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No Standard Treatment is Available for Advanced Pancreatic Cancer

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All randomised trials, published from 1980 to 1993, of treatments in advanced and locally unresectable exocrine pancreatic carcinoma were critically reviewed to identify the most effective therapeutic strategy for use as a control arm in randomised trials for such patients. All the published randomised trials on patients with pancreatic cancer were identified, and the treatment results summarised by means of published methodological guidelines. Twenty-seven reports, including 21 on hormonal or chemotherapy and six on radio/chemotherapy were identified. Very different treatment programmes were used in the trials, without a rationale sequence for testing hypotheses. Furthermore, several methodological drawbacks undermined both the internal and the external validity of these studies. Therefore, no meta-analysis can be conducted, combining the results of the randomised controlled trials in pancreatic cancer published from 1990 to 1993; no standard treatment is currently available for patients with advanced pancreatic cancer; future studies should screen new drugs or new combinations; and an untreated control group should be included in future comparative studies until real advantages in terms of better quality of life or improved survival are demonstrated.

Key words: pancreatic neoplasms, review article, drug therapy, radiotherapy, therapy, random allocation, randomised controlled trial

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INTRODUCTION

In a recent debate of the ethical committee of the National Institute for Cancer Research (Genoa, Italy), the issue was raised that it would be unethical to include a control arm in which patients were treated only with the best supportive care in a randomised trial of medical treatments in advanced pancreatic cancer. To address this issue, we critically reviewed the available scientific evidence provided by randomised clinical trials. We summarised the results of the randomised trials conducted in patients with advanced pancreatic cancer, analysed possible flaws in the methodology of such trials and evaluated the possibility of reaching a general conclusion concerning the optimal therapeutic strategy in such patients.

MATERIALS AND METHODS

Acquisition of data

Only randomised clinical trials were considered. To identify a complete list of randomised trials, the following sources were used:

1. The MedLine automatic bibliographic search during the period 1983–September 1993 (as far as the CD-ROM on the Silver Platter database allowed), looking for combinations of key words: pancreatic neoplasms, randomised controlled trial, random allocation, drug therapy, radiotherapy and therapy.
2. The bibliography cited in two oncological [1] and one gastroenterological [2] textbook.
3. The trials mentioned in seven review papers [3–9].
4. The abstracts presented at the ASCO and AACR meetings from 1983 to 1993.

Entry criteria

Papers were included in the present review only if they met all the following criteria: randomised clinical trial, carcinomas of exocrine pancreas, patients with advanced or locally unresectable disease, and end points: survival, objective response or quality of life.

When more than one report was describing the same study, the most complete or updated article was used.

Statistical methods

To assess the quality of randomised control trials and the statistical content of medical studies, we adopted the methodology described by Chalmers and Altman [10, 11], and the check list proposed by Gardner [12].

A quantitative analysis conducted with formal statistical methods for pooling data could not be carried out because widely different treatment programmes were used in the trials, and because only published data and not the original raw data were available [13].

RESULTS

Tables 1 and 2 summarise the randomised trials published from 1980 up to now ([14–34] hormonal or chemotherapy; [35–40] radio/chemotherapy).

We obtained a total of 34 reports: five abstracts were excluded

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Table 1. Randomised trials of hormonal therapy or chemotherapy

Ref.	Year	Histology*	Treatments		No. of patients	Median age (years)	PS	R Ev	% OR	95% CI	Median survival (months)	P
14	1993	Yes	FAM-S	g.r.	22	56	D	22	24	8–45	5	
				p.r.	11	66	D	11	0	0–28	4.2	
			MGBG		32	59	D	32	6	1–21	7.6	
			FAM-S	g.r.	18	60	D	18	12	1–35	7	
				p.r.	10	55	D	10	10	0–45	4.8	
			DHAD	g.r.	24	54	D	24	0	0–14	3.1	
				p.r.	5	62	D	5	0	0–52	1.4	
			FAM-S	g.r.	4	55	D	4	0	0–60	4.6	
				p.r.	6	55	D	6	0	0–46	3.2	
			AZQ	g.r.	16	57	D	16	0	0–21	2.3	
				p.r.	5	66	D	5	0	0–52	1.3	
15	1993	Yes	TAM		22	64	70				2.5	
			Placebo		22	65	70				4.3	
16	1993	Yes	FEM		22	62‡	?				6.6	
			Epirubicin		25	64‡	?				5.2	
17	1992	Yes	LH–RH		15	62	?	15	0	0–22†	7.4	
			No treatment		18	60	?	18	0	0–19†	4.4	
18	1992	Yes	Somatostatin		43	64	0–3	64	0	0–6†	3.8	
			LH–RH		39	64	0–3				6	
			Somatostatin + LH–RH		38	65	0–3				5.5	
			No treatment		43	66	0–3				4.3	
19	1991	Yes	CAC		40	60	80	27	6	0–15	5	0.008
			SMF		42	58	80	31	10	1–22	10	
20	1991	Yes	FEM		35	?	?	18	11	1–35†	D	
			Epirubicin		34	?	?	26	4	0–19†	D	
21	1991	Yes	TAM		92	66	80				3.8	
			Placebo		84	66	80				4.1	
22	1990	Yes	5FU		64	60	0–3	14	7	0–34†	3.5	
			CMFV + FM		61	62	0–3	14	21	5–51†	4.5	
			FAP		59	62	0–3	13	15	2–45†	3.5	

Table 1 continued overleaf

since the same data were also published as full papers. One paper was not included since it was a phase I–II randomised study of patients with both pancreatic and gastric carcinoma. One paper was not included since it considered patients with both pancreatic and biliary tract carcinoma. Finally, one abstract and 26 papers were selected; 21 reports concerned with hormonal and/or chemotherapy and six with radio/chemotherapy.

General clinical information

Histologically or cytologically proven pancreatic carcinoma was an eligibility criteria reported in all but four reports. In the abstract, this criterium was not mentioned; in one paper the pancreatic carcinoma was proved "surgically"; in one paper 35% of the patients included had pancreatic cancer which was "histology unconfirmed".

The extent of disease was generally described as locoregional extension, metastatic disease, locally advanced, residual or recurrent and as locally unresectable or localised carcinoma.

The patient performance status was not mentioned in 7/27 (26%) of all reports. In 8/27 (30%) no mention was made of treatments possibly administered to patients before entering the trial.

Toxicity was described in all but one report. Since methods used to describe toxicity were very different, it is not possible to provide any summary estimate of the toxicity associated with the various regimens. Twenty-five episodes of life-threatening toxicity [25, 26] and six toxic deaths [27, 30, 31, 40] were reported.

Clinical information from trials of hormonal or chemotherapy

The stage of disease was assessed by means of the TNM classification of malignant tumours in only four reports.

The objective response rate was reported in 13 trials, and ranged between 0 and 50%. The range of the 95% confidence intervals (reported by the authors in three reports) was between 0 and 25%. We calculated the confidence limits on response rate for nine reports: the range was 0–77% (all the values are reported in Table 1).

Median survival ranged from 2.3 to 4.4 months in the eight groups of patients not receiving active treatment, and from 1.3 to 11 months in the groups of patients treated with active therapy. Three trials [19, 31, 34] demonstrated a statistically significant difference in survival between the two treatment arms.

The first was a phase III comparison trial of two chemotherapy regimens: streptozotocin, mitomycin, 5-fluorouracil (SMF) versus cisplatin, cytosine arabinoside, caffein. The endpoint of this study was the proportion of patients experiencing a response; 40

Table 1. *Continued*

Reference	Year	Histology*	Treatments	No. of patients	Median age (years)	PS	R Ev	% OR	95% CI	Median survival (months)	*P*
23	1990	?	FAM	14	?	0–1	14	50	23–77†	6.1	
			FAM + AG	14	?	0–1	14	43	17–71†	4.3	
24	1989	Yes	TAM	37	65‡	100–<50				5.3	
			Cyproterone	32	63‡	100–<50				4.3	
			No treatment	39	64‡	100–<50				3	
25	1986	Yes	FAM	30	61	0–3	30	13	4–31†	2.9	
			SMF	48	57	0–3	48	15	6–28†	4.4	
			SMF(5)	40	61	0–3	40	14	5–28†	3.3	
26	1986	Yes	FAM	90	D	0–3	65	14	7–25	6.5	
			SMF	94	D	0–3	68	4	1–12	4.5	
27	1985	Yes	5FU	50	D	0–1	20	30	7–65†		
			FA	44	D	0–1	23	30	7–65†	5.5	
			FAM	50	D	0–1	26	8	0–36†		
28	1983	Yes	FCV	25	60	100–70				5	
			No treatment	22	61	100–70				4	
29	1983	Yes	SMF	72	59	0–3	56	34	21–47†	4.5	
			MF	73	61	0–3	60	8	3–19†	4.3	
30	1981	Yes	Melphalan	43	?	0–1	43	2	0–13	2	
			FC	41	?	0–1	41	10	3–23	3.5	
			FCS	43	?	0–1	43	7	2–19	3	
31	1981	?	FA	21	?	100–60	14	30	8–58†	7	< 0.05
			BFA	21	?	100–60	14	7	0–34†	4.5	
32	1981	Yes	FC	65	D	?				3	
			No treatment	87	D	?				3.9	
33	1981	Yes	FB	20	?	?				3.3	
			Placebo	20	?	?				3.5	
34	1980	Y/N	CMF + FM	21	63	?				11	< 0.00006
			No treatment	19	66	?				2.3	

* Histologically or cytologically proven pancreatic carcinoma. † Calculated from the text. ‡ Mean.
Y/N, not available for all patients; PS, performance status; R Ev, No. of patients in which response was evaluated; OR, objective response; CI, confidence intervals; g.r., good risk; p.r., poor risk; D, expressed differently. FAM, 5-fluorouracil (5-FU) + doxorubicin + mitomycin C; FAM-S, FAM + streptozotocin; MGBG, methyl-glyoxal-bis-guanylhydrazone; DHAD, dihydroxanthracenedione; AZQ, aziridinyl-benzoquinone; TAM, tamoxifen; FEM, 5-FU + epirubicin + mitomycin-C; LH-RH, goserelin; CAC, cisplatin + cytosine arabinoside + caffeine; SMF, streptozotocin + mitomycin C + 5-FU; CMFV-FM, (cyclophosphamide + methotrexate + 5-FU + vincristine) + (5-FU + mitomycin C); FAP, 5-FU + doxorubicin + cisplatin; AG, aminoglutethimide; FA, 5-FU + doxorubicin; FCV, 5-FU + CCNU + vincristine; MF, mitomycin C + 5-FU; FC, 5-FU + methylCCNU; FCS, FC + streptozotocin; FA, 5-FU + doxorubicin; BFA, 5-FU + doxorubicin + ftorafur; FB, 5-FU + BCNU; RT, radiation; MFL, methotrexate + 5-FU + leucovorin; RT + A, radiation + doxorubicin; IORT, intra-operative radiation therapy.

patients per arm were recruited to detect a difference of 25% (between 15 and 40%) with greater than 80% power. A low response rate was reported in this study, which was not significantly different in the two arms; however, a statistically significant increase in survival was observed in the SMF arm.

The second trial was a phase III study of doxorubicin and 5-fluorouracil versus BCNU, doxorubicin, ftorafur. 51 patients entered the study; 21 patients per arm were evaluated, 6 died early and 3 were considered unevaluable; 14 patients per arm had measurable disease. The response rate was not significantly different in the two arms, while survival was better in the doxorubicin + 5-fluorouracil arm.

The third trial was a multicentre trial comparing multiple chemotherapy (5-fluorouracil, cyclophosphamide, methotrexate, vincristine followed by 5-fluorouracil and mitomycin) versus no treatment. Survival of 21 and 19 accrued patients was evaluated and compared, with a significant advantage in the group actively treated.

The impact of treatment on patient's quality of life was mentioned only in four papers, and was evaluated by means of Karnofsky index and Hospital Anxiety and Depression Scale questionnaire [15]; gain in body weight, Zubrod performance status score, and improvement in subjective symptoms [27]; Karnofsky performance status score [28]; rate of weight loss, hospitalisation time and need for analgesics [33]. No difference in quality of life was found between the treatment arms in any of the three papers.

Only in one trial [34] was the administration of chemotherapy to pancreatic cancer patients recommended. 5-fluorouracil alone, and 5-fluorouracil and doxorubicin were mentioned as the possible treatment of choice in two papers [27, 31].

In all other trials, the authors stated that they would not recommend the combination tested in their own trial as standard treatment, and/or that newer approaches were needed. More than 1800 patients were enrolled in these studies of advanced disease, and they were treated with 27 different regimens

Table 2. Randomised trials of radio/chemotherapy

Reference	Year	Histology	Treatments	No. of patients	Median age (years)	PS	Median survival	*P*
35	1992	?	IORT	15	?	?	4.8	0.05
			IORT + MFL	17	?	?	8.5	
36	1988	Yes	SMF	21	60	0–2	8	< 0.02
			FU +RT + SMF	22	61	0–2	10.5	
37	1985	Yes	RT + A	70	62	0–2	8.3	
			RT + FU	73	62	0–2	9.3	
38	1985	Yes	FU	Total 91	?	0–2	8.2	
			FU + RT + FU		?	0–2	8.3	
39	1981	Yes	RT(60 Gy)	25	54	0–3	5.8	< 0.01
			RT + FU(40 Gy)	83	61	0–3	10.5	< 0.01
			RT + FU(60 Gy)	86	60	0–3	10	
40	1980	Yes	RT + CCNU + FU	Total 62	?	0–4	9.5	
			RT + CCNU + FU+ testolactone		?	0–4	7.5	

See Table 1 legend for abbreviations.

(without considering the modification of a given regimen as a different regimen), in 48 experimental arms. Almost 350 patients were assigned to no treatment or placebo arms. The most frequently used regimens were streptozotocin, mitomycin C and 5-fluorouracil (297 patients in four trials [19, 25, 26, 29]) and 5-fluorouracil, doxorubicin and mitomycin C (198 patients in four trials [23, 25–27]). Neither regimen was compared with an untreated control group in any of these trials. Only in nine of the 27 trials was an untreated control group used [15, 17, 18, 21, 24, 28, 32–34]. One of these trials [34], based on a total of 40 patients, showed a significantly better survival in treated patients, with a median survival of 44 weeks in the treated group and of 9 weeks in the control group. No trial of the same combination was reported in the following 10 years. In 1990, a three-arm study [22] comparing this combination with a three-drug and a single-drug regimen, but not with a no-treatment arm, purportedly failed to confirm the results of the original trial (respectively, 61, 59 and 64 patients were enrolled).

In the other nine trials with an untreated control group, five [15, 17, 18, 21, 24] used different hormonal treatments and four [28, 32–34] used different multidrug regimens. No significant difference in median survival was observed in any of these studies.

Clinical information from trials of radio/chemotherapy

The median survival for patients treated with radio/chemotherapy was between 4.8 and 10.5 months. These patients had generally localised disease not amenable to radical surgery. Two of six studies [36, 39] demonstrated a statistically significant difference in survival for patients treated with a combined modality (chemotherapy and radiotherapy) versus a single modality (chemotherapy alone or radiotherapy alone).

The impact of the treatment on the quality of life was never reported.

Although these studies provide some evidence of a therapeutic gain in the treatment of locally unresectable pancreatic carcinoma, the gain was not considered substantial by different authors. The combination of intra-operative radiotherapy (IORT) and methotrexate, 5-fluorouracil, leucovorin was mentioned as a possible treatment of choice in one paper [35]; this was a trial of patients with clinical TNM stage III or IV cancer randomised to receive IORT or IORT and chemotherapy (methotrexate, 5-fluorouracil, leucovorin). Respectively, 15 and 17 patients were recruited. Survival and hospital-free survival were significantly increased in the combination arm of treatment.

Only in one report [36] was the combined modality therapy considered to be superior to either optimal radiotherapy or chemotherapy alone and of substantial benefit for individual patients. 565 patients were enrolled in these studies of inoperable disease, and were treated with 13 different experimental arms. None of these regimens was compared with an untreated control group.

Statistical content of all 27 reports

The objective of the study was sufficiently described both in papers and in abstracts. The primary end-point was response rate in four trials [14, 19, 25, 30] and survival in the other 23, but in almost all evaluations of both response rate and survival were reported.

All trials were randomised. How randomisation was performed was specified only in three cases (11% of all trials): in two studies by means of a central office and in one by means of sealed sequentially numbered envelopes.

Beta error and expected rate for both arms of trials was specified only in five papers (19% of all trials).

The expected sample size was specified only in five trials. In one trial [36], it was clearly stated that because of no further funding, the accrual was interrupted. In a second trial [32], no justification was provided for accruing only a part of the projected number of patients. Only in two trials [19, 24] did the accrued sample size equal the projected sample size.

After randomisation, the percentage of patients not evaluated in the final analysis was between 0 and 15% in 10 trials (37% of all trials) and ≥ 15% in six trials (22% of all trials). Only in 11/27 (41%) trials were all randomised patients evaluated. Reasons for excluding patients from the final analysis were incorrect histology, uncertain staging, ineligibility not adequately specified, patient refusal, follow-up too short protocol violation, lost to follow-up, treatment not administered, early death.

Accrual duration was specified in 12/27 reports (44%). Response rates were evaluated in 13 reports, but only in eight (62%) were the criteria to evaluate responses specified. Authors

reported 95% confidence intervals of response rate in four of 13 reports. Progression-free interval was evaluated in five papers. The statistical methods employed to compute survival curves and to compare them were not specified in three reports.

The survival time was calculated from time of diagnosis in two trials, from time of randomisation in six trials, from protocol entry in one and was not specified in 18. In two papers, survival was compared in responders and non-responders to chemotherapy. In one of these, the difference in survival rate was statistically significant (the statistical methodology was not described), in the other it was not (the Mantel–Byar method was adopted).

Institutional review board or ethical committee approval was mentioned in five papers, while in 11 it was said that patients had given an informed consent meeting federal or institutional requirements.

DISCUSSION

Pancreatic cancer is among the five leading causes of cancer death in most western countries, and is a highly lethal disease [41]; as most patients have advanced disease at diagnosis, there is a pressing need to identify the appropriate therapeutic strategies.

Currently, the evaluation of medical treatments in solid tumours rests on two steps [42]. First, the activity of a drug (or a combination of drugs) is assessed in patients with advanced and measurable disease. Then treatments showing promising activity in advanced disease are tested for efficacy (ability to prolong survival) in phase III trials, usually in the adjuvant setting. The successes obtained by means of this research strategy cannot conceal the fact that a large proportion of cancer patients are metastatic at diagnosis or relapse with metastatic disease at some time following surgery. Management of these patients cannot be based on the results of phase II trials, due to their intrinsic limitations (limited sample size, lack of a control group, highly selected patient population). Surprisingly, few randomised trials are carried out in patients with advanced disease and, from a methodological viewpoint, many of these trials are far from satisfactory. This picture contrasts with the high methodological standards which have become common practice in trials of adjuvant therapy.

Our review was based on 27 randomised trials published during the last decade. It indicates that the evidence collected so far is of very little use for the identification of the appropriate management of the patient with metastatic or locally unresectable cancer of the pancreas. Yet, our review suggests that chemotherapy may be of some use in this disease, but no definitive conclusion can be drawn from the results of these studies.

Besides obvious considerations concerning the inaccurate reporting of the clinical characteristics of the patients and, particularly, the insufficient number of patients enrolled in most studies [43], two aspects deserve further discussion: the treatments chosen for comparison and the selection of the study end-points.

It has long been stated that treatments of unproven efficacy should be administered within clinical trials. Unless extraordinarily promising results are obtained in uncontrolled studies, the efficacy of new treatments in a disease for which no standard treatment exists, should be tested in randomised studies with an untreated control group. Once a treatment has proved effective, it becomes the standard and new approaches (new drugs or combined treatments) are tested against it.

However, our review shows that the current situation seems extremely confused, and suggests a lack of any rationale strategy for the development and testing of hypotheses.

As a consequence of this erratic research path, it is impossible to establish whether or not chemotherapy or hormonal therapy can modify survival or progression-free survival in patients with advanced and unresectable pancreatic cancer. It is reasonable to assume that if it does, survival prolongation is likely to be very limited. Moreover, no meta-analysis is possible since it would involve combining the results of trials of very different treatment programmes.

Furthermore, few trials evaluated the impact of medical treatment on patients' quality of life, and those that did provide only scanty results. The conclusion reported in one of these trials was that the Karnofsky score is not sensitive for subtle changes [28]. In another paper [15], no significant difference in quality of life between the two treatment arms (tamoxifen and placebo) was seen.

Other review papers [3–9] published from 1985 up to now, emphasised that continuing research is needed, and that patients should be treated only within controlled clinical trials. In those papers, however, no mention was ever made on the quality of the reviewed randomised trials. Thus, three conclusions are possible from this review: (1) No medical treatment can be considered as standard therapy in advanced or locally unresectable pancreatic carcinoma, and no patients should receive any of these treatments outside clinical trials. (2) Future studies should focus on phase II screening with new drugs or new combinations supported by a strong biological rationale, and on the development of a valid, and acceptable tool for evaluating quality of life in such patients. (3) Until a medical treatment has been clearly shown to increase survival or to ameliorate the quality of life of these patients, future randomised studies in advanced pancreatic cancer of treatments with proven activity should always include an untreated control group.

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