REVIEW ARTICLES

ADVANCED PANCREATIC CANCER: PAST, PRESENT AND FUTURE OF TREATMENT

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ABSTRACT

Pancreatic cancer is highly lethal disease that is rising in incidence. Chemotherapy based on 5-fluorouracil (5-FU) has shown to prolong survival in advanced pancreatic cancer modestly. Gemcitabine improves major symptoms and survival outcomes compared with 5-FU. Many compounds have been investigated. These compounds are based on classical mechanisms of action as well as biological therapies targeting cellular pathways, and include fluoropyrimidines, nucleoside cytidine analogues, platinum analogues, topoisomerase inhibitors, antimicrotubule agents, proteasome inhibitors, vitamin D analogues, arachidonic acid pathway inhibitors, histone deacytylator inhibitors, farnesyltransferase inhibitors, epidermal growth factor receptor therapies and many more. Out of these some have shown their promise. Many more compounds are being tested and real advances are anticipated in the near future.

Keywords: Chemotherapy, 5-FU, gemcitabine, molecular targeting

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in United States [1]. When all stages are combined, 1-year relative survival rate for patients with pancreatic cancer is 23% and the 5-year survival rate is about 4%. Median survival is 8 to 12 months for patients with locally advanced unresectable disease, and only 3 to 6 months for those who present with metastases. Because the symptoms of pancreatic cancer are quite nonspecific, most patients present with advanced disease. Only when a tumor develops in the head of the pancreas, which may cause jaundice, is an earlier diagnosis possible. Surgery, radiation therapy, and chemotherapy are treatment options that can extend survival and /or relieve symptoms but they seldom produce a cure. Over the years there has been extensive advancement in the understanding of etiology, molecular biology, diagnosis and treatment of this disease. Presently, surgical resection is the only potentially curative option available for these patients. It is now clear that surgery alone cannot increase the survival of this patient group [2]. With the understanding of molecular biology of pancreatic cancer new management strategies are under a preclinical stage of development. These new diagnostic and therapeutic modalities hopefully will improve the outcome of patients with pancreatic cancer [3]. Recent clinical trials have provided reason for hope that new chemotherapy combinations and molecularly targeted agents will lead to improved clinical outcomes for patients with this disease [4]. Relief of pain and suffering associated with critical illness is required in managing patients with cancer [5]. An overview of the past, present and future of treatment for advanced pancreatic cancer will be discussed here.

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CHEMOTHERAPY

Assessment of traditional objective responses to therapy is often inadequate in pancreatic cancer. More recent trials have included quality of life (QOL), since patients with pancreatic cancer present with pain and depression more often than other malignancies. In addition, a new terminology “clinical benefit” has been added in cancer pancreas. So, clinical benefit and survival are determinants of efficacy in this tumor. Statistically significant correlations between the percentage of CA19-9 decline, and both overall survival and TTF were found [6].

Single Agent Chemotherapy

Single agent therapy has been associated with objective response rates above 10%. 5-fluorouracil (5-FU) has been extensively studied and objective response rates vary widely from 0 to 67%. However, contemporary studies of leucovorin (LV)-modulated 5-FU in patients with advanced disease suggest a very low response rate (0 to 9%) using infusional as well as bolus schedules, and a median survival that ranges from 10 to 24 weeks [7]. Capecitabine is an oral fluoropyrimidine that is converted to 5-FU. The final requisite enzyme, thymidine phosphorylase, is present more in tumor than normal tissue, thereby providing the basis for enhanced benefit. The efficacy of Capecitabine monotherapy (1250 mg/m^2 orally twice daily for 14 of every 21 days) was seen in chemotherapy-naive advanced pancreatic cancer. Although only 7% had an objective response, the clinical benefit was 24%. Treatment was well tolerated [8].

Initial studies suggested 6 to 11% objective response rate in chemotherapy-naive patients administered single agent gemcitabine (800 mg/m^2 IV weekly for three of every four weeks) [9]. However, clinical benefit defined as an improvement in pain, performance status or weight without deterioration in any other factor has been observed in patients who lack an objective response. An important phase-II study of gemcitabine (1000 mg/m^2 weekly for seven weeks followed by a one week rest, and thereafter every week for three weeks followed by one week rest), although the objective response rate for patients with measurable disease was only 11%, a clinical benefit was observed in 27%. Nevertheless, on the basis of significant improvements in clinical benefit and survival, gemcitabine was approved as first line therapy of metastatic pancreatic cancer. There is no evidence that increasing the dose intensity of gemcitabine above 1000 mg/m^2 per week when administered as a 30-minute infusion improves antitumor activity. However, longer infusion times with high dosage appear to have a pharmacokinetic advantage. Based upon these results, a randomized phase-II study with constant dose rate infusion was associated with a significantly better median survival (8 versus 5 months) and one year survival (29 versus 2%) [10]

Anthracyclines have limited activity in advanced pancreatic cancer. An EORTC study of epirubicin with advanced disease showed an objective response rate of 24%, but median survival was only three months. Streptozocin has limited activity in pancreatic ductal adenocarcinoma. In a series of early studies, only 11% had an objective response to single agent therapy. Single agent ifosfamide also has limited activity; in two phase-II studies, the objective response rate was only 7 and 10%, and median survival was only 11 to 12 weeks.

Taxanes are of limited benefit in advanced pancreatic cancer. In one phase-II study, in which patients received single agent docetaxel with hematopoietic growth factor, the objective response rate was only 6%, but a disease stabilizing effect was suggested because the one year survival was 36% [11]. In a second report with advanced disease, who received docetaxel alone (100 mg/m^2 every three weeks), the objective response rate was 15% while stable disease was observed in an additional 38%. Others have reported little to no benefit from single agent docetaxel [12]. Single agent paclitaxel was also studied and the objective response was 8%, and the median survival was five months.

Camptothecins such as topotecan, irinotecan, and 9-nitro-camptothecin have limited activity in advanced pancreatic cancer, with objective response rates of 0 to 29%, and median survival duration of 4 to 6.5 months [13]. Trials of rubitecan in combination with gemcitabine are planned. DX-8951f (a novel hexacyclic topoisomerase I inhibitor) was tested as a single agent in patients with metastatic pancreatic cancer. Results to date of the compound as a single agent show objective responses in 13% of previously untreated patients, with a median survival of 9.3 months [14].

Combination Chemotherapy

5-FU and 5-FU-based combination have been shown to be superior to observation alone, and to best supportive care in palliative therapy trials [15]. An important breakthrough was the demonstration that gemcitabine was able to improve the major symptoms of pancreatic cancer as well as achieving a modest survival benefit compared to bolus 5-FU [16]. Randomized trials do not support a survival benefit for 5-FU based combination compared to 5-FU alone. Additional support for a beneficial impact was derived from a

meta-analysis that included 29 randomized trials [17]. Newer regimens that combine LV-modulated 5-FU with irinotecan and oxaliplatin show promise for advanced pancreatic cancer. In one study, patients received the "Folfirinox" regimen every two weeks, which consisted of oxaliplatin 85 mg/m^2 day 1 over 2 hours, followed by irinotecan 180 mg/m^2 day 1 over 90 minutes, followed by leucovorin 400 mg/m^2 over 2 hours, then 5-FU 400 mg/m^2 bolus, then 2400 mg/m^2 as a 46 hour continuous infusion [18]. 26% objective responses, with 4% complete response. The median time to progression (TTP) and overall survival durations were 8.2 and 10.2 months, respectively. Treatment-related toxicity included grade 3 or 4 neutropenia, nausea, vomiting, diarrhea, and neuropathy in 52, 20, 17, 17, and 15%, respectively. With a good safety profile, a promising response rate, and an improvement in QOL recommends Folfirinox to be further assessed by phase-III trials [19]. In spite of toxicity cisplatin plus cytarabine has shown surprising results.

Gemcitabine has been combined with many other active cytotoxic agents including 5-FU, cisplatin, docetaxel, oxaliplatin, and irinotecan. Gemcitabine has been combined with both bolus and infusional 5-FU. In a phase-III trial of the Eastern Cooperative Oncology Group (ECOG) gemcitabine (1000 mg/m^2 weekly for three of every four weeks) alone or with 5-FU (600 mg/m^2 weekly bolus injection after gemcitabine), median progression free survival (PFS) was modestly but significantly better with the combination (3.4 versus 2.2 months), objective response rates were similar (7 versus 6%) as was median survival (6.7 versus 5.4 months) [20]. Better results were noted in a phase-II trial using gemcitabine (1000 mg/m^2 every 15 days) plus LV-modulated 5-FU (daily bolus 5-FU 400 mg/m^2 plus leucovorin 100 mg/m^2 on days 1 to 3, every 15 days). There were two complete and 11 partial responses in 42 patients, and the median TTP was almost 10 months. There were seven cases of grade 2 or 3 gastrointestinal toxicity. Infusional 5-FU plus gemcitabine has also been evaluated. There was 19% objective response, and median survival was 10 months [21]. FOLFUGEM 2 had leucovorin 400 mg/m^2 in 2 hours followed by 5-FU 1000 mg/m^2 in 22 hours, then gemcitabine 800 mg/m^2 (10 mg/m^2/min) with cycles every 14 days. FOLFUGEM 2 has an antitumoral effect with acceptable toxicity [22]. Early results suggest a greater degree of efficacy when gemcitabine is combined with Capecitabine. In one combined phase-I/II study, in which 27 of 36 patients received Capecitabine 650 mg/m^2 twice daily for 14 days plus gemcitabine 1000 mg/m^2 days 1 and 8 of every 21 day cycle, there were five objective responses and one complete response.

In many studies evaluating the same regimen of gemcitabine (1000 mg/m^2, on days 1, 8, and 15), plus cisplatin (50 mg/m^2 on days 1 and 15) in patients with advanced pancreatic cancer, treatment has been well tolerated and associated with objective response rates ranging from 11 to 36% [23]. A few phase-III trials have compared gemcitabine alone to the combination of gemcitabine plus cisplatin. In the only completed trial, patients with locally advanced or metastatic disease were randomly assigned to gemcitabine alone (1000 mg/m^2 weekly for seven of the first nine weeks, then on days 1, 8, and 15 of every 28 day cycle) or to the same gemcitabine dose plus cisplatin 25 mg/m^2 weekly for six of the first nine weeks, then on days 1, 8, and 15 of every 28 day cycle. Objective response rates (26 versus 9%) and median TTP (20 versus 8 weeks) were significantly longer with the combination, but less difference in median survival (50 weeks versus 40 weeks). In contrast, the possibility of prolonged survival was suggested in a preliminary report of a second phase-III trial of gemcitabine with and without cisplatin (50 mg/m^2 day 1 and 15 of every 28 day cycle) [24]. Both PFS (5.4 versus 2.8 months) and median survival (8.3 versus 6 months) were significantly better with the combination. Phase-II studies combining gemcitabine and docetaxel have shown encouraging response rates with good tolerability. Use of docetaxel in combinations with other drugs as well, was recommended [25].

Gemcitabine at a dose of 800 mg/m^2 on day 1 and 8, 5-FU 1,000 mg/m^2/day from day 1 to 3 for 72 hours, and cisplatin 60 mg/m^2 on day 2, 24 hours after the start of gemcitabine were administered every 3 weeks. Combination chemotherapy with gemcitabine, 5-FU, and cisplatin for advanced pancreatic cancer is active and well-tolerated, warranting a phase-III study [26]. In a phase-II study of gemcitabine by fixed dose rate infusion plus cisplatin, patients received gemcitabine 1000 mg/m^2 at a fixed-dose infusion

rate of 10 mg/m^2/minute plus cisplatin 20 mg/m^2 on days 1 and 8 of a 21-day cycle. Major grade 3 or 4 toxicities were hematologic. Median time to progression and overall survival times were 121 days and 215 days, respectively [27]. The potential benefit of this regimen over single agent gemcitabine appears to be very modest, especially when balanced against added toxicity.

Some of the most impressive activity has been noted with the combination of gemcitabine with 5-FU, cisplatin, and epirubicin (PEFG) administered every 28 days. In one study the objective response rate was 58%, clinical benefit was noted in 78%, the median TTP was 7.5 months, and survival was 11 months [28]. Grade 3 to 4 neutropenia complicated one-half of all delivered cycles, but nonhematologic toxicity, particularly gastrointestinal toxicity was infrequent. The PEFG regimen was compared to gemcitabine alone (1000 mg/m^2 weekly for seven of eight weeks, then three of every four weeks). In a preliminary report, PEFG was associated with a significantly higher response rate (40 versus 8.5%), and four month PFS (60 versus 28%), but there was only a trend towards improved one year survival. In another randomised multicentre phase-III trial, 52 patients were randomly assigned to 40 mg/m^2 cisplatin and 40 mg/m^2 epirubicin both given on day 1, 600 mg/m^2 gemcitabine given intravenously over 1 h on days 1 and 8, and 200 mg/m^2 fluorouracil a day given by continuous infusion on days 1-28 of a 4-week cycle (PEFG regimen), and 47 were assigned to 1000 mg/m^2 gemcitabine given intravenously over 30 min once a week for 7 of 8 consecutive weeks in cycle 1 and for 3 of 4 weeks thereafter. The PEFG regimen could be considered for treatment of advanced pancreatic carcinoma [29].

In one multicenter study, the objective response rate with gemcitabine (1000 mg/m^2 on day 1 over 100 minutes) and oxaliplatin (100 mg/m^2 over 2 hours on day 2) both administered every 2 weeks was 31%, and toxicity was modest (grade 3 or 4 neutropenia, thrombocytopenia and nausea/vomiting in 11, 11, and 14%, respectively). Given the promising phase-II results obtained with the Gem-oxaliplatin (GemOx) combination, a phase-III study comparing GemOx with Gem alone in advanced pancreatic cancer (gemcitabine 1 g/m^2 as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2 every 2 weeks) or Gem (gemcitabine 1 g/m^2 as a weekly 30-minute infusion). These results confirm the efficacy and safety of GemOx, but failed to demonstrate a statistically significant advantage in terms of OS compared with Gem.30 The efficacy of this same GEMOX regimen was compared to gemcitabine alone in a multicenter trial of 326 patients with either locally advanced or metastatic pancreatic cancer (the GERCOR/GISCAD Intergroup study). GEMOX was associated with significantly higher response rates (29 versus 17%), and significantly longer median PFS (5.5 versus 3.7 months) but only a trend towards improved median survival (9 versus 7.1 months).

The combination of DX-8951f with gemcitabine resulted in an objective response rate of 23% with a median duration of response of 9.3 months. Phase-3 trials addressing the efficacy of DX-8951f alone or in combination with gemcitabine have been completed; results are eagerly awaited.14 Chemonaive patients with advanced adenocarcinoma of the pancreas were treated with a combination of raltitrexed (3.5 mg /m2 on day 1 of a 21-day treatment cycle) and gemcitabine (800 mg/m^2 intravenously (i.v.) on days 1 and 8 of a 21-day cycle). Study results were negative [31].

SECOND LINE THERAPY

Second line therapy for patients who have failed gemcitabine containing chemotherapy has been poorly studied, and there is no standard of care. Oxaliplatin as second line treatment for patients with unresectable pancreatic cancer is well tolerated and associated with improvement of tumor related symptoms despite its failure to induce objective responses. One randomized phase-II study compared 21 day cycles of raltitrexed (3 mg/m^2 on day 1) versus irinotecan (200 mg/m^2 day 1) plus raltitrexed (3 mg/m^2 day 2) who failed gemcitabine based chemotherapy [32]. Combined therapy had a superior objective response rate (16 versus 0%), clinical benefit (29 versus 8%), PFS (4 versus 2.5 months), and overall survival (6.5 versus 4.3 months). 58 patients with failed or relapsed advanced pancreatic cancer were enrolled to receive eight consecutive weeks of treatment with rubitecan at a dose of 1.5 mg/m^2 orally on five consecutive days per week, followed by 2 days off therapy, repeatedly. Among 43 patients with measurable

disease, 7% achieved partial responses and 16% had disease stabilization for an overall response and disease stabilization rate of 23%. Oral rubitecan produced responses and was well tolerated by heavily pretreated patients with refractory pancreatic cancer [33]. Weekly paclitaxel was studied as a second line agent in a series of 18 patients who failed gemcitabine with or without 5-FU [34]. In a preliminary report, one patient obtained a complete remission, and five others had stable disease. Combination of Oxaliplatin, Leucovorin and 5-FU, following relapse to Gemcitabine was tolerated with manageable toxicity, offering encouraging second line management [35].

Some investigators have shown benefit for GEMOX or irinotecan/oxaliplatin after gemcitabine failure. In a preliminary report of 30 patients receiving second line GEMOX, seven had partial responses, while 52% had clinical benefit. In another series of 30 patients treated with irinotecan and oxaliplatin, three had a partial response (two of whom subsequently underwent resection) and six had clinical benefit. 23% were still alive at one year. Chemotherapy with irinotecan and oxaliplatin was found to be active and well tolerated combination in patients with advanced pre-treated pancreatic cancer [36].

It is unclear which regimen represents the best choice for second line therapy in patients who have failed gemcitabine containing initial therapy. Confirmatory trials are needed. The observation that normal and malignant pancreatic tissue contains estrogen and somatostatin receptors provided the rationale for hormone manipulation in advanced disease. Tamoxifen as a single agent (usually 10 mg orally twice daily) has minimal activity, with objective response rates less than 10%, without any survival advantage [37]. Octreotide has shown marginal activity [38].

NEWER THERAPEUTIC APPROACHES

Conventional cytotoxic therapy has not produced a significant impact on the natural history of pancreatic cancer. Although standard chemotherapy with gemcitabine achieves only modest improvements in survival and QOL, classic cytotoxic agents, such as 5-FU, pemetrexed, irinotecan, exatecan, cisplatin, or oxaliplatin, either given alone or in combination with gemcitabine, have not proved superior. Thus, more recent trials have focused on targeting the biologic characteristics of pancreatic cancer. Phase-III trials of farnesyl transferase and matrix metalloproteinase inhibitors have not improved survival [39]. Mutations of the ras gene, present in approximately 90% of pancreatic cancers, lead to targeting ras mutations by vaccines and antisense molecules [40]. Pemetrexed plus gemcitabine therapy did not improve OS. PS-341 is a proteasome inhibitor with preclinical activity in pancreatic cancer and synergistic activity with gemcitabine. PS-341 alone or in combination with gemcitabine did not result in better overall survival or RR than gemcitabine alone [41]. Selective COX-2 inhibitor celecoxib enhances the growth inhibition of pancreatic cancer induced by gemcitabine through the arrest of cell cycle and induction of cell apoptosis. The addition of celecoxib to gemcitabine (by FDR) and cisplatin did not appear to increase the efficacy [42]. S-1 was administered orally at 40 mg/m^2 twice daily for 28 days with a rest period of 14 days as one course and was well tolerated [43]. Thalidomide was well tolerated and effective at attenuating loss of weight and lean body mass in patients with cachexia due to advanced pancreatic cancer [44]. Thirty-three chemonaive patients with measurable disease received the TOMGEM regimen consisting of Raltitrexed 3 mg/m^2 in 15 min followed by Gemcitabine 1,000 mg/m^2 in 30 min on day 1, Gemcitabine alone 1,000 mg/m^2 on day 8 and repeated on day 21. Combination of raltitrexed/gemcitabine was very convenient regimen with an acceptable toxicity in advanced pancreatic cancer [45].

Angiogenesis through vascular endothelial growth factor (VEGF) signaling is thought to play a major role in pancreatic cancer progression. The monoclonal anti-VEGF antibody bevacizumab was tested as a component of therapy in advanced pancreatic cancer. In a recent phase-II trial among patients with advanced pancreatic cancer, bevacizumab was combined with gemcitabine [46]. The results were promising, given the fact that 7 (27%) of the first 26 patients had a confirmed partial response and the median time to progression was 6 months. The estimated survival rate after 1 year was 53%, which compares favorably with the historical control of approximately 18%. The toxicity profile of the

combination was acceptable, with 36% of patients developing grade 3 or 4 neutropenia. One patient died due to bleeding caused by tumor erosion into the duodenum.

In another phase-2 study of gemcitabine and bevacizumab forty-five patients with advanced disease received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle and bevacizumab 10 mg/kg on days 1 and 15. The primary end point of the study was objective tumor response [47]. Grade 3 or 4 toxicities were predominantly hematologic. Nonhematologic toxicities attributable to bevacizumab included bleeding, headache, hypertension, thromboses, proteinuria, and gastrointestinal perforation. The partial response rate was 21%. The median survival time was 9 months, with an estimated 1-year survival of 37%. Median time to progression was 5.8 months. This treatment outcome compared favorably with published reports on single agent activity of gemcitabine in patients with advanced pancreatic cancer, who showed a median survival time of 5-6 months. A randomized phase-3 study of gemcitabine plus bevacizumab vs gemcitabine alone in advanced pancreatic cancer has already been proposed by the Cancer and Leukemia Group B. A refractory stage IV pancreatic cancer patient was successfully treated with bevacizumab 5 mg/kg and combination chemotherapy consisting of gemcitabine, fluorouracil leucovorin, irinotecan and cisplatin (GFLIP) every two weeks [48].

The combination of cetuximab and gemcitabine was at least additive in preclinical models [49]. Cetuximab was given in a loading dose of 400 mg/m^2, followed by weekly doses of 250 mg/m^2 until progression. After two courses of therapy, 12% achieved a partial response, and 39% had stable disease. The 1-year survival rate was 32.5%. Treatment related toxicities were mild to moderate. These results prompted the investigators to design a phase-III trial of gemcitabine with or without cetuximab. A larger phase-3 trial (SWOG 0205) is currently ongoing examining the combination of gemcitabine and cetuximab in a similar population of patients with advanced pancreatic cancer [50]. The administration of combined gemcitabine and trastuzumab to 18 patients with HER-2-overexpressing advanced pancreatic tumors produced four partial responses (22%) and CA19-9 falls greater than 50% in 9 cases [51]. No unexpected toxicity was seen in this study.

An encouraging combination is erlotinib, a small molecule inhibitor of the epidermal growth factor receptor (EGFR), plus gemcitabine. In a preliminary report of a phase-III trial comparing gemcitabine (1000 mg/m^2 weekly) with and without erlotinib (100 mg daily), combined therapy was associated with few objective responses [52]. However, overall survival was better compared to gemcitabine alone. Erlotinib may be safely combined with gemcitabine [53]. In another study of erlotinib with conventional chemotherapy an improvement in both overall survival and progression free survival in the patients who received the combination of gemcitabine plus erlotinib, compared with those who received only chemotherapy was seen [54]. The corresponding 1-year survival rates were 24% for the patients on the combination regimen vs 17% for those who received single agent gemcitabine. In a phase-3 trial of gemcitabine with or without erlotinib the dose of erlotinib was 100 mg or 150 mg per day. Hematologic toxicity to the erlotinib/gemcitabine combination was similar to that found with gemcitabine alone. The authors concluded that there was no detrimental effect on quality of life by the addition of erlotinib.

The cytokine tumor necrosis factor (TNF)-alpha has antitumor activity, but its use is limited by the toxicity of systemic administration. However, gene transfer to the tumor may be used to generate high concentrations of TNF-alpha within the tumor environment. TNFerade is a replication-deficient adenovirus containing the human TNF-alpha gene. The preliminary results of a dose escalation study using weekly intratumoral delivery of TNFerade during a 5-week course of chemoradiation (50.4 Gy radiation therapy plus 5-FU 200 mg/m^2/day for 5 days) in 3 cohorts of TNFerade, with doses ranging from 4x109 particle units to 4x1011 particle units were presented. Local delivery was by either EUS or percutaneous transabdominal administration. The treatment was well tolerated. Results suggested a dose dependent response to therapy [55]. Several other immunotherapeutic approaches to treat pancreatic cancer are being pursued [56]. Among them, immunization with naturally occurring or synthetic peptides, often conjugated with adjuvants, has been shown to elicit immunologic responses in patients with pancreatic cancer [57]. Another immunotherapeutic approach consists in the administration of vaccines made with allogeneic

pancreatic tumor cells. These cells may be genetically modified to express immunologic adjuvants. In one study, 3 of 14 patients receiving two different pancreatic tumor cell lines that expressed granulocyte-macrophage colony-stimulating factor developed an enhanced delayed-type hypersensitivity to autologous tumor collected at the time of surgery [58]. Preclinical studies also suggest a role for dendritic cell based vaccination of patients with pancreatic cancer [59]. Several other vaccine approaches are theoretically possible, and their potential as targeted therapies for patients with cancer are under investigation [60].

SUMMARY & RECOMMENDATION

At present single agent gemcitabine remains the standard of care for the treatment of patients with advanced pancreatic cancer. The administration of gemcitabine by dose rate infusion may improve efficacy. The addition of cisplatin or oxaliplatin to gemcitabine increases the response rate and PFS when compared to gemcitabine alone in phase-III studies. However, there is no significant improvement in overall survival and the addition of these agents to gemcitabine cannot be routinely recommended. Better survival results from newly developed compounds are eagerly awaited.

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