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Review paper

Chemotherapy in pancreatic cancer: a rational pursuit?

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A review on the chemotherapy in advanced pancreatic cancer is presented. Pancreatic cancer is an extremely chemotherapy resistant tumor and results of cytostatic drug treatment so far are unsatisfactory. For patients with locally advanced disease the combination of chemo- and radiotherapy may palliate some patients. To date no standard treatment is available and patients should be entered in clinical protocols assessing new treatment options.

Key words: Chemotherapy, pancreatic cancer.

Introduction

The incidence of pancreatic carcinoma is rising in Western countries and has a major impact on cancer deaths. The disease is highly lethal, the median survival is 3–4 months and 90% of patients die within 1 year of diagnosis. Overall survival at 3 years is practically zero.

The diagnosis is most often made when the disease is already advanced and earlier diagnosis might enhance the incidence of curative resections. Endoscopic sonography is a potentially useful method that with further technical improvement and increasing experience may make it possible to disclose lesions that are not visualized with currently available tools. Furthermore the potential role of nuclear magnetic resonance (NMR) should be investigated.

Theoretically surgery offers the best hope for cure but only a small minority of patients are resectable and even the survival of these patients after 3 years drops to approximately 15% and after 5 years to 4%.[1] All patients must be carefully evaluated as candidates for 'curative' surgery. Although only a small minority of the patients will be resectable, these patients are the only ones with a potential for long-term survival. Adjuvant treatment after resection can potentially enhance the treatment outcome.

Palliation and improvement of the survival for patients with advanced stages with other treatment modalities (i.e. irradiation, chemotherapy, or a combination of both) must be continuously pursued.

Radiotherapy

Conventional photon irradiation with 4000–6000 rads may offer some palliation for locally advanced disease without measurable impact on the survival. The Gastrointestinal Tumor Study Group (GITSG) study has shown some evidence that combination of irradiation and 5-fluorouracil (5-FU) is superior to radiotherapy alone for locally advanced disease. In this study patients were randomized to receive either 4000 rads + 5-FU or 6000 rads ± 5-FU. The radiotherapy alone group was discontinued with 25 patients because early analysis had shown a statistically inferior survival for this group. Median survival in patients treated with 6000 rads + 5-FU was slightly but not significantly better than that for patients receiving the lower dose of irradiation, but this early benefit was not sustained much beyond 1 year. At 60 weeks both survival curves intercepted and at 2 years all curves approached zero.[2] A subsequent study has evaluated doxorubicin and radiation vs the superior 5-FU + radiation combination. Among 143 evaluable patients median survival in the doxorubicin group was 32.5 weeks and in the 5-FU group 38 weeks, suggesting no benefit of doxorubicin over 5-FU in addition to radiotherapy for locally advanced disease.[3] A small phase II study reported

no major toxicity and symptomatic relief in 10 patients treated with three cycles of chemoradiotherapy consisting of 5-FU given as continuous infusion for 5 days and irradiation to a total dose of 6000 rads. Two weeks rest periods were given between the cycles.[4] In a study conducted by the Eastern Cooperative Oncology Group (ECOG), however, 91 evaluable patients with locally advanced disease were randomized between 5-FU alone or 5-FU combined with 4000 rads. The median survival time was 8 months for both treatment programs, but serious toxicities were significantly increased in the combined modality group, thus making questionable the relative merit of conventional irradiation in addition to single agent 5-FU. Palliation of pain however was not investigated and the question whether the combined approach is superior in terms of response or attenuation of pain has not been answered by this study.[5]

A beneficial role for combined radiation and chemotherapy is further suggested by the results of a prospective trial comparing adjuvant radiation (4000 rads) + 5-FU vs no adjuvant treatment in 43 patients following potentially curative surgery. The median survival of 20 months for the treated group was significantly better than the 11 months for the control group.[6] In a subsequent study 30 patients received the same adjuvant treatment and the therapeutic outcome for these patients was equal to the former study. The median survival time was 18 months and the actuarial 2 years survival 46%. The conclusion of the authors was that adjuvant treatment is effective and should be preferred over no adjuvant treatment.[7] The European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Group is currently conducting a similar randomized trial in order to reproduce these results.

Some phase II studies have assessed combination chemotherapy in addition to irradiation. The sequential use of 5-FU, adriamycin (A), mitomycin-C(M) and radiotherapy was reported to yield an overall median survival in 26 patients of 12+ months.[8] In another study six cycles of 5-FU, A and cisplatin(P) (FAP) followed by irradiation (40 Gy) + 5-FU resulted in four partial responses in 10 patients and a median overall survival of 13+ months.[9] In a small randomized study conducted by the GITSG a significant survival advantage was found for patients treated with irradiation (54 Gy) and 5-FU followed by streptozotocin + mitomycin + 5-FU (SMF) vs SMF alone. The study was prematurely closed with only 43 patients because of insufficient funding. The median survival time for 22 patients in the combined group was 42 weeks vs 32 weeks for 21 patients in the chemotherapy group ($p < 0.02$). In this study there was substantial toxicity and more than one-third of the patients had major protocol violations and refused further chemotherapy.[10] In a subsequent phase II study the GITSG assessed hyperfractionated radiation (5.4 Gy) and 5-FU followed by SMF. The median survival was 35 weeks which the authors stated to be disappointing, considering the high grade (67%) of severe toxicity.[11]

New radiation techniques for locally advanced disease such as implantation of radioactive materials, intraoperative radiotherapy[12] and the use of specialized beams (neutrons, protons, mesons, etc.) are of interest and may benefit some patients. Impact on survival, however, can be expected to be relevant only if these techniques are combined with some form of systemic treatment. Irradiation with high-energy neutrons resulted in a median survival of 6 months in 77 patients; 26 of these patients, however, experienced severe late side effects or complications and there were two treatment-related deaths.[13] The combination of external radiation, implantation of iodine-125 and chemotherapy resulted in a median survival of 11 months in 20 patients with locally advanced disease, which was better than that of historical control groups of patients who were treated otherwise.[14] However, randomized studies with these new radiation technique have until now not been performed, so no final conclusions can be made.

Nevertheless, these studies encourage exploration of new radiation techniques combined with new drugs for patients with locally advanced disease and in adjuvant setting.

Chemotherapy

Introduction

Nihilism still prevails when approaching the role of chemotherapy in pancreatic cancer. Patients frequently present with a low performance status, which makes the tolerance of chemotherapy and therefore the evaluation of its efficacy particularly difficult. The assessment of the impact of chemotherapy is a problem on its own because it is difficult to evaluate the response, especially on the primary. The interpretation of computed tomography (CT) and especially ultrasound is limited by

the operator's expertise but should be accepted if the lesions are clearly demarcable. Clinical measurements of vaguely defined abdominal masses are even less accurate.

Single agents

5-FU is the most extensively evaluated single agent with a response rate of 28%[1,15] which is probably an overestimation because this result is obtained from a compilation of 15 series with response rates ranging from 0 to 67%. All these studies were performed between 1960 and 1971 using non-standardized response criteria, the greater part of which would be unacceptable today. Other drugs with reported activity include mitomycin C (12/44; collected series), streptozotocin (8/22; collected series)[16] and ifosfamide. Very high response rates have been reported for ifosfamide in two small studies, 10/13[17] and 6/10,[18] but in a more recent phase II trial a response rate of 6/27 was reported,[19] while three other phase II studies yielded insignificant activity.[20–22] All other drugs tested so far were reported to have an activity of less than 20%. These drugs include doxorubicin, idarubicin, melfalan, the nitrosoureas, methotrexate, actinomycin and vindesine. Cisplatin has not been tested as a single agent. An overview of single agent studies is presented in Table 1.

Table 1. Activity of single agents in pancreatic cancer

Drug	Number of responses/ patients	Response rate (%)	Reference
5-FU[a]	60/212	28	1, 15
Mitomycin[a]	12/44	27	1, 16
Streptozotocin[a]	8/22	36	1, 16
Ifosfamide[a]	43/164	26	17–22
Epirubicin			See text
Adriamycin	2/15	13	23
Melphalan	2/15	13	24
Ibroplatin	3/30	10	25
Methyl CCNU	3/34	9	26
Idarubicin	2/32		27
Menogaril	2/38		28
Vindesine	1/15		29
Methotrexate	1/25		23
Actinomycin C	1/28		23
BCNU	0/20		30
Trimetrexate	0/14		31

[a] Collected series.

Combination chemotherapy

Despite the relatively few drugs there has been continued interest in combination chemotherapy. Table 2 provides an overview of phase II pilot studies in advanced pancreatic carcinoma. FAM and SMF are the most employed regimens. The response rate is approximately 27% in phase II studies, the median survival of responders is ± 10 months, but the overall median survival does not exceed 6 months. Around 10% of patients survive over 1 year. Results of randomized studies, however, have resulted in much lower response rates. A randomized study comparing FAM vs SMF in 184 patients yielded only a 14 and a 4% response rate and a median overall survival of 26 and 18 weeks, respectively.[43] In another randomized study of 116 patients with measurable disease conducted by the South West Oncology Group (SWOG), SMF was compared with MF. The response rates were 34 and 8%, respectively, showing apparent activity of streptozotocin, but median survivals were similar, 18 vs 17 weeks.[44] The GITSG has reported the results of a randomized study conducted in 133 patients with measurable disease comparing FAM with two different SMF regimens. The response rates were 13, 15 and 14% and the median survivals 3–4.5 months. The conclusion of the authors was that neither regimen should be used in the routine treatment of advanced pancreatic cancer.[45] SMF has further been compared with CAC (cisplatin, arabinoside and caffeine), a regimen that yielded a 39% response rate in a phase II study.[46] In this randomized trial the response to SMF was 3/30 (10%) and to CAC 2/27(7%) and median survival 5.3 vs 3.5 months.[47] A randomized comparison of FAM, FA and 5-FU alone in 144 patients demonstrated no benefit for combination chemotherapy over single agent 5-FU in terms of survival and resulted in the same survival time of 22 weeks in all three groups of the study. Because of a too small sample of patients with measurable disease in this trial, differences in response rates could be inadequately assessed (response rates 1/13 vs 3/10 vs 3/10).[48]

Two randomized trials have compared chemotherapy with controls. In the first the survival in 21 patients treated with a 5-drug regimen was significantly better than in 19 controls. The number of patients in this study was limited and more than one-third of the patients did not have their tumor histologically confirmed.[49] Moreover, in a study encompassing 172 patients and randomly comparing the same 5-drug regimen with FAP or 5-FU,

Table 2. Phase II studies of combination chemotherapy in advanced pancreatic carcinoma (excludes E + F, E + I, I + F—see text)

Regimen	No. of patients	No. of responders	Median survival responders (months)	Median survival all patients (months)	Survivors >1 year	Reference
SMF	23	10	10	6	4	32
SMF	22	7	9	6		33
FAM	27	10	12	6	4	34
FAM	15	6	13+	4	1	35
FAM-S	25	12	10	7	7	36
FAP	15	3	10+			37
FAP	29	6		4	2	38
HEXA-FAM	30	5		4		39
HEXA-FM	21	2		10		40
FAMTX	25	4		7	5	41
VP-16 + F	14	1	36	4, 5	1	42
	246	66 (27%)	10	6	24 (10%)	

S, streptozotocin; M, mitomycin; F, 5-fluorouracil; A, adriamycin; P, cisplatin; HEXA, hexamethylmelamine; E, epirubicin; I, ifosfamide; MTX, methotrexate; VP-16, etoposide.

the response rates were below 15% in all three groups and the median survival was not different and ranged between 3.5 and 4.5 months.[50] In the second trial involving a total of 152 patients, no survival benefit was detected for treatment with 5-FU + CCNU vs controls, the median survival was 3 and 4 months, respectively.[51]

New schedules of old drugs

It is possible that other schedules of currently available drugs can enhance the therapeutic outcome. For instance there has been a renewed interest in 5-FU in the treatment of gastrointestinal cancer, especially colorectal cancer, since several studies have suggested that dose-intensification by the use of protracted continuous venous infusion[52] or by weekly high-dose 24- or 48-h infusions, or modulation of the activity of 5-FU by leucovorin, can enhance the therapeutic results.[53–55]

These treatment schedules appear worthy of study in pancreatic cancer and some data have already been reported. In one trial employing a protracted continuous venous infusion of 5-FU in a dose of 300 mg/m^2/day, three of 16 patients with pancreatic cancer responded and eight of the 16 patients experienced improvement in performance status while the treatment was extremely well tolerated.[56] In another trial 5-FU was administered in a 5-day continuous infusion every 4 weeks and methyl-CCNU and mitomycin-C were added on day 1 every 8 weeks. The response rate was 27% (6/22).[57] Adding weekly cisplatin in a dose of 20 mg/m^2 to a continuous infusion schedule of 5-FU resulted in 9/55 (16%) responses but 44% of the patients experienced at least one episode of severe toxicity.[58] The combination of 5-FU and high dose leucovorin (5-FU, 600 mg/m^2 bolus midway a 2-h infusion of leucovorin, 500 mg/m^2, weekly) was assessed in one study and resulted in a low response rate of 8% (2/27) and considerable toxicity.[59] PALA is another modulator of 5-FU and three responses were noted among 16 patients given PALA (250 mg/m^2) followed after 24 h by 5-FU (2.6 g/m^2) in a 24-h continuous infusion, every week.[60]

Results of EORTC Gastrointestinal Group trials

Since 1982 the EORTC Gastrointestinal Group has completed three phase II studies assessing, respectively, epirubicin, epirubicin + 5-FU and epirubicin + ifosfamide. The results have been reported[61–63] and are summarized in Table 3.

Although these were not randomized trials, the results suggest that neither the addition of 5-FU nor ifosfamide to epirubicin offer an advantage over epirubicin alone.

Considering all eligible patients entered in the three trials ($n = 116$), the main prognostic factor was the stage of the disease. Patients with locally advanced disease ($n = 34$) had a significantly longer survival than patients with distant metastases ($n = 82$).

Table 3. Summary of results of EORTC trials

	E	E + F	E + I
Response	8/40(20%)	6/44(14%)	4/32(12.5%)
Median duration of response (range)	7 mths (2–17)	7 mths (2–9)	7 mths (3–9)
Median survival all patients (range)	5 mths (1–23)	4 mths (1–15+)	5 mths (1–22)

E, epirubicin; F, 5-fluorouracil; I, ifosfamide.

The difficulty in evaluating the response is substantiated by the fact that of 18 objective responders in the three trials (116 patients), only nine experienced subjective improvement (seven patients no subjective improvement, some being free of symptoms at the start of treatment; two patients unknown), while nine non-responders reported subjective improvement.

The EORTC Gastrointestinal Group has initiated two new trials evaluating the combination of epirubicin + cisplatin followed by irradiation in locally advanced disease, and assessing cisplatin vs ifosfamide, 5 days continuous infusion, as single agents in advanced disease. Preliminary results suggest activity for cisplatin, one complete response (CR) and three partial responses (PR) in 16 evaluable patients and no activity of ifosfamide (no responses in 14 patients).

The combination of epirubicin and cisplatin appears particularly active, 2 CR and 5 PR in 25 evaluable patients (response rate: 28%). The responses in this study were all documented before the start of radiotherapy and there were no further regressions after the irradiation. In one patient with clinically CR a laparotomy was performed, and residual tumor was resected. The median survival in this study so far is 10+ months (DJTh Wagener, unpublished data).

Endocrine treatment

There are some data suggesting that pancreatic cancer might be sensitive to endocrine therapy. Pancreatic tumor cytosols can bind estradiol at high levels and pancreatic adenocarcinoma cell lines have shown *in vitro* steroid sensitivity.[64] Tamoxifen was reported to yield a median survival of 8.5 months in 14 patients; three male patients with locally advanced disease survived 22 months.[65] Another study reported a median survival of 7 months in 24 patients with advanced pancreatic cancer treated with tamoxifen; six patients survived over 1 year of which three survived over 2 years. These six patients were all postmenopausal women.[66] An anecdotal report of a response to LH–RH analog treatment has been published.[67] In another study, however, none of 13 patients responded to endocrine treatment; nine of these patients were treated with tamoxifen.[68]

Moreover, results of two multicenter randomized studies do not corroborate these data. In the first trial 44 patients with histologically confirmed pancreatic cancer were randomized between tamoxifen, 40 mg daily and control. Data were reported on 39 patients, 19 on tamoxifen and 20 controls. There was no difference in the survival.[69] In the second study 108 patients were randomized between tamoxifen, cyproterone acetate and control without significant differences.[70]

New treatment options

Possible new treatment modalities are the loco-regional application of radiofrequency hyperthermia,[71] the use of biologic response modifiers (BMRs) such as interferons, interleukin-2 (IL-2) with or without lymphokine-activated killer (LAK) cells or with tumor infiltrating lymphocytes (TILs), and the use of monoclonal antibodies (MAbs) directed against a cell-surface glycoprotein that can be present on pancreatic cancer cells. MAbs can be conjugated to radionuclides (radio-immunotherapy), to cytotoxic agents (chemo-immunotherapy) and on their own they can interact with the host immune system to produce a cytotoxic effect (specific immunotherapy). This antibody-dependent cell-mediated cytotoxicity is effected by macrophages and cells with 'natural killer activity' (NK cells). The application of BMRs in combination with MAbs may result in better therapeutic results. In its present form immunotherapy with MAbs, however, still has limited use. One of the many problems is the development of human antibodies

against the murine MAbs (HAMAs), which partly could be abolished by the production of humanized antibodies. A comprehensive review on the application of MAbs has been published.[72]

Discussion

The results of the EORTC Gastrointestinal Group studies have shown that epirubicin can be grouped among the agents with limited activity in pancreatic cancer. These results have been confirmed by others, who reported three partial responses of 16 patients, nine of whom were pretreated. The dose used in that study ranged between 75 and 90 mg/m^2.[73] In another trial, however, only two partial responses of 34 patients have been reported. Of these patients, 35% had prior chemotherapy and 24% prior radiotherapy and the dose of epirubicin ranged between 60 and 75 mg/m^2.[74] The toxicity of epirubicin administered in doses between 90 and 120 mg/m^2 has been found acceptable and it is suggested that higher doses might have a better therapeutic effectiveness. In a recent study from Israel, however, epirubicin was administered in a dose of 110–150 mg/m^2 and in 20 patients no responses were observed.[75] These data are difficult to reconcile with the EORTC experience.

The addition of 5-FU or ifosfamide to epirubicin did not enhance the therapeutic results, neither did the addition of 5-FU to ifosfamide, which was tested by the same investigators who reported activity for ifosfamide as a single drug,[19] led to better therapeutic results. Only two responses were achieved in 29 patients.[76] These data question the value of combination chemotherapy over single agents. These results are still rather disappointing and do not obviate the skepticism that exists in the treatment of advanced pancreatic carcinoma. Preliminary results of ongoing EORTC studies suggest activity for cisplatin and for the combination of cisplatin and epirubicin. Final data of these studies, however, should be awaited.

In an effort to ameliorate the outlook for patients with pancreatic adenocarcinoma all current treatment modalities must be improved and must be integrated in an optimal way. It is possible that adjuvant chemo- and radiotherapy may have an impact on the survival of resectable cases. For locally advanced disease the combined modality treatment with cytotoxic agents and irradiation should be further investigated. More active drugs or more optimal treatment schedules must be continuously assessed and the combination of cytotoxic agents with biologic agents should be explored.

It is obvious, however, that to date treatment of advanced pancreatic cancer still remains experimental, with no measurable impact on survival and patients should be treated only within controlled clinical trials. It will be a challenge for the oncologist to pursue progress in the treatment of this disease by well-designed future studies.

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