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Cytotoxic Chemotherapy for Pancreatic Cancer

Advances to Date and Future Directions

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Abstract

Chemotherapy remains the mainstay of treatment for pancreatic cancer as most patients present with advanced disease, which precludes locoregional treatment. However, the efficacy of chemotherapy is limited. Gemcitabine is the only agent that improves symptoms and confers a modest survival advantage. Many combination therapy regimens have been studied in phase II settings. Eleven randomised phase III trials have been conducted to compare gemcitabine-containing regimens with gemcitabine monotherapy since gemcitabine became available clinically. The combination of gemcitabine plus capecitabine has demonstrated a survival advantage over gemcitabine, whereas gemcitabine plus oxaliplatin and gemcitabine plus cisplatin have shown improved progression-free survival or time to tumour progression but failed to demonstrate a survival advantage over gemcitabine. The search for effective therapy for advanced pancreatic cancer continues. Gemcitabine in combination with cytotoxic agents or molecular targeted agents hold promise.

Pancreatic cancer remains a devastating health problem. It is the fourth leading cause of cancer death in the US. An estimated 32 000 new cases of pancreatic cancer were diagnosed in 2005 and most patients diagnosed will die of the disease.[1] Cure is rare, even in patients who undergo complete surgical resection. Neoadjuvant and adjuvant therapies to improve surgical outcomes have been studied, and recent data indicate that adjuvant chemotherapy improves overall survival in patients who have undergone surgical resection. Chemoradiation provides palliative care for locally advanced pancreatic cancer. Chemotherapy remains the mainstay of treatment for pancreatic cancer as most patients present with advanced disease, which precludes locoregional treatment. However, the efficacy of chemotherapy is limited. Gemcitabine is the only agent that improves symptoms and confers a modest survival advantage. Gemcitabine in combination with other cytotoxic agents is being actively studied. Recent advances in molecular biology have allowed a detailed understanding of pancreatic tumourigenesis and may now present a novel approach to its treatment. This article discusses recent advances in cytotoxic chemotherapy for advanced pancreatic cancer.

Table I. Trials of single agents in advanced pancreatic cancer

Study	Agents	Response rate (%)	Stable disease rate (%)	Median survival (mo)
Stevenson et al. 1998[2]	Topotecan	2/26[a] (7.7)	3/26[b] (11.5)	4.7
O'Reilly et al. 1996[3]	Topotecan	0/27 (0)	NA	4.1
Scher et al. 1996[4]	Topotecan	3/30 (10)	11/30 (36.7)	4.4
Wagener et al. 1995[5]	Irinotecan	3/34 (8.8)	13/34 (38.2)	5.2
Sakata et al. 1994[6]	Irinotecan	4/35 (11.4)	NA	
Wils et al. 1993[7]	Cisplatin	7/33 (21.2)	NA	NA
Ducreux et al. 2004[8]	Oxaliplatin	0/15 (0)	2/17 (11.8)	3.4
Loehrer et al. 1985[9]	Ifosfamide	3/27 (11.1)	5/27 (18.5)	6
Ajani et al. 1988[10]	Ifosfamide	2/31 (6.5)		3
Wils et al. 1985[11]	Epirubicin	8/34 (23.5)	9/34 (26.5)	5
Aoki et al. 1992[12]	Epirubicin	0/14 (0)	3/14 (21.4)	NA
Halford et al. 2001[13]	Doxil	0/16 (0)	6/16 (37.5)	3.2
Lenzi et al. 2002[14]	Docetaxel	1/21 (4.8)	7/21 (33.3)	5.9
Rougier et al. 2000[15]	Docetaxel	6/40 (15)	15/40 (37.5)	NA
Androulakis et al. 1999[16]	Docetaxel	6/33 (18.2)	19/33 (57.6)	8.4
Whitehead et al. 1997[17]	Paclitaxel	3/39 (7.7)	5/39 (12.8)	5
Miller et al. 1999[18]	Pemetrexed	2/35 (5.7)	17/35 (48.6)	6.5
Cartwright et al. 2002[19]	Capecitabine	4/42 (9.5)	17/42 (40.5)	6.1
Casper et al. 2002[20]	Gemcitabine	5/44 (11.4)	14/44 (31.8)	5.6
Carmichael et al. 1996[21]	Gemcitabine	2/32 (6.3)	6/32 (18.8)	6.3

a Number of patients whose disease responded to treatment/total number of evaluable patients.

b Number of patients with stable disease/total number of evaluable patients.

NA = data not available.

1. Single-Agent Chemotherapy for Advanced Pancreatic Cancer

Chemotherapy has limited efficacy in pancreatic cancer. Many cytotoxic agents that are active against a variety of human cancers have undergone trials in pancreatic cancer (table I).[2-21] Most of them have demonstrated little or no activity against pancreatic cancer in phase II studies in which the response rate was the primary endpoint. Several anthracyclines that have been successfully used to treat breast cancer and other human malignancies have demonstrated essentially no activity against pancreatic cancer.[11-13] Docetaxel and paclitaxel are active against breast, ovary and lung cancers, but show only modest activity against pancreatic cancer and a wide range of activity was reported across trials.[14-17] Studies of camptothecans have also produced disappointing results.[2-5] Ifosfamide showed moderate activity against pancreatic cancer in an initial trial but not in a subsequent trial.[9,10] Platinum compounds, such as cisplatin and oxaliplatin, are frequently used in combination with other cytotoxic agents, but as single agents their cytotoxic activity in pancreatic cancer is marginal to moderate.[7,8]

Before gemcitabine became clinically available, fluorouracil was frequently used to treat pancreatic cancer, and early studies showed a significant response to it. However, more recent studies using a more accurate assessment of objective response showed that fluorouracil was only marginally active. Recent studies of pemetrexed have demonstrated its activity against mesothelioma but only a modest activity against pancreatic cancer.[18] Several other

cytotoxic agents such as rubitecan (9-NC) and exatecan (DX8951F) have been extensively investigated in pancreatic cancer, but none has proved to be superior to gemcitabine. Rubitecan, an oral inhibitor of topoisomerase I that belongs to the camptothecin class showed modest activity against pancreatic cancer in phase II trials.[22-24] A randomised phase III trial that compared the effect of rubitecan with the best choice of therapy in 409 patients with refractory pancreatic cancer showed no survival advantage with rubitecan treatment (108 days vs 94 days, $p = 0.626$). However, interestingly, it did show a significant survival advantage for crossover from best choice of therapy to rubitecan (147 days vs 60 days, $p < 0.0001$).[25]

Another topoisomerase inhibitor, exatecan, demonstrated modest efficacy in a phase II trial in which the response rate was 5% (2/39 patients, 20 of whom received one prior therapy) and the median survival was 5.5 months.[26] A randomised phase III trial of exatecan versus gemcitabine in 339 patients with advanced pancreatic cancer showed no increased efficacy in terms of median survival (5 months vs 6.6 months).[27] Both exatecan and rubitecan have demonstrated encouraging activity in phase II trials, but this has not been substantiated in phase III trials.

Gemcitabine is a deoxycytidine analogue that is metabolised to a triphosphate that inhibits DNA and RNA synthesis. An initial phase II trial of gemcitabine in advanced pancreatic cancer demonstrated only modest activity, with an overall objective response rate of 11% and a median survival of 5.6 months.[20] Despite the limited objective response, investigators noticed a clear improvement in the symptoms of many patients without a radiographic tumour response. To evaluate this observation, a phase II trial was conducted in patients with fluorouracil-refractory pancreatic cancer, with the alleviation of cancer-related symptoms (termed a 'clinical benefit response') as the primary endpoint.[28] Clinical benefit response was defined as a ≥50% reduction in pain intensity, a ≥50% reduction in daily analgesic consumption or a ≥20 point improvement in the Karnofsky performance score, which was sustained for ≥4 consecutive weeks. Clinical benefit response was observed in 27% of patients in this trial. Another phase II trial of gemcitabine in chemotherapy-naive patients with advanced pancreatic cancer demonstrated an overall tumour response rate of 6.3% and a median survival of 6.3 months.[21] These encouraging results led to a randomised trial comparing gemcitabine with fluorouracil in terms of clinical benefit response, objective tumour response and survival.[29] In this study, gemcitabine produced a better clinical benefit response rate (23.8% vs 4.8%) and a better median survival (5.7 vs 4.4 months). This trial thus established the role of gemcitabine in the control of tumour-related symptoms in patients with pancreatic cancer and led the US FDA to recommend it as first-line therapy for advanced pancreatic cancer.

Gemcitabine is commonly administered as a 30-minute infusion; however, pharmacological studies have demonstrated that the accumulation of gemcitabine triphosphate is saturable and that gemcitabine is more effectively metabolised to gemcitabine triphosphate when administered at a fixed-dose rate of 10 mg/m^2/minute.[30] A randomised phase II trial compared gemcitabine administered as a 30-minute infusion with gemcitabine administered using a fixed-dose rate and showed that the median survival of patients who received fixed-dose rate gemcitabine was better than that of patients who received the 30-minute infusion (8 vs 5 months, $p = 0.013$).

Gemcitabine represents a great success in cancer drug development for several reasons. First, gemcitabine addressed a great medical need in advanced pancreatic cancer, namely, alleviation of the debilitating symptoms caused by pancreatic cancer including cachexia, intractable pain, severe fatigue

and anorexia.[21] Secondly, the investigators observed that the clinical benefit conferred by gemcitabine might not necessarily depend on the objective tumour response. Thirdly, the investigators carefully designed a phase III clinical trial to study the observed clinical benefit scientifically using the clinical benefit response as the primary endpoint. The fact that gemcitabine produced a clinical benefit response without producing a significant tumour response underscores the limitations of using the traditional tumour response as a common surrogate for treatment efficacy. Many subsequent clinical trials in advanced pancreatic cancer have adopted the clinical benefit response as one of their secondary endpoints, although variations in its definition between trials and the frequent lack of a run-in phase make the interpretation and comparison of results difficult.

2. Combination Chemotherapy for Pancreatic Cancer

Combination chemotherapy has been demonstrated to be more effective than monotherapy for the treatment of many solid tumours. Many combination regimens for the treatment of advanced pancreatic cancer were tested before gemcitabine became available, but none demonstrated superiority over fluorouracil alone. These regimens included fluorouracil, doxorubicin and mitomycin (FAM); streptozotocin, mitomycin and fluorouracil (SMF); fluorouracil, doxorubicin and cisplatin (FP); and the Mallinson regimen (fluorouracil, cyclophosphamide, methotrexate, vincristine and mitomycin).[31]

Since the introduction of gemcitabine, investigators have tested it in combination with other cytotoxic agents in pancreatic cancer. A long list of gemcitabine-containing regimens has been investigated and is summarised in table II.[32-66] Several of these combination regimens warrant special mention. A combination of gemcitabine with oxaliplatin, which is active against several pancreatic cancer cell lines including some that are resistant to cisplatin, has shown supra-additive effects against human leukaemia and colon cancer cells. Administering gemcitabine first and oxaliplatin 24 hours later appears to be more active than the opposite sequence. A phase II trial of this combination demonstrated a median survival duration of 9.2 months and a 1-year survival rate of 36% in patients with advanced pancreatic cancer.[37] In this trial, gemcitabine was administered first, with a total dose of 1000 mg/m^2 delivered at a rate of 10 mg/m^2/minute on day 1, and then oxaliplatin was administered with a total dose of 100 mg/m^2 as a 2-hour infusion on day 2, with treatment every 2 weeks.

As a single agent, docetaxel demonstrates significant activity against pancreatic cancer xenografts, but only modest activity was demonstrated in clinical settings.[14-16] Several independent phase II trials of the combination of gemcitabine and docetaxel revealed moderate activity.[32-36] The combination of gemcitabine with fluorouracil administered using different schedules and with or without folinic acid (leucovorin) as a modulator has shown a wide range of activity.[49-57] The combination of cisplatin, epirubicin, fluorouracil and gemcitabine (PEFG) showed the most impressive activity, with a response rate of 58% (51% by intent-to-treat analysis), a median survival of 11 months and a 1-year survival of 39%.[45]

As shown in table II, many phase II trials have demonstrated encouraging activity of the various combination regimens containing gemcitabine, although the activity ranges widely between different regimens and between different trials of similar regimens. Therefore, the results of these phase II trials should be interpreted with caution since many factors other than the treatment may confound the outcomes. These confounding factors include patient selection bias, the inherently small sample size of phase II trials, the percentages of patients with

Table II. Phase II trials of gemcitabine-containing combination therapy regimens in advanced pancreatic cancer

Study	Regimen	No. of patients	RR (%)	SD (%)	TTP/PFS (mo)	Median survival (mo)	1-year survival (% patients)
Ryan et al. 2002[32]	Gemcitabine + docetaxel	34	18	39	3.8[a]	8.9	29
Stathopoulos et al. 2001[33]	Gemcitabine + docetaxel	54	13	33	7.5	6	30
Schneider et al. 2003[34]	Gemcitabine + docetaxel	40	27	35	4.2[a]	7	19.3
Shepard et al. 2004[35]	Gemcitabine + docetaxel	32	13		2.1[a]	4.7	NA
Jacobs et al. 2004[36]	Gemcitabine + docetaxel	33	30	36	6	10.5	41.2
Louvet et al. 2002[37]	Gemcitabine + oxaliplatin	64	31	36	5.3[a]	9.2	36
Alberts et al. 2004[38]	Gemcitabine + oxaliplatin	47	11		4.5	6.2	NA
Brodowicz et al. 2000[39]	Gemcitabine + cisplatin	16	31	44	7.4	9.6	75
Heinemann et al. 2000[40]	Gemcitabine + cisplatin	41	11	57	4.3	8.2	27
Philip et al. 2001[41]	Gemcitabine + cisplatin	42	28	38	5.4	7.1	19
Cascinu et al. 2003[42]	Gemcitabine + cisplatin	45	9	46	3.6	5.6	NA
El-Rayes et al. 2003[43]	Gemcitabine + cisplatin + fluorouracil	47	23	57	7.2	8.6	36
Novarino et al. 2004[44]	Gemcitabine + cisplatin+ fluorouracil	32	19	40	4.7[a]	9	26
Reni et al. 2001[45]	Cisplatin + epirubicin + fluorouracil + gemcitabine	43	58	33	7.5	11	39
Rocha Lima et al. 2002[46]	Gemcitabine + irinotecan (CPT-11)	45	20	36	2.8	5.7	27
Stathopoulos et al. 2003[47]	Gemcitabine + irinotecan	60	25	37	7	7	22.5
Oettle et al. 2000[48]	Gemcitabine + fluorouracil + folinic acid (leucovorin)	38	5	89	7.1	9.3	32
Louvet et al. 2001[49]	Gemcitabine + fluorouracil + folinic acid	62	23	23	4.8[a]	9	32.3
Correale et al. 2003[50]	Gemcitabine + fluorouracil + folinic acid	42	31	55	9.8	13.1	NA
Oztop et al. 2004[51]	Gemcitabine + fluorouracil + folinic acid	22	27			13	60.4
Andre et al. 2004[52]	Gemcitabine + fluorouracil + folinic acid	58	19	28	3.1[a]	7.2	NA
Marantz et al. 2001[53]	Gemcitabine + fluorouracil + folinic acid	29	21	55	4.5[a]	8.4	36
Berlin et al. 2000[54]	Gemcitabine + fluorouracil	36	14	17	2.4	4.4	8.6
Cascinu et al. 2000[55]	Gemcitabine + fluorouracil (bolus)	34	17	32	3.7	5.7	NA
Kurtz et al. 2000[56]	Gemcitabine + fluorouracil (portal vein infusion)	29	10	42	2.8[a]	4	NA
Rauch et al. 2001[57]	Gemcitabine + fluorouracil (continuous infusion)	25	20	25		6.3	27

Continued next page

Table II. Contd

Study	Regimen	No. of patients	RR (%)	SD (%)	TTP/PFS (mo)	Median survival (mo)	1-year survival (% patients)
Feliu et al. 2000[58]	Gemcitabine + tegafur/uracil	42	16	39	4	7	21
Feliu et al. 2002[59]	Gemcitabine + tegafur/uracil	43	33	30	6	11	32
Lee et al. 2004[60]	Gemcitabine + tegafur/uracil	22	23	18	4.2	5.8	NA
Kim et al. 2002[61]	Gemcitabine + tegafur/uracil + fluorouracil	30	17		3	7.2	20.1
Ianniello et al. 2001[62]	Gemcitabine + epirubicin	30	20	30	3.2	6	23
Neri et al. 2002[63]	Gemcitabine + epirubicin	44	25	41	4.1	10.9	34.8
Stathopoulos et al. 2004[64]	Gemcitabine + capecitabine	53	19	42	6.5	8	18
Tuinmann et al. 2004[65]	Gemcitabine + mitomycin	55	29	33	4.7	7.3	28
Xiros et al. 2005[66]	Gemcitabine + carboplatin	47	17	32	4.4	7.4	19

a PFS

NA = data not available; **PFS** = progression-free survival; **RR** = response rate; **TTP** = time to tumour progression.

locally advanced versus metastatic disease and the Karnofsky performance status.

Eleven randomised phase III trials have been conducted comparing gemcitabine-containing regimens with gemcitabine monotherapy during the last 5 years (table III).[46,67-76] Despite the impressive activity of gemcitabine plus fluorouracil in phase II trials, phase III trials of gemcitabine versus gemcitabine plus fluorouracil showed no improvement in overall survival or 1-year survival with the addition of fluorouracil.[67,68] A phase III trial of gemcitabine versus gemcitabine plus oxaliplatin (GEMOX) showed that GEMOX was superior to gemcitabine in terms of response rate, progression-free survival and clinical benefit.[71] However, the improvement of overall survival did not reach statistical significance. Similarly, when compared with gemcitabine alone in a randomised phase III trial, gemcitabine plus cisplatin (GEMCIS) significantly improved the median time to disease progression, but the improvement in the median survival was not statistically significant.[69]

Another phase III trial compared gemcitabine with PEFG using progression-free survival at 4 months as the primary endpoint.[72] Consistent with phase II observations, patients who received PEFG had better progression-free survival than those who received gemcitabine (60% [95% CI 46, 72] vs 28% [95% CI 17, 42]). The improvement in 1-year survival rate associated with PEFG was statistically significant, although the median overall survival seemed to be similar. Despite these encouraging results, the PEFG regimen has not been widely used in clinical practice because of concerns about the trial's small sample size and the potential toxicity of PEFG. Nevertheless, this regimen warrants further investigation, preferably in a larger patient population with overall survival or progression-free survival as the primary endpoint.

Two phase III trials that compared gemcitabine plus capecitabine (GEMCAP) with gemcitabine alone were conducted in Europe.[75,76] One of these studies,[75] conducted jointly by the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group, showed that GEM-

CAP does not improve the overall survival duration compared to the present standard of gemcitabine alone. However, a subgroup analysis revealed that patients with a good performance status (Karnofsky score 90–100%) who received the combined therapy had a significant improvement in the median overall survival duration. A similarly designed trial was conducted in the UK[76] in which a much larger patient population was enrolled. The study reported a statistically significant improvement in the overall survival duration (7.4 vs 6 months) in patients who received GEMCAP compared with those who received gemcitabine alone. This study, together with the previous trial, demonstrated that GEMCAP is an active regimen in pancreatic cancer, especially for patients with a good performance status. This is the first randomised phase III trial that demonstrated survival advantage of a combination regimen over gemcitabine alone, although two other regimens, GEMOX and GEMCIS, showed improved progression-free survival or time to tumour progression (table III).

Numerous phase II trials of gemcitabine-containing regimens and at least 11 randomised phase III trials (table III) have been conducted in patients with advanced pancreatic cancer, but the progress has been incremental and less than satisfactory. It is time to reassess our research strategies. It must be

Table III. Phase III trials of gemcitabine vs gemcitabine-containing combination therapy regimens in advanced pancreatic cancer

Study	Regimens	No. of patients	RR (%)	TTP/PFS (mo)	Median survival (mo)	1-year survival (%)
Berlin et al.[67] (2002)	Gemcitabine	162	5.6	2.2[a]	5.4	18
	Gemcitabine + fluorouracil	160	6.9	3.4[a]	6.7	18
Riess et al.[68] (2005)	Gemcitabine	236	7.2	3.5	6.2	22
	Gemcitabine + fluorouracil + folinic acid (leucovorin)	230	4.8	3.5	5.9	21
Heinemann et al.[69] (2003)	Gemcitabine	100	8	2.5	6	NA
	GEMCIS	98	10.2	4.6	7.6	
Rocha Lima et al.[46] (2002)	Gemcitabine	180	4.4	3	6.6	22
	Gemcitabine + irinotecan (CPT-11)	180	16.1	3.5	6.3	21
Stathopoulos et al.[70] (2005)	Gemcitabine	42	8.2	NA	NA	19.6
	Gemcitabine + irinotecan	50	12.8			24
Louvet et al.[71] (2005)	Gemcitabine	156	17.3	3.7[a]	7.1	27.8
	GEMOX	157	26.8	5.8[a]	9	34.7
Reni et al.[72] (2005)	Gemcitabine	47	8.5	3.3	NA	21.3
	PEFG	52	38.5	5.4		38.5
Oettle et al.[73] (2005)	Gemcitabine	282	7.1	3.3[a]	6.3	20
	Gemcitabine + pemetrexed	283	14.8	3.9[a]	6.2	21.4
O'Reilly et al.[74] (2004)	Gemcitabine	157	7.1	3.8	6.2	21
	Gemcitabine + exatecan	168	8.2	4.1	6.7	23
Herrmann et al.[75] (2005)	Gemcitabine	159	7.9	4	7.3	NA
	GEMCAP	160	10.1	4.8	8.4	
Cunningham et al.[76] (2005)	Gemcitabine	266	7	NA	6	19
	GEMCAP	267	14		7.4	26

a PFS

GEMCAP = gemcitabine plus capecitabine; **GEMCIS** = gemcitabine plus cisplatin; **GEMOX** = gemcitabine plus oxaliplatin; **NA** = data not available; **PEFG** = cisplatin, epirubicin, fluorouracil and gemcitabine; **PFS** = progression-free survival; **RR** = response rate; **TTP** = time to tumour progression.

remembered that gemcitabine was approved as a treatment for pancreatic cancer primarily on the basis of its ability to alleviate cancer-related symptoms (i.e. produce a clinical benefit response); it has only modest activity in terms of tumour response and prolonging survival. In pancreatic cancer, the activity of gemcitabine as a single agent is essentially no better than that of many other cytotoxic agents (see table I). Although it makes logical sense to combine gemcitabine, which remains the only cytotoxic agent approved for the treatment of pancreatic cancer, with a drug under investigation, one needs to remember that, as pharmacological studies of cancer drugs have shown, the combination of marginally active agents (i.e. ones with a response rate of <20%) often adds toxicity without improving efficacy. Lack of an effective single agent for pancreatic cancer may be the most important obstacle to significant progress.

Current trial designs also warrant reassessment. Tumor response rates have been frequently used as a surrogate for anticancer activity in phase II trials, but their usefulness in pancreatic cancer may be limited. Primary pancreatic cancer is associated with significant desmoplastic changes, which make accurate measurement of primary tumour mass essentially impossible. In addition, investigators are frequently challenged to distinguish between the unopacified duodenum and the head of the pancreas, which further hampers accurate tumour measurement. Furthermore, unlike most other human cancers, the tumour size or tumour burden of pancreatic cancers does not correlate closely with survival and clinical performance. It remains a mystery as to how patients with pancreatic cancer may die of a relatively small tumour burden.

The success of gemcitabine underscores the importance of using endpoints other than (or in addition to) tumour response in clinical trials. Symptom burden, clinical benefit response, time to tumour progression and 6-month or 1-year survival should be just as useful in designing phase II trials for advanced pancreatic cancer. Meanwhile, in phase III trials, overall survival remains the gold standard endpoint especially when there are no other treatment options, as in the case of advanced pancreatic cancer. Nevertheless, there are still a significant number of patients with advanced pancreatic cancer who receive other forms of therapy or who crossover to investigational therapies. These therapies are not generally considered to be highly effective, but they may be effective enough to impact on overall survival. For example, in the phase III trial reported by Louvet et al.,[71] >50% of patients in both treatment arms received second-line therapies, and >70% of these patients in the gemcitabine arm crossed over to the GEMOX arm. This may, in fact, account for their failure to demonstrate an overall survival advantage for GEMOX.

Most phase II and III studies enroll patients with both locally advanced and metastatic pancreatic cancers, and this may be another confounding factor. Patients with locally advanced pancreatic cancer (i.e. tumours that are confined to the pancreas but unresectable) make up a heterogeneous group of patients with a median survival of approximately 9–13 months. It is reasonable to include them in trials, and especially phase III trials, since their treatment options are also very limited. However, it is advisable to stratify patients by disease status (locally advanced vs metastatic) and performance status. Sample size is an important factor as well. In several studies, sample size was calculated based on the initial observation that patients who received gemcitabine had a median survival duration of 5.7 months.[29] It should be noted that, in that study, all patients had symptoms and thus poor survival was expected. Many subsequent trials, where asymptomatic patients were allowed, showed that the median survival duration was frequently over 6 months in gemcitabine-treated patients (table I). Therefore, sample size calculations based on the median sur-

vival duration of 5.7 months might result in an underestimate of the true efficacy of gemcitabine and thus an under-powered sample size. Two European trials of the same regimen (GEMCAP vs gemcitabine) were conducted; one showed a statistically significant improvement in overall survival with GEMCAP and the other did not. One of the differences between these two trials was sample size.

3. Future Directions

The prognosis of advanced pancreatic cancer remains extremely poor and the search for effective chemotherapy agents continues. As summarised in table I, most single agents, including gemcitabine, have only modest activity against pancreatic cancer. Although effort has been focused on the development of gemcitabine-containing regimens since gemcitabine became available more than 8 years ago, pancreatic cancer should remain a disease model for the investigation of monotherapy of novel cytotoxic agents.

S1 is a combination of three oral agents: tegafur, a prodrug of fluorouracil; 5-chloro-2, 4-dihydroxypyridine, an inhibitor of dihyropyrimidine dehydrogenease activity; and oteracil (potassium oxonate), an orotate phosphribosyltransferase inhibitor that reduces gastrointestinal toxicity. Theoretically, this combination should maximise the anti-tumour activity of fluorouracil (in this case, tegafur) by inhibiting dihyropyrimidine dehydrogenease through 5-chloro-2, 4-dihydroxypyridine, while at the same time minimising gastrointestinal toxicity via the activity of oteracil. In a recent phase II trial of S1 in patients with metastatic pancreatic cancer in Japan, the response rate was 37.5% and the median survival was 8.8 months.[77] In a phase II trial of S1 and gemcitabine that enrolled 28 patients with pancreatic cancer, the response rate was 50% and the median survival time was 8.8 months.[78] In the US, a phase II trial of S1 in patients with pancreatic cancer refractory to gemcitabine is ongoing.

Drugs such as paclitaxel and docetaxel that target microtubules have a broad spectrum of anti-tumour activity but no significant activity against pancreatic cancer (table I). One of the reasons may be the intrinsic expression of the drug efflux protein P-glycoprotein by pancreatic cancers. Many synthetic or semisynthetic taxane analogues have proved superior to taxanes in preclinical studies; some of these taxane analogues are, in fact, less susceptible to P-glycoprotein-mediated resistance. Most agents in this class are still in the early stages of clinical development. In a phase II trial of one such agent, ixabepilone (BMS-247550), in 60 patients with advanced pancreatic cancer, the response rate was 16% and the median survival was 6.9 months.[79] Whether the advantage of taxane analogues observed preclinically and their more tolerable formulation translates into clinical benefits warrants further investigation.

Despite the disappointing results obtained with GEMOX from a previous phase III trial (table III, efforts to develop this regimen continue. The Eastern Cooperative Oncology Group (ECOG) is sponsoring a randomised phase III trial comparing 30-minute gemcitabine infusion alone with fixed-dose gemcitabine and GEMOX. The results of this trial, which has just finished recruiting patients, are eagerly awaited. It will be interesting to see whether the ECOG trial demonstrates any overall survival advantage associated with the GEMOX regimen.

Many non-gemcitabine-containing regimens are under investigation as therapy for advanced pancreatic cancer. In a previous phase II trial, the combination of irinotecan and docetaxel produced a response rate of 24.2%, a stable disease rate of 39.4% and a median survival of 8.7 months.[80] This combination is now being investigated in a randomised phase II trial of therapy with versus without the addition of cetuximab. Several oxaliplatin-containing regimens

other than GEMOX are under clinical investigation. In a randomised phase II trial that compared oxaliplatin alone versus fluorouracil alone with oxaliplatin plus infusional fluorouracil, patients who received the combination had a response rate of 10%, progression-free survival of 4.9 months and overall survival of 9 months.[8] An ongoing phase II trial of oxaliplatin plus fluorouracil plus folinic acid (FOLFOX-6) had an impressive response rate of 32% (8 of 25 evaluable patients).[81] Another randomised phase II trial compared capecitabine plus oxaliplatin (CAPOX) with GEMCAP and GEMOX. The analysis of CAPOX versus GEMCAP versus GEMOX demonstrated response rates of 22%, 16% and 13%, progression-free survival of 4.2, 4.8 and 3 months and the median overall survival of 8.1, 7.6 and 8 months, respectively.[82] Encouraging results were observed with all three regimens. An ongoing phase II trial of irinotecan (CPT-11) plus oxaliplatin plus fluorouracil/folinic acid showed encouraging activity against pancreatic cancer.[83]

Although this article is focused on the discussion of cytotoxic chemotherapy, it is worthwhile to mention the recent developments of molecular-targeted agents for the treatment of pancreatic cancer. The development, continued growth and metastasis of pancreatic cancer are driven by multiple genetic and epigenetic changes, including inactivation of tumour suppressor genes and activation of proto-oncogenes. A key event is the overexpression or activation of the epidermal growth factor receptor and its downstream signaling molecules. Two approaches have been developed that target the epidermal growth factor receptor: small molecule tyrosine kinase inhibitors, such as erlotinib, and monoclonal antibodies, such as cetuximab. A randomised, placebo-controlled phase III trial compared the combination of gemcitabine plus erlotinib with gemcitabine plus placebo in patients with advanced pancreatic caner.[84] This study found that patients who received erlotinib had an improved median survival of 6.4 months compared with those who received a placebo (5.9 months). The improvement is small but statistically significant. In addition, the 1-year survival rate improved from 19% to 24% and progression-free survival improved from 3.5 to 3.8 months. On the basis of the incremental improvement in survival gained with the addition of erlotinib, the drug is now indicated for the first-line treatment of advanced pancreatic cancer. It is a welcome addition for patients whose treatment options remain very limited. However, one has to remember that the improvement was disappointingly small.

Cetuximab in combination with gemcitabine showed promising activity against pancreatic cancer in a phase II trial.[85] An ongoing phase III trial that compares gemcitabine plus cetuximab with gemcitabine alone is rapidly recruiting patients. Bevacizumab in combination with gemcitabine has shown significant activity in metastatic pancreatic cancer.[86] A similarly designed trial that compares gemcitabine plus bevacizumab with gemcitabine alone is ongoing. These studies will define the usefulness of cetuximab and bevacizumab in patients with advanced pancreatic cancer. Their results should be available in the near future.

4. Conclusion

Pancreatic cancer remains a great medical challenge. Its deadly nature and rising incidence call for greater efforts to combat it. Gemcitabine was the first cytotoxic agent to demonstrate modest activity against pancreatic cancer 8 years ago. Since then, many gemcitabine-containing regimens have been investigated. Recent studies have demonstrated that the GEMCAP regimen confers a survival advantage over gemcitabine alone. Two other regimens, GEMCIS and GEMOX, showed improvement in progression-free survival or time to tumour progression and their effects in prolonging overall survival warrant further investigation.

Meanwhile, tremendous progress has been made in understanding the molecular biology of human malignancies, including pancreatic cancer, and has led to novel therapeutic approaches. Erlotinib in combination with gemcitabine has shown a small but statistically significant survival advantage over gemcitabine. The ongoing phase III trials will define the clinical usefulness of other molecular targeted agents in pancreatic cancer, such as cetuximab and bevacizumab in the near future.

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