Changes in chemotherapy for pancreatic cancer

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Objective. To review the systemic chemotherapy regimens for pancreatic cancer.
Data sources. *Medline* and non-*Medline* literature search (1966-1999).
Study selection. The following key words were used: pancreatic carcinoma; chemotherapy; antineoplastic agent; fluorouracil; gemcitabine.
Data extraction. Reports of phase II studies, randomised controlled studies, and preclinical studies were reviewed.
Data synthesis. Less than 20% of patients are suitable candidates for surgery; for the remainder, palliative chemotherapy is of only marginal benefit. Combining fluorouracil with folinic acid or interferon has not led to any significant improvement in tumour response or the patient survival rate. The early encouraging results with combination chemotherapy have not been confirmed in subsequent controlled studies. New approaches include immunotherapy and novel cytotoxic drugs. In vitro studies of monoclonal antibodies have shown promise but have failed to show clinical efficacy. Recently, gemcitabine has been shown to be more effective than fluorouracil in delivering pain relief and reducing disease-related symptoms.
Conclusions. Systemic chemotherapy is generally ineffective in increasing the survival time of patients with pancreatic cancer. Future clinical investigations concerning treatment should focus on gemcitabine-based combination chemotherapy or combined modality treatment with radiotherapy.

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Key words: Antineoplastic agents/therapeutic use; Deoxycytidine/analogs & derivatives; Pancreatic neoplasms; Survival rate

Introduction

Pancreatic cancer is a malignant cancer with associated pain and suffering and has a rapidly fatal course. The incidence of pancreatic cancer in the Chinese population is relatively low (3.7/100 000) compared with western populations (9/100 000), but the mortality rates are equally high.[1] Less than 20% of patients survive for 1 year and only 3% survive for 5 years after diagnosis.[2] Almost 90% of patients experience pain, jaundice, or both, during the course of their illness.[3] Other common symptoms include anorexia, vomiting, and weight loss. Most patients are symptomatic at the time of diagnosis.

Unfortunately, the results of surgical intervention are generally disappointing. Less than 20% of patients have resectable tumours[2] and even after apparently curative resections, the 5-year survival rate is only 20%.[4,5] As the perioperative mortality rate of pancreatoduodenectomy (Whipple's operation) is low—currently less than 5% at the experienced centres[6,7]—the majority of patients actually die from local recurrence or metastatic disease after surgical resection.[8] Patients with unresectable or metastatic pancreatic cancer are frequently symptomatic and require palliative intervention. Obstructive jaundice can be relieved with a surgical bypass or by endoscopic stent placement[9] and pain can usually be managed with analgesics. External beam radiation may also palliate symptoms but has little impact on survival.[10]

Systemic chemotherapy is commonly used in the treatment of advanced pancreatic cancer but the response rate and survival outcome are poor.[2] One problem is the fact that the assessment of the response by measuring the tumour size may not be accurate, especially as pancreatic lesions are usually not palpable. In addition, measurement of tumour size by computed tomography (CT) is not always accurate because the tumour often invades nearby structures, thus causing inflammatory changes that result in unclear radiological margins. Consequently, cancer regression is not necessarily associated with a

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reduction in tumour size on the CT scan. Because any measurement of tumour size is unlikely to be accurate, other objective end-points to evaluate the response to chemotherapy in the treatment of pancreatic cancer are needed. The aim of this paper is to summarise the results of standard systemic chemotherapy regimens from the past, and to explore new information regarding novel cytotoxic agents and evaluation end-points.

The past

Single-agent fluorouracil

The most widely studied cytotoxic agent in the treatment of pancreatic cancer is fluorouracil (FU) [5-fluorouracil]. Carter et al[11] reviewed 15 studies (involving a total of 212 cases) that looked at the clinical efficacy of FU. The response rates varied from 0% to 67%, with a mean figure of 28%. However, many investigators consider this to be a high figure, because in most of the prospective randomised comparative studies, the response rates in the single-agent FU arm have been consistently below 20%.[12] Differences in patient selection, dosage, duration of infusion, and means of measuring the tumour size could explain the discrepancy. A recent report on the circadian infusion of FU over 14 days noted that stable disease occurred in 50% of patients but without any overall improvement in outcome.[13] Despite these poor results, single-agent FU has been the standard treatment for pancreatic cancer and, until the introduction of gemcitibine, no other single agents or combinations had been shown to be superior.

Modulation of the activity of fluorouracil

Leucovorin (calcium folinate), interferon, or a combination of the two, seem to enhance the cytotoxic effect of FU. Leucovorin is a reduced folate cofactor in pyrimidine synthesis. The drug may prolong the inhibition of thymidylate synthase by increasing the concentration of a FU metabolite—namely, 5-fluorodeoxyuridine monophosphate (F-dUMP). The modulating effect of leucovorin on FU has been demonstrated in vitro and proven clinically in the treatment of colon cancer.[14] Clinical studies using combinations of FU in the treatment of pancreatic cancer are shown in Table 1.[15-20] Both Crown et al and DeCaprio et al[15,16] used high-dose leucovorin (500 mg/m^2). The schedules of administration were slightly different and the results were similarly poor. The most prominent toxicity problem was mucositis, which resulted in hospitalisation in more than 20% of treated patients. The investigators concluded that modulation with leucovorin resulted in no meaningful improvement in the efficacy of FU in the treatment of pancreatic cancer.

Meanwhile, the synergism of FU and interferon gamma or interferon alfa-2a is still under investigation. Interferon may inhibit thymidylate synthase production when exposed to FU[21] but the clinical usefulness of the enhanced cytotoxic effect remains debatable.[22] In the phase II studies of FU plus interferon alfa-2a, the response rates ranged from 4% to 14%. Severe neutropenia was reported in 25% of patients[18,19] and the median survival rates were not better than those reported in single agent FU studies. Dippold et al[20] combined both leucovorin and or interferon alfa-2a with FU in a phase II study of 57 patients. In addition to a response rate of 14%, they reported that 22 of the 36 patients became free of tumour-related pain. However, no prospective comparative study with the conventional single agent FU is available. The conclusion is that biochemical modulation of FU does not improve the clinical outcome of patients with pancreatic cancer.

Fluorouracil plus radiotherapy

The combination of FU and radiotherapy may be useful as adjuvant or palliative treatment for patients with pancreatic cancer. The Gastrointestinal Tumour Study Group (GITSG) conducted a randomised study in which 75 patients received adjuvant FU plus radiotherapy or no adjuvant treatment, after undergoing

Table 1. Summary of results of studies that used fluorouracil in the treatment of pancreatic cancer

Study	Regimen	Patients (No.)	Response rate (%)*	Median survival time (months)
Crown et al,[15] 1982	FU† + LV‡	20	0	4
DeCaprio et al,[16] 1991	FU + LV	42	7	6.2
Weinerman et al,[17] 1994	FU + LV	30	13	4
Pazdur et al,[18] 1992	FU + INFa§	46	4	4.5
Scheithauer et al,[19] 1992	FU + INFa	32	12.5	5.5
Dippold et al,[20] 1997	FU + LV + INFa	57	14	10

* Probability ratio + confidence ratio
† FU fluorouracil
‡ LV leucovorin
§ INFa interferon alfa-2a

curative surgery.[23] Patients were treated with 40 Gy of radiation with anterior and posterior parallel-opposed fields. A daily bolus of FU was given for 3 days during a split course of radiotherapy and then weekly for 2 years. The median survival time for the treatment and control groups was 21 months and 11 months, respectively. These encouraging results, however, have not yet been confirmed by other studies. Adjuvant FU plus radiotherapy should be offered to selected postoperative patients who have a good performance status.

Radiotherapy alone does not improve the survival time of patients with locally unresectable disease,[24] but selected patients may benefit from the combination of FU and radiotherapy. The GITSG conducted a three-arm study that compared radiotherapy (60 Gy) alone, radiotherapy (40 Gy) plus FU, and increased radiotherapy (60 Gy) plus FU.[25] The figures for median survival were 23 weeks, 36 weeks, and 49 weeks, respectively. This study established that the combined modality should be used as the standard treatment. Some investigators have, however, suggested that this survival benefit could have been obtained from FU alone.[24] This led to the Eastern Cooperative Oncology Group (ECOG) study, which compared FU with radiotherapy plus FU. The results confirmed this suggestion—the median survival times found were 8.2 months and 8.3 months, respectively.[26]

Another study compared FU-based combination chemotherapy (streptozotocin, mitomycin, and FU [SMF]) with a combined radiotherapy plus SMF chemotherapy.[27] The median survival time of the combined modality group was 42 weeks, compared with 32 weeks for the chemotherapy group. When radiotherapy was combined with a more aggressive combination chemotherapy regimen (FU, streptozotocin, cisplatin, and leucovorin), the response rate was 42.8% and median survival time was 31 months.[28] Hence, the additional benefit of adding radiotherapy or chemotherapy to FU remains to be established. Potential benefit has been shown but a firm conclusion cannot be drawn from the current information.

Combination chemotherapy using fluorouracil

The two most widely used combination chemotherapy regimens for advanced pancreatic cancer are FU, doxorubicin, and mitomycin (FAM) and SMF. Results from using these two regimens are shown in Table 2.[29-35] The initial findings were encouraging, with response rates of up to 48% being obtained.[29-33] Unfortunately, subsequent comparative studies were much less encouraging. The GITSG compared the FAM regimen to two different schedules of SMF and found the response rates to be similar (14% versus 14% and 15%).[34] The median survival time varied from 11.3 weeks to 17.7 weeks. In addition, Oster et al[35] randomised 196 patients to receive either FAM or SMF; the response rates were 14% and 4%, respectively, and no significant difference in either response rate or median survival time was found. It was noted that the outcome of these regimens was much worse than those of the early phase II studies, with patient selection bias and different evaluation criteria being the main reasons for the discrepancy.

The 'Mallinson regimen' (FU, cyclophosphamide, methotrexate, and vincristine, followed by FU plus mitomycin) aroused enthusiasm with its initial results.[36] In this randomised study, 21 patients in the treatment group were compared with 19 patients in a control

Table 2. Summary of results of studies that used fluorouracil-based combination chemotherapy in the treatment of pancreatic cancer

Study	Combination chemotherapy regimen	Patients (No.)	Response rate (%)	Median survival time (months)
Smith et al,[29] 1980	FAM*	39	37	12
Bukowski et al,[30] 1982	SMF†	25	48	6.8
Wiggans et al,[31] 1978	SMF	23	43	6
Bukowski et al,[32] 1983	SMF	56	34	4.5
	MF‡	60	8	4.3
Smith et al,[33] 1982	FAM	23	13	6.4
Gastrointestinal Tumour Study Group,[34] 1986	FAM	29	14	3
	SMF I	28	14	4.5
	SMF II	27	15	3.5
Oster et al,[35] 1986	FAM	90	14	6.5
	SMF	94	4	4.6

* FAM fluorouracil, doxorubicin, and mitomycin
† SMF mitomycin, streptozotocin, and fluorouracil
‡ MF fluorouracil and mitomycin

group (ie receiving no chemotherapy). The median survival in the treatment group was significantly better (44 weeks versus 6 weeks). This study has, however, been criticised for its lack of histological confirmation in one third of patients and the extremely poor outcome obtained by the control group. The same protocol has been tested in a phase III study by Cullinan et al.[37] Patients were randomised to receive FU; the Mallinson regimen; or FU, doxorubicin, and cisplatin (FAP). The response rate was 7% for the FU group, 21% for those given the Mallinson regimen, and 15% for the FAP cohort. The median survival, which was the primary end-point for all study patients, was 3.5 months, 4.5 months, and 4.5 months, respectively. Once again, the larger randomised trial did not support the initial phase II study results.

Many other FU-based combination chemotherapies have been studied. These include FU plus carmustine (1,3-bis-[2-chloroethyl]-1-nitrosourea [BCNU]),[38] FU plus lomustine (1-[2-chloroethyl-3-cyclohexyl]-1-nitrosourea [CCNU]),[39] FU plus cisplatin,[40] FU plus melphalan,[41] and FU plus methotrexate.[42] The response rates achieved range from 20% to 33%, but the median survivals have been poor and there is no convincing evidence that any of these combinations is better than FU alone. In addition, the toxicities of combination chemotherapy were more severe than those associated with single agent therapy.

Other anticancer drugs

Other single agents that have shown activity in pancreatic cancer include anthracycline, nitrosourea, and ifosphamide. Doxorubicin and epirubicin have also been used in single-agent therapy and give response rates that range from 13% to 37%.[43,44] While the initial study of ifosphamide was encouraging,[45] subsequent studies have shown that it has only limited activity.[46,47] The response rate to nitrosoureas is only 5%[48]; because of their limited activity, these drugs are only used in combination with FU, although no significant synergism has been observed.

Hormonal therapy, including the use of tamoxifen (an anti-oestrogen) and compounds that act as anti-androgens, have also been extensively studied; the results have been generally disappointing. A UK study randomised 108 patients with advanced pancreatic cancer to receive either tamoxifen, cyproterone acetate, or no treatment.[49] No survival benefit was observed in the two treatment groups. A double blind study that compared tamoxifen with placebo also did not show any survival benefit in the tamoxifen group.[50]

The present

Immunotherapy

As noted previously, interferon α-2a has been shown to be an ineffective modulator of FU. A new and exciting concept has been to use monoclonal antibodies (MoAbs) in the treatment of pancreatic cancer. MoAb 494/32 has been shown to be able to bind to 90% of human pancreatic carcinoma cells.[51] Because in vitro studies confirmed its ability to suppress tumour cell growth.[52] Buchler et al[53] conducted a phase II study using this antibody to treat 87 patients with advanced pancreatic cancer. The results showed that one (1.1%) patient had a partial response and 39 (44.8%) of the patients had stable disease that lasted for 3 months. Unfortunately, a subsequent study conducted by the same group was less encouraging.[54] Sixty-one patients with resectable pancreatic cancer were randomised postoperatively to receive either 10 days of intravenous infusion of MoAb 494/32 or no further treatment. The median survivals of the treatment group and control group were not found to be statistically different. The authors of the study concluded that MoAb 494/32 was not helpful in treating patients with resectable pancreatic cancer.[54] Other forms of immunotherapy, such as interleukin 12 or interferon gamma, are being investigated in clinical trials but no significant benefit has been observed to date.[55]

New drugs

Numerous new cytotoxic drugs that have innovative mechanisms of action have shown promising activity. These drugs include gemcitabine (an antimetabolite), taxane (an inhibitor of microtubule polymerisation), marimastat (a metalloproteinase inhibitor), and irinotecan (a topoisomerase-I inhibitor). Information on the latter two is only experimental or from early phase I/II clinical data.[56-58] Hence, this review will focus on the mature clinical data that is available for the taxanes (paclitaxel or docetaxel) and gemcitabine.

The taxanes inhibit cell replication by disrupting microtubule assembly. The process involves destabilisation of the microtubule polymer and interference with the assembly competency of tubulin—the protein involved in the process. Extensive clinical studies have confirmed their cytotoxicity in ovarian, breast, head and neck, and lung cancers. However, the results of taxane trials in the treatment of pancreatic cancer have been disappointing. In a phase II study, paclitaxel was given to 35 patients with granulocyte colony-stimulating factor.[59] Only one objective patient

response (2.9%) was observed. An early phase II study using docetaxel in 28 patients has reported a response rate of 17%.[60] Two other phase II trials from Japan and Greece have yielded low response rates of 0% and 6%, respectively.[61,62] Unfortunately, the results of these studies have not been encouraging. A further study using a combination of paclitaxel and cisplatin is ongoing.[63]

Gemcitabine is a new antimetabolite that has a biochemical structure similar to cytarabine. This pyrimidine analogue can be phosphorylated by deoxycytidine kinase and incorporated into DNA. When this occurs, DNA synthesis is inhibited. By a unique process called 'masked-chain termination', gemcitabine is protected from excision by the normal DNA repair mechanisms.[64] The preclinical studies investigating the cytotoxicity of gemcitabine have been encouraging.[65] The phase I/II clinical trials have confirmed its effectiveness as a single agent in the treatment of several malignancies, which include non–small-cell lung,[66] breast,[67] and ovarian cancer.[68] Dosages of 800 to 1250 mg/m^2 have been given weekly for 3 weeks in a 28-day cycle; the observed toxicities have been mild. Grade 3 or 4 myelosuppression (according to the World Health Organization classification system) occurs in fewer than 10% of patients. Nausea and vomiting are uncommon and while about 50% of patients had mild proteinuria, none developed significant renal dysfunction.[66-68]

Casper et al[69] conducted the first multicentre phase II study of gemcitabine versus placebo in 44 patients with advanced pancreatic cancer. Although only five (11.4 %) patients had radiological evidence of a partial response, the median survival time for this group was 13.0 months. In comparison, the median survival of all treated patients was only 5.6 months. Despite the fact that only a few had a partial response, researchers have noted that these patients and those with stable disease had a significant improvement of disease-related symptoms, and that most patients were able to return to performing normal activities. This aspect of clinical improvement in the treatment of pancreatic cancer had never been prospectively studied before.

Development of a new primary end-point for drug evaluation purposes

The evaluation of the tumour response in pancreatic cancer has not been easy. The traditional end-point of assessing tumour size reduction is not always accurate. In addition, pancreatic cancer frequently infiltrates the surrounding structures and causes inflammation and fibrosis. Ultrasonography or CT may fail to accurately measure a tumour if the tumour margins are not clearly defined. Furthermore, regression of malignant growth is not always demonstrated by a reduction in the tumour size if inflammation and fibrosis are prominent components of the tumour mass.

Because of the difficulty of assessing clinical benefit, clinical investigators have tried to develop an objective measurement symptom improvement as a new end-point for clinical trials.[70] In recent clinical trials of gemcitabine in pancreatic cancer, 'clinical benefit' has become the new primary end-point and tumour response has become a secondary end-point. According to this concept, a positive response implies a decrease in pain intensity, a reduction of analgesic consumption, or an increase in the Karnosky performance status (KPS) Score.[70] All patients enrolled in these trials underwent a 2 -to 7-day 'pain-stabilisation period' before undergoing chemotherapy. Each patient's pain intensity was assessed by using a 'memorial pain assessment card',[71] which is a visual analogue scale that measures pain intensity. An improvement in pain intensity is defined as 50% or greater of a reduction in pain from the baseline level, that lasts for at least 4 consecutive weeks. A similar definition is also applied to the reduction of analgesic consumption. Two independent observers assess the patients to determine the KPS score. An increase of 20 points or more in the KPS score indicates a positive response in performance status. The patient is considered to have a positive response in terms of 'clinical benefit' if at least one of the three evaluations is positive and none is negative. If all three parameters are stable, weight gain is considered the determining factor for a positive response.

Gemcitabine improves the treatment of pancreatic cancer patients

Carmichael et al[72] documented pain score, analgesic requirement, and performance status in a phase II study of gemcitabine in 34 patients with pancreatic cancer. In this study, only two patients had a partial response (5%-9%) and the median survival time of all patients was 6.3 months. However, 28.6% of patients reported improvements in pain score and 17.2% had a better performance status after treatment. The symptom improvement was significant, but the tumour response and survival time were still primary end-points of the study.

In another phase II study, 'clinical benefit' was the primary endpoint used to assess 74 patients with FU-refractory pancreatic cancer.[73] Seventeen (27%) of the 63 evaluable patients attained a positive response

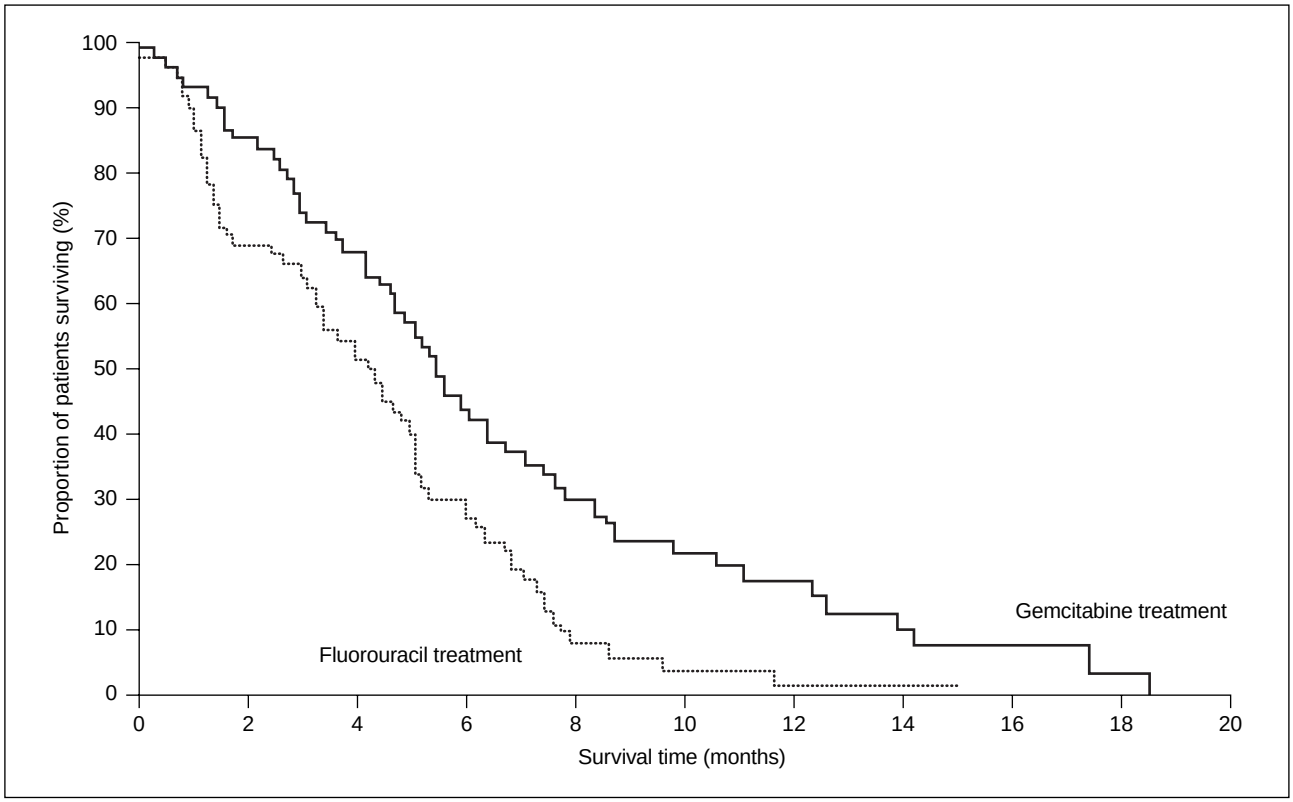

Fig. Survival curves of patients treated with gemcitabine or fluorouracil in a multicentre randomised study[74]

in 'clinical benefit', which lasted for an average of 14 weeks. The median survival time for all patients was 3.9 months. The findings suggest that FU and gemcitabine are not cross-resistant—that is, patients who fail treatment with FU can benefit from receiving gemcitabine. Because this group of patients had received previous chemotherapy and because the median interval between the cessation of prior treatment with FU and the initiation of gemcitabine was 1 month, the modest survival duration was expected.

The effectiveness of gemcitabine in the treatment of pancreatic cancer has been confirmed by a multicentre phase III study that compared gemcitabine with FU.[74] One hundred and twenty-six patients were randomised to receive either gemcitabine 1000 mg/m^2 weekly for 3 weeks every 28 days or FU 600 mg/m^2 once weekly. The 'clinical benefit' response was the primary end-point used in this study. Tumour response and median survival time were secondary measurements of efficacy. The 'clinical benefit' response rates in the gemcitabine arm and FU arm were 23.8% and 4.8%, respectively. One year after enrolment, 18% of the gemcitabine-treated patients were still alive compared with only 2% of patients in the FU arm (Fig). The survival benefit for the gemcitabine-treated patients was modest but statistically significant (median survival time, 5.7 months versus 4.4 months; P=0.025).

Conclusion

Systemic chemotherapy is generally ineffective in increasing the survival time of patients with pancreatic cancer. Combined modality treatment with radiotherapy and FU can have a small impact on the survival of selected patients with locally unresectable disease. When assessing patient response to treatment, palliation of symptoms should be objectively evaluated. A new end-point, termed 'clinical benefit', has been shown to be a relevant measurement of impact of therapy on disease-related symptoms. Recent studies have confirmed that gemcitabine is more effective than FU in reducing symptoms in pancreatic cancer patients and confers a small, but statistically significant, survival benefit. Future clinical investigations concerning the treatment of pancreatic cancer patients should focus on gemcitabine-based combination chemotherapy or combined modality treatment with radiotherapy.

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