table 3). There was one early death as a consequence of a cerebral infarction. With a median observation time of 9 months, median TTP was 4.7 months and median overall survival 7.25 months. One-year survival was 18%. One patient is still alive for more than 1.5 years. Those 16 patients who responded had a median TTP of 7.5 months and a median overall survival of 9.75 months.

Discussion

GEM is still considered the standard treatment for patients with APC. Recently, to increase the efficacy of the single agent, GEM has been evaluated in combination with different agents such as 5-FU, capecitabine, cisplatin, oxaliplatin, docetaxel, pemitrexed and irinotecan. To our knowledge, the current study is the first to evaluate the combination of GEM and MMC in APC. Since MMC offers a comparably low toxicity profile and can be delivered in an outpatient setting, it seemed to be a reasonable, cost-effective candidate for a combination therapy. In particular, in the 1970s and 1980s, MMC was used in several combination regimens for the treatment

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of APC. More recently, Maisey *et al.* [18] conducted a phase III study comparing protracted venous infusion (PVI) of 5-FU with PVI 5-FU plus MMC. Data of 208 patients are available. They observed an overall response rate of 8.4% and a medium survival 5.1 months for the single-agent therapy. The combination resulted in an overall response rate of 17.6% and a medium survival of 6.5 months. The authors concluded that the combination of PVI 5-FU with MMC is superior to single-agent 5-FU as far as overall response rate is concerned. The moderate benefit in survival was not statistically significant, which might have been due to the fact that 65% of patients in the 5-FU alone arm had metastatic disease, whereas only 56% of patients in the combination arm had presented in stage IV.

The combination of MMC and GEM evaluated in this trial produced a response rate of 29% and median survival of 7.25 months, and was thus comparable to other combination regimens. On the other hand, a high percentage of hematological side-effects occurred. However, they did not result in bleeding complications or lethal infections. Ten of our patients experienced dyspnea, two of them with X-ray proven pneumonitis. This complication is seen in approximately 1–10% of patients who are treated with MMC and/or gemcitabine. Whereas the dyspnea might also symbolize a progression of the underlying disease, the pneumonitis resolved after steroid medication or cessation of treatment.

Another MMC-specific side-effect—a HUS—was lethal in one patient. Usually this adverse event only occurs after a cumulative dosage of MMC above 60 mg/qm, but never accounts for more than 1% of treated patients. A HUS can be determined by laboratory findings, which are an increase in creatinine level, a drop in platelet count and a microangiopathic hemolysis as defined by the detection of fragmentocyts in the peripheral blood smear. The treatment of choice is plasmapheresis and outcome may be improved by steroid application. Since patients received a prophylactic application of steroids, we did not experience another case of HUS. GEM in combination with other agents seems to be comparably active in terms of response rates and disease stabilization. However, recent phase III studies have so far failed to demonstrate a clear survival benefit when GEM was combined with 5-FU bolus, oxaliplatin or irinotecan [19–21].

Concerning the efficacy of additional 5-FU or 5-FU prodrugs such as capecitabine, one has to pay special attention to the mode of 5-FU application. This may influence the results, as it is now well recognized that the efficacy of 5-FU is schedule dependent. Continuous infusional regimens are being associated with significantly higher response rates and a lower rate of toxicity in comparison to bolus regimens [22,23]. Also, in pancreatic cancer, the concept of continuous 5-FU administration is evolving with the introduction of capecitabine, an oral precursor of 5-FU. Capecitabine simulates a continuous application of 5-FU with the advantage of oral administration. Scheithauer *et al.* [13] explored a biweekly schedule of high-dose gemcitabine (2200 mg/m^2) with and without capecitabine 2500 mg/m^2 given from day 1 to 7 in a randomized phase II trial in patients with stage IV pancreatic cancer. They observed no advantage over single-agent gemcitabine in terms of objective efficacy parameters. A phase I/II trial was performed by Hess *et al.* [24], investigating the addition of increasing doses of capecitabine b.i.d. daily for 14 days followed by a 1-week rest to a fixed dose of GEM 1000 mg/m^2 on days 1 and 8. The recommended dose for capecitabine was 650 mg/m^2 b.i.d. The efficacy of two different combinations of GEM and capecitabine is currently being tested in ongoing phase III trials [25].

In light of the synergy between GEM and platin compounds observed in the preclinical setting [26], several investigators have performed phase II studies to evaluate toxicity and efficacy of cisplatin or oxaliplatin in combination with GEM [8,27,28]. Response rates and median TTP observed in these phase II trials could then be confirmed in two phase III trials where these two parameters proved to be superior as compared to GEM alone. With a response rate of 24.6 versus 9.2% and a median TTP of 20 versus 8 weeks, the addition of cisplatin to GEM significantly improved activity [29]. The same could be demonstrated for the addition of oxaliplatin to GEM with a response rate of 25.8 versus 16.1% and a median TTP of 25 versus 16 weeks [20]. However, overall survival was not significantly improved.

Conclusion

In light of the poor prognosis of patients with APC, special attention should be paid to quality of life and a low toxicity profile when choosing a treatment protocol. In this respect an outpatient regimen is clearly advantageous as is the avoidance of 5-FU continuous infusion. The combination of GEM and MMC offers a reasonable cost-effective alternative to other regimen as toxicity is comparably low and its schedule is simple. A randomized phase II trial comparing MMC or GEM alone versus GEM combined with MMC has been initiated by our institution.

References

1 Smith FP, Hoth DF, Levin B, Karlin DA, MacDonald JS, Wolley 3rd PV, *et al.* 5-Fluorouracil, adriamycin and mitomycin C (FAM) chemotherapy for advanced adenocarcinomas of the pancreas. *Cancer* 1980; **46**:2014–2018.

2 Bukowski RM, Balcerzak SP, O'Bryan RM, Bonnet JD, Chenn TT. Randomised trial of 5-FU and mitomycin C with or without streptozotocin for advanced pancreatic cancer. *Cancer* 1983; **52**:1577–1582.

3 Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, *et al.* A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and

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doxorubicin vs fluorouracil and doxorubicin and mitomycin. *J Am Med Ass* 1985; **253**:2061–2067.
4 The Gastrointestinal Tumor Study Group. Phase II studies of drug combinations in advanced pancreatic carcinoma: fluorouracil plus doxorubicin plus mitomycin C and two regimens of streptozotocin plus mitomycin plus fluorouracil. *J Clin Oncol* 1986; **57**:29–33.
5 Burris HA III, Moore MJ, Anderson J, Green JA, Rothenberg ML, Modiano MR, *et al.* Improvements in survival and clinical benefit with GEM as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**:2403–2413.
6 Jacobs AD, Otero H, Picozzi V, Aboulafia D, Rudolph R, Weiden P, *et al.* Gemcitabine and taxotere in patients with unresectable pancreatic carcinoma. *Proc Am Soc Clin Oncol* 1999; **18**:288a (abstr 1103).
7 Kakolyris S, Stathopoulos G, Tsavaris N, Andoulakis N, Kourousiss CH, Samantas E, *et al.* First line treatment with docetaxel and gemcitabine in patients with advanced pancreatic cancer: a multicenter phase II study. *Proc Am Soc Clin Oncol* 1999; **18**:250a (abstr 960).
8 Heinemann V, Wilke H, Mergenthaler HG, Clemens M, König H, Illiger HJ, *et al.* Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. *Ann Oncol* 2000; **11**:1399–1403.
9 Philip PA, Zapuski M, Vaitkevicius VK. Phase II study of gemcitabine an cisplatin in advanced or metastatic pancreatic cancer. *Proc Am Soc Clin Oncol 1999*; **18**:274a (abstr).
10 Rocha Lima CMS, Savarese D, Bruckner H, Dudek A, Eckardt J, *et al.* Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. *J Clin Oncol* 2002; **20**:1182–1191.
11 Kindler HL. The pemetrexed/gemcitabine combination in pancreatic cancer. *Cancer* 2002; **95**(**4 suppl**):928–932.
12 Feliu J, Mel R, Borrega P, Lopez Gemez L, Escudero P, Dorta J, *et al.* Phase II study of a fixed dose-rate infusion of gemcitabine associated with uracil/tegafur in advanced carcinoma of the pancreas. *Ann Oncol* 2002; **13**:1756–1762.
13 Scheithauer W, Schull B, Ulrich-Pur H, Schmid K, Raderer M, Haider K, *et al.* Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol* 2003; **14**:97–104.
14 Carter SK, Comis RL. The integration of chemotherapy into a combined modality approach for cancer treatment IV: pancreatic adenocarcinoma. *Cancer Treat Rev* 1975; **2**:193.
15 Whittington RM, Close HP. Clinical experience with mitomycin C. *Cancer Chemother Rep* 1970; **54**:195.
16 Carter SK. Mitomycin C—clinical brochure. *Cancer Chemother Rep* 1968; **1**:99.
17 Moore GE, Bross ID, Ausmans R, Nadler S, Jones Jr R, Slack N, *et al.* Effects of mitomycin C in 346 patients with advanced cancer. Eastern Clinical Drug Evaluation Program. *Cancer Chemother Rep* 1968; **52**:675.
18 Maisey N, Chau I, Cunningham D, Norman A, Seymour M, Hickish T, *et al.* Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. *J Clin Oncol* 2002; **20**:3130–3136.
19 Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson 3rd AB. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002; **20**:3270–3275.
20 Louvet C, Labianca R, Hammel P, Lledo G, De Braud F, Andre T, *et al.* Gemcitabine versus GEMOX (gemcitabine + oxaliplatin) in non respectable pancreatic adenocarcinoma: interim results of the GERCOR/GISCAD Intergroup Phase III. *Proc Am Soc Clin Oncol* 2003; **22**:A1004.
21 Rocha Lima CMS, Rotche R, Jeffery M, Trudeau M, Cisar LA, Morganti A, *et al.* A randomized phase 3 study comparing efficacy and safety of gemcitabine (GEM) and irinotecan (I), to GEM alone in patients (pts) with locally advanced or metastatic pancreatic cancer who have not received prior systemic therapy. *Proc Am Soc Clin Oncol* 2003; **22**:A1005.
22 Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Hitt R, *et al.* Phase I–II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J Clin Oncol* 1999; **17**:585–592.
23 Louvet C, Andre T, Hammel P, Selle F, Landi B, Cattan S, *et al.* Phase II trial of bimonthly leucovorin, 5-fluorouracil and gemcitabine for advanced pancreatic adenocarcinoma (Folfugem). *Ann Oncol* 2001; 12:675–679.
24 Hess V, Salzberg M, Borner M, Morant R, Roth AD, Ludwig C, Herrmann R. Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. *J Clin Oncol* 2003; **21**:66–68.
25 Roa S, Cunningham D. Advanced pancreatic cancer—5 years on. *Ann Oncol* 2002; **13**:1165–1168.
26 Faivre S, Raymond E, Woynarowski JM, Cvitkovic E. Supraadditive effect of 2′,2′-difluorodeoycytidine (gemcitabine) with oxaliplatin in human cancer cell lines. *Cancer Chemother Pharmacol* 1999; **44**:177–123.
27 Philip PA, Zalupski MM, Vaitkevicius VK, Arlauskas P, Chaplen R, Heilbrun LK, *et al.* Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. *Cancer* 2001; **92**:569–577.
28 Louvet C, Andre T, Lledo G, Hammel P, Bleiberg H, Bouleuc C, *et al.* Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study. *J Clin Oncol* 2002; **20**:1512–1518.
29 Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, *et al.* Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma. A prospective, randomised phase III study of the Truppo Oncologico dell Italia Meridionale. *Cancer* 2002; **94**:902–910.

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