Latest Update in the Management of Pancreatic Cancer

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Introduction

Worldwide, pancreatic cancer poses a significant health hazard with more than 200,000 cases diagnosed annually and the majority of cases are in the developed countries. It is the eighth most common cause of cancer-related deaths and the number of deaths is nearly equivalent to the number of newly diagnosed pancreatic cancer. This reflects the typical dismal prognosis associated with pancreatic cancer. When the disease is diagnosed at early stages, the overall 5-year survival rate is 20% for patients with localized disease and 8% for patients with locally advanced disease. Unfortunately, most patients with pancreatic cancer have advanced or metastatic disease upon presentation. The prognosis of this group of advanced pancreatic cancer patients is disappointing. In general, the median survival of untreated advanced pancreatic cancer is only three to four months. Even in treated patients, their median overall survival is only approximately 6 months with chemotherapy.

Patients suffered from pancreatic cancer often present with disease-related symptoms out of proportion to their tumour burden. The typical symptoms, such as pain and cachexia severely impact on the quality-of-life of the patients. Also, due to the poor performance status of the patients, they are more prone to develop treatment-related complications, especially after chemotherapy. It is a challenging disease for the oncologists to deal with and there is an urgent need to develop effective systemic therapy to improve the outcome of the patients.

In recent years, a better understanding of the molecular signalling pathways in cancer cells has led to the identification of new therapeutic targets for intervention and the discovery of promising targeted therapy for the treatment of otherwise chemo-resistant tumours, such as renal cell carcinoma. Similar to other solid malignancies, progresses have also been made in the management of pancreatic cancer patients. This article will concisely summarise the latest development in the systemic therapy of pancreatic cancer.

Early Stage Disease And the Role of Neo-adjuvant And Adjuvant Therapy

Patients with localised pancreatic cancer, usually involving the head of the pancreas are candidates for surgery if the tumour is resectable as defined by the absence of vascular involvement. Notably, complete surgical resection is the only curative choice. However, despite recent advances in staging and surgical techniques, the outcome of patients treated with primary resection remains poor with a median survival of 13 months and the 5-year survival of 15-20% only. As a result, oncologists are keen to use adjuvant and neoadjuvant therapy to improve the prognosis of patients with resectable pancreatic cancer.

The main purpose of the adjuvant therapy is to reduce the chance of local and distant recurrence in good performance patients after resection for localised pancreatic cancer. Previously, post-operative chemo-irradiation was often employed as two trials from the Gastrointestinal Tumour Study Group had demonstrated better survival in using adjuvant chemo-irradiation than surgery alone in treating resectable pancreatic cancer patients. These trials had been criticised for their small sample size and poor accrual, albeit post-operative chemo-irradiation was still adopted as the standard treatment. More recently, a large randomised adjuvant phase III trial-- European Study Group for Pancreatic Cancer 1(ESPAC-1) trial conducted mainly in Europe had challenged the role of adjuvant chemo-irradiation. In this randomised phase III trial with a 2x2 factorial design, the data suggested significant survival benefit of using adjuvant chemotherapy consisted of intravenous fluorouracil (5-FU) and folinic acid (overall survival of 20.1 versus 15.5 months in the chemotherapy and non-chemotherapy arm, respectively). Interestingly, patients who received chemo-irradiation had a detrimental effect on overall survival (15.9 and 17.9 months in the chemo-irradiation arm and no chemo-irradiation arm, respectively). Furthermore, another pivotal phase III trial-CONKO-001 demonstrated that patients who had received gemcitabine as adjuvant therapy had a significant longer disease-free survival than patients without adjuvant therapy (13.4 versus 6.9 months, p=0.001). Moreover, the overall survival also favoured the use of gemcitabine as adjuvant (22.1 versus 20.2, p=0.06). However, the US Gastrointestinal Intergroup trial had shown no statistically significant difference in overall or disease-free survival in patients received gemcitabine or 5-FU as systemic chemotherapy before and after 5-FU-based chemo-irradiation as adjuvant therapy for patients with resectable pancreatic cancer. However, oncologists nowadays still prefer to use gemcitabine as adjuvant therapy for patients with resectable pancreatic cancer due to its easy tolerability. In the near future, with optimal patient selection, improved operation techniques and peri-operative care,
more patients who undergo pancreatic resection will recover adequately to receive postoperative adjuvant therapy. Therefore, it is important to develop more effective adjuvant therapy, especially by incorporation of biologics to improve the overall survival of resectable pancreatic cancer.

With respect to the role of neo-adjuvant therapy in down-staging the advanced pancreatic cancer for potential curative resection, it is still unclear. Treatment with 5-FU based chemo-irradiation or gemcitabine only downstage the disease in a minority of patients with locally advanced disease. In daily practice, oncologists tend to treat locally advanced pancreatic cancer patients with chemo-irradiation with 5/FU as radiosensitiser followed by palliative chemotherapy. However, two recent meta-analyses did not show that chemoradiation was better than chemotherapy alone in patients with locally advanced pancreatic cancer. In contrast, the addition of radiotherapy to chemotherapy increases survival benefit in resectable pancreatic cancer patients. Therefore, the use of combination therapy is better than gemcitabine alone for the treatment of advanced pancreatic cancer. Subsequently, gemcitabine became the standard of care for advanced pancreatic cancer for the past decade as in a phase III trial of patients with advanced pancreatic cancer, gemcitabine was found to be better than 5-FU in alleviating the symptoms and associated with a significant longer median survival.

Systemic chemotherapy has its established role in the treatment of advanced pancreatic cancer. The results of the GEMCAP trial are the first in the literature which show that combination chemotherapy is superior to bolus 5-FU, its efficacy is modest, with a median survival of only 6 months in most randomised trials and a 12-months survival of < 20%. Therefore, in the past decade, numerous attempts were made to improve the efficacy of gemcitabine treatment by adding other chemotherapeutic or biological agents. Unfortunately, a lot of gemcitabine-based doublets or triplets have been done with very disappointing results. Recently, against a background of numerous negative randomised trials of gemcitabine-based treatment, two trials have reported significant survival improvements with the use of combination treatment: the United Kingdom National Cancer Research Institute GEMCAP trial and the National Cancer Institute of Canada Clinical Trials Group PA.3 trial.

The results of the GEMCAP trial are the first in the literature which show that combination chemotherapy is better than gemcitabine alone for the treatment of advanced pancreatic cancer. In this randomised phase III trial, 533 patients were randomised to receive either single agent gemcitabine (n=266) or gemcitabine and capcitabine. In patients who received gemcitabine and capcitabine combination, the median OS was 7.4 months, compared with 6.0 months for gemcitabine alone (hazard ratio 0.8, 95% confidence interval 0.65-0.98; p=0.026) and absolute 1-year survival improvement of 7%. The combination regime was well-tolerated with a similar incidence of grade 3 / 4 toxicities in both treatment arms, except more neutropenia in the combination arm.

On the other hand, the PA.3 trial demonstrated the survival benefit in combining erlotinib and gemcitabine for the treatment of advanced pancreatic cancer patients. Erlotinib is a small-molecule tyrosine kinase inhibitor (TKI) of the human epidermal growth factor receptor (EGFR), which has been approved for the treatment of non-small cell lung cancer. EGFR is dysregulated in many tumour types, including 40-65% of pancreatic tumours. PA.3 was a multi-centre, randomised, double-blind, placebo-controlled phase III clinical study of erlotinib in combination with gemcitabine in patients with advanced pancreatic cancer. A significant survival improvement in median PFS was observed in the gemcitabine and erlotinib arm when compared with gemcitabine single agent (3.8 versus 3.5 months, p=0.006). Moreover, the treatment was well-tolerated with incidence of adverse events similar in both arms of PA.3. However, patients who received erlotinib and gemcitabine complained of more rashes, diarrhoea, infection and stomatitis. Although the survival improvement is only modest---14 days in this study, this is still a significant step forward in the management of patients with this notorious malignancy.

Management of Metastatic Pancreatic Cancer

Only a few patients (10-15%) diagnosed to have pancreatic cancer and have limited stage disease are amenable to surgical resection. However, even with surgery, disease recurrence will occur in the majority of patients despite adjuvant therapy. Therefore, systemic therapy for patients with advanced pancreatic cancer is a pressing issue nowadays. Systemic chemotherapy has its established role in the management of metastatic pancreatic cancer patients. It is usually only offered to carefully selected patients with good performance status. In the treated patients, they usually have a significantly better median overall survival with better quality of life as well. However, despite active treatment, less than 5% of patients are alive at 5 years.

First-line Treatment of Metastatic Pancreatic Cancer

In the past, 5-FU was first used as palliative chemotherapy for patients with metastatic pancreatic cancer. Subsequently, gemcitabine became the standard of care for advanced pancreatic cancer for the past decade as in a phase III trial of patients with advanced pancreatic cancer, gemcitabine was found to be better than 5-FU in alleviating the symptoms and associated with a significant longer median survival. Therefore, the US Food and Drug Administration (FDA) approved the use of gemcitabine in the treatment of advanced pancreatic cancer. The approved schedule of administration is 1000 mg/m2 over 30 mins once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles consist of 30-min intravenous infusions for 3 consecutive weeks out of 4. Side effects associated with single agent gemcitabine include myelosupression, lethargy, an influenza-like syndrome, nausea and vomiting and peripheral oedema. Interestingly, the recent clinical trial results suggested that the efficacy of gemcitabine treatment may be enhanced by giving gemcitabine as a fixed-dose rate infusion of 10mg/m2/min, but at the cost of increased toxicities. However, it has not yet been shown to improve overall survival when compared with the standard administration regimes.

Although the efficacy of single agent gemcitabine is superior to bolus 5-FU, its efficacy is modest, with a median survival of only 6 months in most randomised trials and a 12-months survival of < 20%. Therefore, in the past decade, numerous attempts were made to improve the efficacy of gemcitabine treatment by adding other chemotherapeutic or biological agents. Unfortunately, a lot of gemcitabine-based doublets or triplets have been done with very disappointing results. Recently, against a background of numerous negative randomised trials of gemcitabine-based treatment, two trials have reported significant survival improvements with the use of combination treatment: the United Kingdom National Cancer Research Institute GEMCAP trial and the National Cancer Institute of Canada Clinical Trials Group PA.3 trial.

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Second-line Therapy

Thus far, there is no standard second-line treatment for patients with metastatic pancreatic cancer and only 30-50% of patients will have a chance to receive second-line treatment. It is mainly attributed to the fact that many patients who progress with first-line treatment have suboptimal organ function and poor performance status. Therefore, they may not be able to tolerate the second-line chemotherapy well and many clinicians are quite reluctant to offer systemic chemotherapy in this setting. Lately, the results of CONKO-3 just released in the American Society of Clinical Oncology 2008 Annual meeting. In this pivotal phase III trial, patients who received combination of oxaliplatin plus 5-FU and leucovorin as second-line regime had significant improvement in overall survival than patients on 5-FU and leucovorin alone (26 versus 13 weeks, p=0.014). Other second-line pancreatic trials using similar regimes or other combinations are on-going and their results will better define the role of second-line therapy in the treatment of gemcitabine-refractory patients.

Role of Biologics in the Management of Metastatic Pancreatic Cancer

Two pathways play a significant role in pathogenesis of advanced pancreatic cancer: EGFR and vascular endothelial growth factors (VEGF).

Blockade of the EGFR pathway with TKI-erlotinib has demonstrated encouraging results in the PA. 3 trial. Moreover, another TKI-lapatinib also showed encouraging activity in combining with gemcitabine-based treatment in the management of advanced pancreatic cancer patients. However, blocking the EGFR pathway with monoclonal antibody-cetuximab instead showed disappointing results. In the US Southwest Oncology Group study, the addition of cetuximab to gemcitabine had failed to show survival benefit than gemcitabine alone. It is interesting to note the phenomenon that there is benefit in using TKI but not monoclonal antibody in the management of pancreatic cancer. This phenomenon is in contrast to our experiences in using this class of drug in the treatment of other solid tumours. The exact reason is still not yet known.

Anti-VEGF therapy has shown promising results in the treatment of other solid tumours. Unfortunately, targeting VEGF therapy has not yet shown any success in the management of advanced pancreatic cancer. The interim results of the US Cancer and Leukemia Group B failed to show any survival benefits in the addition of bevacizumab to gemcitabine in the management of advanced pancreatic cancer patients. More mature data from this and other on-going trials in using bevacizumab in the management of advanced pancreatic cancer will better define the benefits of addition of bevacizumab to gemcitabine-based regimen.

Conclusion

Despite recent survival improvement with the addition of capecitabine and tarceva to gemcitabine-based treatment of metastatic pancreatic cancer, the benefit is only modest. Moreover, there is additional cost and risk of toxicity from combination regime, particularly the use of erlotinib. Thus, more active and new systemic regimes are desperately needed to improve the outcome of patients with advanced pancreatic cancer. Moreover, further research in the treatment of pancreatic cancer should be underpinned by an improved understanding the underlying pathogenesis of the disease at a cellular, molecular and genetic level.

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References


