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REVIEW ARTICLE

Efficacy of systemic therapy in advanced pancreatic carcinoma

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Abstract

With a worldwide incidence of more than 200 000 cases and almost as many deaths, pancreatic carcinoma (PC) remains one of the leading causes of cancer deaths, especially in the Western world. Due to the late onset of symptoms, almost all patients suffer from disseminated disease at the time of diagnosis and only a minority will ever be candidates for radical surgery. Only about one tenth of the operated patients remain disease free. For these reasons, development of effective palliative systemic therapy is important. Almost a decade ago, gemcitabine replaced 5-Fu as the gold standard in systemic treatment of advanced PC. Since then, a number of trials have investigated the potential additional effect of several cytotoxic or targeted agents in combination with gemcitabine. As shown in this review, nearly all these trials have proved disappointing. This review provides an overview of the results of current phase III trials of gemcitabine based systemic therapy. Furthermore, we discuss the role of systemic therapy compared to BSC only and the potential future role of targeted therapies.

Survival in patients with infiltrating ductal adenocarcinoma of the pancreas (PC) is limited [1]. The majority of patients have metastases or locally advanced disease at diagnosis rendering them unsuitable for potentially curative resections [2]. This fact, as well as the relative ineffectiveness of existing treatments for localized disease, implies that most patients will be considered for systemic therapy. For many years, 5-Fu was considered the most active chemotherapeutic agent for systemic treatment in patients with advanced PC. Currently, gemcitabine has taken the role as the drug of choice and it is, despite its limited activity, considered gold standard for the control arm in the evaluation of new therapies. This far, combination chemotherapy has not proven more efficacious than single drug therapy. This fact has increased the interest for alternative therapeutic strategies, e.g. targeted therapies. The relative inefficacy of systemic therapy has also raised the question whether patients with advanced PC still should be recommended best supportive care (BSC) only. An overview of systemic chemotherapy in pancreatic cancer of all stages was performed by the Swedish Council of Technology Assessment in Health Care (SBU) in 2001 [3]. Herein, we present an update of the current status on and the indication for systemic therapy for advanced PC.

Material and results

A Medline search of all published phase III- and selective phase II trials of systemic therapy in advanced pancreatic carcinoma until June 2005 was undertaken with the headings: "chemotherapy", "targeted therapy", "novel therapy" and "pancreas/pancreatic cancer/carcinoma/neoplasm". We have also included abstracts presented at ASCO Annual Meetings 2002–2005 and ASCO Gastrointestinal symposium 2005. We have focused on studies comparing gemcitabine as standard treatment with gemcitabine and one or several other additional agents in the experimental arms.

Historical background

The efficacy of 5-Fu based chemotherapy in PC in terms of improvement of quality of life and survival

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compared to BSC only has been tested in six studies [4–9]. Patients treated with chemotherapy had better improvement in QOL (EORTC quality of life questionaire QLQ-C30 scale) [7]. Three of the studies, mainly the more recent ones, detected an increase of overall survival in excess of 3 months among treated patients compared to the controls [7–9]. Three small, older (>20 yrs) trials failed, however, to detect a survival advantage for active treatment [4–6]. Worth mentioning is that the latter studies used drugs that are no longer in use, e.g. CCNU, BCNU and orally administered 5-Fu. 5-Fu should not be given orally because of the presence of high levels of the degrading enzyme DPD in the gut mucosa, which leads to low bioavailability. However, when all reported studies on treatment vs. BSC are considered, as was done by Fung et al. [10], a beneficial effect in term of survival (6.4 vs. 3.9 moths, $p < 0.0001$) is still evident among patients treated with chemotherapy.

It is beyond the scope of this review to discuss the numerous tested 5-Fu based multichemotherapy treatments in detail. In summary, past controlled studies have not confirmed any superiority of combination chemotherapy compared to bolus 5-Fu only [11,12]. Furthermore, neither alternate schedules, e.g. infusion regimens, nor 5-Fu modulation, e.g. with interferon, methotrexate, or leucovorin, have led to increased efficacy in advanced PC [13–17].

Gemcitabine, single drug

Gemcitabine is a nucleoside analogue with broad antitumor activity including pancreatic adenocarcinoma. In a phase III trial of 129 patients, Burris et al. [18] showed a small but significant improvement in median survival (5.7 vs. 4.4 months) as well as one year survival (18 vs. 2%) in patients treated with gemcitabine as compared to 5-Fu. It is noteworthy, as pointed out in the previous overview by SBU, that 5-Fu in this study was administered as a 30 min infusion and not as a true bolus injection. This way of administrating 5-Fu may be less active because of rapid degradation of the drug, thus influencing the result of the study in favor of gemcitabine [3]. As a result of this trial, and a few earlier phase II trials which showed improvements in important clinical parameters such as weight gain, pain reduction and performance status [19,20], gemcitabine was further investigated in a treatment investigational new drug program by Storniolo et al. [21]. In this program a total of 3023 patients with advanced PC were treated. A retrospective analysis of 2380 of the enrolled patients found symptomatic improvements as well as reasonable response rates in terms of median survival (4.8 months) and one year survival (15%). Based on these studies, gemcitabine was approved for treatment of patients with advanced PC in 1995.

In the above-described study by Burris et al. [18], gemcitabine was administrated as a 30-min intravenous bolus injection of 1000 mg/m^2 weekly for 7 of 8 weeks as induction and then weekly for 3 of 4 weeks. This 30-minute infusion schedule has become the standard of administration. A phase II trial comparing the conventional schedule to a fixed dose rate regimen (10 mg/m^2/min) has suggested an improvement in median survival and one year survival in favor of the latter schedule [22]. A phase III trial is currently ongoing to confirm these findings (ECOG-6201). A recent example of the activity of gemcitabine in the treatment of PC is the phase III trial by Neuhaus and colleagues comparing 6 months of standard schedule gemcitabine as adjuvant treatment after radical surgery to observation alone [23]. The latest survival data was presented at ASCO 2005 and showed a significant increase in disease-free survival in favor of treatment (14.2 vs. 7.5 months, $p = <0.001$).

Gemcitabine based combination chemotherapy

Cytotoxic agents. An overview is found in Table I. Two studies have compared gemcitabine to a combination of gemcitabine and cisplatin [24,25]. Colucci and colleagues compared gemcitabine given as a 30-minute bolus injection at a dose of 1000 mg/m^2 (i.e. standard schedule) to bolus gemcitabine plus cisplatin given at a dose of 25 mg/m^2 on day 1 and 22. There was no difference in median survival. The median time to disease progression, however, was 8 weeks in the gemcitabine arm and 20 weeks in the combination arm ($p = 0.048$) [24].

In a larger study, Heinemann and co-workers compared bolus gemcitabine to a combination of bolus gemcitabine and cisplatin given at a dose of 50 mg/m^2 on day 1, 8 and 15 of a 28-day cycle. Again, there was no difference in median survival. Progression free survival was clearly superior for the combination therapy (5.4 vs. 2.8 months, $p < 0.001$) [25]. Berlin et al. investigated the potential additional effect of 5-Fu when combined with gemcitabine [26]. One hundred and sixty-three patients were randomized to receive bolus gemcitabine and 164 patients were treated with gemcitabine 1000 mg/m^2 plus 5- Fu 600 mg/m^2 on day 1, 8, 15 of a 28-day cycle. Median survival was 5.4 months in the gemcitabine arm and 6.7 months in the combination arm ($p = 0.09$). The retrospective analysis of the results suggested that the difference in OS may have reached the level of significance in favor of the combination arm had patients been stratified by

Table I. Results of randomized phase III studies of gemcitabine combinations in advanced pancreatic cancer.

Study	regimen	no pats	survival (months)	p-value
Colucci [24]	Gemc.	54	4.7	0.43
	Gemc./cispl.	53	7.0	
Heinemann [25]	Gemc.	99	6.0	0.12
	Gemc./cispl.	98	8.3	
Berlin [26]	Gemc.	163	5.4	0.09
	Gemc./5-Fu	164	6.7	
Riess [27]	Gemc.	236	6.2	0.68
	Gemc./5-Fu	230	5.9	
Louvet [30]	Gemc.	156	7.1	0.13
	Gemc./oxalipl.	157	9.0	
Rocha Lima [31]	Gemc.	169	6.6	0.79
	Gemc./irinotecan	173	6.3	
Richards [33]	Gemc.	282	6.3	0.85
	Gemc./pemetrexed	283	6.2	
O'Reilly [34]	Gemc.	174	6.2	0.52
	Gemc./exatecan-mesylate	175	6.7	
Herrmann [36]	Gemc.	157	7.3	0.31
	Gemc./capecitabine	159	8.4	
			1-yr OS%	
Reni [35]	Gemc.	47	21	0.11
	Gemc./PEF	52	38.5	
Stathopoulos [32]	Gemc.	50	24	n.s.
	Gemc./irinotecan	42	19.6	

Abbreviations: Gemc. = Gemcitabine; cispl. = cisplatin; 5-Fu = 5-fluorouracil; oxalipl. = oxaliplatin; PEF = cisplatin, epirubicin, 5-Fu; OS = overall survival; no pats = number of patients.

performance status. However, the authors stress that, regardless of p-value, the study did not reach the 50% increase in survival that the trial was originally designed for, why the result of this regression analysis should not change clinical practice. There was however a significant improvement in PFS among the patients in the combination arm (3.4 vs. 2.2 months; $p = 0.02$).

In a larger study, Riess et al. treated 230 patients with gemcitabine plus 5-Fu 750 mg/m^2 as a continuous 24 hour infusion, modulated with folinic acid 200 mg/m^2 given on day 1, 8, 15 and 22 every six weeks [27] and 236 patients in the control arm with standard schedule gemcitabine. Median survival was 6.2 months in the gemcitabine arm and 5.9 months in the combination arm ($p = 0.68$).

Two phase II trials have suggested an additional effect of oxaliplatin when combined with gemcitabine [28,29]. In a phase III trial Louvet and colleagues randomized 156 patients to receive gemcitabine at standard schedule. In the combination arm 157 patients were treated with gemcitabine at a dose of 1000 mg/m^2 as a fixed dose 100 min infusion (10 mg/m^2/min) day 1 and oxaliplatin 100 mg/m^2 as a 2 h infusion day 2 every two weeks. Median survival was 7.1 months in the gemcitabine arm and 9.0 months in the combination arm. This difference did not reach the level of statistical significance [30].

In an American multicenter study by Rocha Lima and co-workers, a total of 342 patients were assigned to compare gemcitabine in combination with irinotecan to gemcitabine alone [31]. One hundred and sixty-nine patients were treated with standard bolus gemcitabine. In the combination arm 173 patients received gemcitabine at a dose of 1000 mg/m^2 and irinotecan 100 mg/m^2 weekly for 2 of 3 weeks. There was no difference in median survival. A subset analysis of patients with locally advanced disease suggested a difference in TTP in favor of the combination regimen (median, 7.7 vs. 3.9 months).

In a more recent phase III trial, Stathopoulos and colleagues randomised 50 patients to receive gemcitabine 900 mg/m^2 on day 1, 8 and 15 of a 28 days cycle and 42 patients to receive gemcitabine 900 mg/m^2 on day 1 and 8 plus irinotecan 300 mg/m^2 on day 8 of a 21 days cycle [32]. One year survival rate was similar in both arms.

Two novel cytotoxic agents, the topoisomerase-1 inhibitor exatecan mesylate (DX) and the antifolate

pemetrexed (ALIMTA), have been investigated in phase III trials [33,34]. Both agents were combined with gemcitabine and compared to standard gemcitabine arms. There was no difference in median survival in either of these studies.

Reni et al. compared gemcitabine alone to a combination of gemcitabine, cisplatin, epirubicin and 5-Fu (PEFG) [35]. Forty-seven patients received standard 30 min infusion gemcitabine. In the combination arm 52 patients received cisplatin (P) and epirubicin (E) 40 mg/m^2 on day 1, gemcitabine (G) 600 mg/m^2 on days 1 and 8 and 5-Fu (F) as continuous infusion 200 mg/m^2/day on days 1 to 28 of 4-week cycles. One year overall survival was 21.3% in the gemcitabine arm and 38.5% in the combination arm with a p-value of 0.11. Overall survival at one year was, however, not the primary endpoint in this trial (the primary endpoint was four months progression free survival), why the authors suggest a careful interpretation of the result. Also, median survival in months has not been presented, which makes it difficult to compare the results with the trials presented above.

Finally, Herrmann and co-workers investigated the potential additional effect of capecitabine in combination with gemcitabine [36]. One hundred and fifty-seven patients were randomised to the gemcitabine standard schedule and 159 patients to gemcitabine 1000 mg/m^2 on day 1 and 8 plus capecitabine 650 mg/m^2 orally b.i.d on day 1 to 14 every three weeks. There was no difference in OS (7.3 v.s. 8.4 months, $p = 0.31$). A regression analysis showed, however, a significant improvement in OS in the combination arm among patients with a KPS ≥ 90 (10.1 v.s. 7.5 months, $p = 0.033$). Although this was an unplanned subgroup analysis, it suggests that this combination therapy may be an option for the fittest patients. This hypothesis should, however, be confirmed in a new study.

Gemcitabine plus targeted therapies. An overview is given in Table II. Targeted agents in combination with chemotherapy have recently become treatment options in the palliative setting in a number of tumours, e.g. metastastic colorectal cancer [37]. This far, three phase III trials have been published on gemcitabine and targeted therapies for advanced PC. In a study by Bramhall and colleagues, a total of 239 patients were randomized to receive gemcitabine in combination with placebo or the matrix metalloproteinase inhibitor marimastat [38]. One hundred and nineteen patients received gemcitabine at a dose of 1000 mg/m^2 weekly plus placebo. One hundred and twenty patients were treated with gemcitabine in the same fashion plus marimastat (10 mg b.i.d given orally). Median overall survival was 5.5 months in both arms.

Van Cutseem and co-workers randomized a total of 690 patients to receive either gemcitabine alone or in combination with the farnesyltransferase inhibitor tipifarnib, R115777 [39]. Three hundred and forty-seven patients received bolus gemcitabine plus placebo. In the combination arm 343 patients were treated with gemcitabine in the same fashion plus tipifarnib given at 200 mg b.i.d orally continuously. There was no difference in median survival between the treatment groups.

Moore et al. compared gemcitabine plus placebo to gemcitabine plus the EGFR (epidermal growth factor receptor) inhibitor erlotinib [40]. Five hundred and sixty-nine patients were randomized to receive bolus gemcitabine plus either erlotinib 100 mg daily given orally or a placebo. In an abstract presented at the ASCO 2005 Gastrointestinal symposium, the first preliminary analysis performed when 485 of the 569 enrolled patients had died, was presented. Median survival was 6.4 months in the combination arm and 5.9 months in the gemcitabine arm ($p = 0.025$). The analysis also suggested significant improvements in PFS and one year overall survival in favor of the combination regimen (24 vs. 17%).

In an ongoing phase II trial, Kindler and collegues have reported a median TTP of 5.8 months, a

Table II. Results of randomized phase III studies of gemcitabine + targeted agents in advanced pancreatic cancer.

Study	regimen	no pats	survival (months)	p-value
Bramhall [38]	Gemc.	119	5.5	0.95
	Gemc./marimastat	120	5.5	
Van Cutsem [39]	Gemc.	347	6.1	0.75
	Gemc./tipifarnib	343	6.4	
Moore [40]	Gemc.	284	5.9	0.025
	Gemc./erlotinib	285	6.4	
Shapiro [42]	Gemc.	184	6.7	0.10
	Gemc./G17DT	199	5.9	

Abbreviations: Gemc. = Gemcitabine; OS = overall survival; no pats = number of patients.

median survival of 9.0 months and a six month survival of 74% when combining gemcitabine and the antiangiogenic agent bevacizumab [41]. A confirmatory phase III trial is presently underway in the US.

Although mainly an immunotherapeutic agent, rather than targeted, a phase III trial by Shapiro and co-workers on G17DT immunogen should be mentioned [42]. This trial investigates the potential additional effect of this agent which induces antibodies to gastrin-17 and has shown to be effective as monotherapy in advanced PC [43,44]. One hundred and eighty-four patients were treated with gemcitabine 1000 mg/m^2 plus placebo and 199 patients received gemcitabine 1000 mg/m^2 plus G17DT as intramuscular injection at week 0, 4, 8 and 24. There was no difference in OS between the treatment groups.

Discussion

Recent phase III trials have compared gemcitabine as a single agent to a combination therapy with one or several other cytotoxic or targeted agents for advanced PC. As showed in this article, gemcitabine-based combination chemotherapy has generally proven disappointing in terms of clinically significantly better outcome in overall survival compared to gemcitabine only. However, as shown in the case reports, described by us, in a Letter to the Editor section in this issue, individual patients can benefit well from combination chemotherapy and even be reassessed for radical surgery [45].

Single agent gemcitabine remains, however, the gold standard for systemic treatment in advanced PC for the majority of patients. Three of six trials comparing chemotherapy to BSC only show a small but significant improvement in OS (>3 months) and QOL (20–30%) in a sufficient amount of patients to advocate chemotherapy in advanced PC in fit patients. Still, we must stress the importance of frequent evaluations to avoid unnecessary treatment of patients with progressive disease. We generally evaluate our patients every eight weeks using radiological methods as well as the tumor marker CA 19-9 and QOL-aspects. A careful selection of patients by performance status was also recommended in the previous overview by the SBU [3].

Even though the benefit of systemic treatment in terms of improvements in survival is quite modest one must take in consideration the potential benefit in terms of improvement of QOL. Due to the limited objective response to chemotherapy in terms of tumor regression in radiological evaluations, the term Clinical Benefit Response (CBR) was developed specifically to facilitate assessment of the efficacy of chemotherapy in PC. CBR pays regard to important clinical parameters such as weight gain, pain reduction, and performance status that influence QOL. Several studies have showed improvements in QOL in favor of chemotherapy as compared to BSC only; in addition gemcitabine has proven to be superior to 5-Fu in terms of CBR [7,18–20]. Perhaps the focus on survival prevents us from recognizing the importance of QOL issues even in the treatment of advanced disease. Palliation is defined as symptom control and not as increasing survival; nevertheless, effect on survival is the primary endpoint in most trials.

In Sweden, the economical reality of today's health care system has forced some cancer units to stop offering systemic treatment in this disease, in order to give priority to other patient groups [46]. A return to a more nihilistic approach to PC is, however, unfortunate, not only because individual patients may miss a potentially beneficial treatment, but also because this may affect the motivation of surgeons to refer these patients to oncological departments, thus influencing the effort to recruit patients into randomized trials on new systemic therapies in a negative way. As new cytotoxic or other agents are continually developed, it is important not to let past disappointments affect the willingness to test new combinations in this disease.

It is essential to recognise that several trials show significant improvement in secondary endpoints and in subgroup analysis, suggesting that selected patients may benefit from the novel treatments. The beneficial effect could, however, be diluted by non-responders and by patients with advanced stage III and IV disease, in whom treatment cannot stabilise the disease before the patient die from disease complications or exhaustion. The challenge to identify subgroups that respond to treatment will probably be even more important in targeted therapies.

Further phase III gemctabine combination trials are on the way, e.g. the ECOG-6201 trial, in which prolonged infusion gemcitabine with or without oxaliplatin versus standard infusion gemcitabine is further evaluated.

To date the only agent that has showed a significant improvement in OS in combination with gemcitabine in advanced PC is the EGFR inhibitor erlotinib [40]. The most promising treatments in the future may be targeted therapies. A number of phase III trials are underway e.g. the ongoing American study that compares gemcitabine to a combination of gemcitabine and the antiangiogenic agent bevacizumab (ECOG-80303).

Another ongoing phase III trial is the American SWOG-S0205 comparing gemcitiabine alone to a combination of gemcitabine and the antibody cetuximab. An American phase III trial called LORUS-LOR-VIR-P03-002 compares gemcitabine alone to a combination of gemcitabine and the biological agent virulizin, interestingly; this trial also investigates a second line treatment comparing 5-Fu alone or in combination with virulizin. Virulizin has shown several immunotherapeutic antitumor effects in preclinical trials e.g. macrophage activation, NK-cellactivation and induction of tumor cell apoptosis [47–51]. Furthermore, a Roche-sponsored European study comparing gemcitabine plus erlotinib with or without bevacizumab has started (the AVITA-study).

Finally, it is worth mentioning the second line phase III trial by Oettle et al., comparing oxaliplatin/5-Fu/folinic acid (OFF) to BSC in gemcitabine refractory PC. When 46 of 165 planned patients had been enrolled the trial design was modified. Preliminary results were presented at ASCO 2005. Median survival time of second line treatment was 21 weeks in the treatment arm compared to 10 weeks in the BSC arm ($p = 0.007$). By demand from participating centers the BSC arm was thus closed early. Enrollment up to 165 patients continues, however, now comparing OFF to FF.

Conclusion

There is enough evidence that single agent gemcitabine improves OS and QOL in a sufficient amount of patients to recommend treatment in selected fit patients. To date no combination chemotherapy has proven superior to single agent gemcitabine in terms of OS why single agent gemcitabine must still be regarded as gold standard in the treatment of advanced PC. Combination chemotherapy is, however, still evaluated in a number of ongoing trials. Individual patients can benefit from existing gemcitabine based combination chemotherapy. Patients should, however, be monitored closely during treatment, e.g. every eight weeks, to avoid continuation if progression occurs.

Targeted therapies are very interesting in the future treatment of advanced PC and may prove the best hope for survival gain in this discouraging disease. Because of the relative ineffectiveness of single agent gemcitabine it is very important to allow as many patients as possible to take part in controlled trials in order to improve outcome.

Since the original preparation of this manuscript, the first evidence of a survival benefit with combination therapy compared to gemcitabine only has emerged. At ECCO 13 in November of 2005, Cunningham et al. presented the interim analysis of a randomised study, which compared gemcitabine vs. gemcitabine plus capecitabine in APC [52]. Two hundred and sixty-six patients were allocated to bolus gemcitabine (1000 mg/m^2 for 7 of 8 weeks and then weekly for 3 of 4 weeks) only and 267 patients were treated with additional oral capecitabine 1660 mg/m^2/day for 3 of 4 weeks. The median survival was 6 months for gemcitabine alone and 7.4 months for the combination therapy (HR: 0.80; 95% CI: 0.65–0.98; $p = 0.026$) and the 1-year survival rate was 19% and 26%, respectively.

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