Role of Chemotherapy in Pancreatic Cancer

Pancreatic cancer is considered to be the fifth leading cause of solid tumor deaths in US and the incidence is rising in developing countries like India. Most patients are diagnosed at an advanced stage and only a few of the patients are suitable candidates for curative surgery. About 80-90% of pancreatic cancers are ductal adenocarcinomas of the exocrine pancreas. The occurrence of these tumors is twice more in the 'head' of the pancreas when compared to the other parts of the organ. These tumors are highly aggressive and are detected only after distal metastases have occurred. Although pancreatic cancer has been studied up to the molecular and genetic depth, the disease still possesses a definite challenge where treatment is concerned. The severity of the disease is indicated by the fact that when untreated, the median life expectancy is 3 to 6 months for metastatic disease and 6 to 10 months for non-metastatic disease.

Presently, the only curative treatment is surgery. However, approximately 15% of the affected patients are diagnosed at a disease stage in which the tumor is resectable. This is because, this cancer spreads early to the regional lymph nodes and the liver, which results in most patients presenting with advanced disease at diagnosis. Even after an apparently curative resection, the 2-year survival rate is only about 15%

Pancreatic cancer being diagnosed at advanced stage chemotherapy is the main mode of palliative treatment. The goals of treatment for advanced pancreatic cancer include control of tumor progression, alleviation of disease-related symptoms, and improvement in quality of life (QOL) of patients.

Resection is an option in locally advanced pancreatic cancer but there is a high possibility of leaving a positive margin after resection of locally advanced tumors, creating the need for neoadjuvant and adjuvant chemotherapy. A few cases with unresectable tumors may get converted to resectable tumors with neoadjuvant chemotherapy, though the possibility is very low.

Chemotherapy- Single agent

Earlier 5-fluorouracil (5-FU) was the most common drug used for chemotherapy in patients with advanced or metastatic pancreatic cancer. However, efficacy of 5-FU was limited with clinical benefit produced in only 10% patients.

The gold standard therapy with gemcitabine was established by a phase III randomised trial that involved 126 symptomatic patients with advanced pancreatic cancer. The study compared the efficacy of gemcitabine and fluorouracil. The results showed that the improvements in 1-year survival (18% versus 2%) and clinical benefit (24% versus 5%, respectively) and established superiority of gemcitabine over fluorouracil.

Though gemcitabine is now accepted as standard treatment for locally advanced and metastatic pancreatic cancer, the median overall survival (OS) times with gemcitabine alone is found to be in the range of 5-8 months with only 17-25% of the treated patients meeting the criteria for 1-year survival rate. The need to improve palliative and adjuvant chemotherapy has prompted many investigators to study new molecules and new approaches for treating pancreatic cancer.

Chemotherapy- Multiple agents

Combination regimens of 5- FU with other anticancer agents e.g. cisplatin, doxorubicin or doxorubicin/ mitomycin were found to be better than 5-FU monotherapy. However, these combined therapies showed toxicity and no significant overall survival benefit.

Many randomised trials were conducted to investigate gemcitabine-based combination with cytotoxic agents such as a platinum analog, a
fluropyrimidine, antifolates or topoisomerase inhibitors. A meta-analysis of randomised trials was conducted by Heinemann. V et al. to investigate overall treatment in three different combinations namely, gemcitabine with a platinum analog like oxaliplatin or cisplatin, gemcitabine with fluopyrimidines like 5-fluorouracil (5-FU) or capecitabine and gemcitabine with other cytotoxic agents such as pemetrexed, irinotecan and exatecan in advanced pancreatic cancer. The aim of the study was to analyse whether gemcitabine based combination chemotherapy could result in improved treatment efficacy when compared with gemcitabine alone. Fifteen trials (published till 2006) with 4465 patients were considered for the analysis of overall survival (OS), the primary end-point of this investigation. The study revealed a significant survival benefit for gemcitabine+ X with a pooled hazard ratio (HR) of 0.91 (95% CI: 0.85-0.97, p=0.004). The overall test for heterogeneity resulted in p=0.82(I2=0%). The analysis of platinum based combinations indicated a HR of 0.85 (95% CI: 0.76-0.96, p=0.010), while for fluropyrimidine-based combinations the HR was 0.90 (95% CI: 0.81-0.99, p=0.030). No risk reduction was observed in the group of trials combining gemcitabine with irinotecan, exatecan or pemetrexed (HR=0.99). Meta-analysis of the trials with adequate information on baseline performance status (PS) was performed in five trials with 1682 patients.

It was found that a combination of irinotecan with gemcitabine increases the tumor response rate but the benefit did not extend to any advantage in terms of survival benefits in locally advanced and metastasised pancreatic cancer.

A significant improvement in survival benefit was observed in the group of patients treated with combination of gemcitabine with platinum analogs and gemcitabine with fluopyrimidines. More severe side effects, including nausea, vomiting, neurotoxicity and thrombocytopenia were observed with the above combination groups but no reduction in the quality of life due to increased adverse effects was observed.

Table 1: Comparison of gemcitabine alone with gemcitabine + cytotoxic agent (Table to be recreated)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n trials</th>
<th>n patients</th>
<th>HR</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine versus Gemcitabine + Platinum Analog</td>
<td>5</td>
<td>1248</td>
<td>0.85</td>
<td>0.01</td>
<td>0.76 – 0.96</td>
</tr>
<tr>
<td>Gemcitabine versus Gemcitabine + Fluopyrimidine</td>
<td>6</td>
<td>1813</td>
<td>0.9</td>
<td>0.03</td>
<td>0.81 – 0.99</td>
</tr>
<tr>
<td>Gemcitabine versus Gemcitabine + other cytotoxic agent</td>
<td>4</td>
<td>1404</td>
<td>0.99</td>
<td>0.8</td>
<td>0.88 – 1.10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>4465</strong></td>
<td><strong>0.91</strong></td>
<td><strong>0.004</strong></td>
<td><strong>0.85 – 0.97</strong></td>
</tr>
</tbody>
</table>

Chemotherapy with radiotherapy

Radiotherapy alone is not effective for disease control and prevention of progression in the advanced stage of pancreatic cancer. Study reports suggest that benefits of combining chemotherapy with radiotherapy are not significant.

Chemotherapy with targeted therapy

The advent of targeted therapy and biological agents in oncology has brought new insights in the treatment of pancreatic cancer. The combination of gemcitabine with erlotinib has shown promising results and is now used for treating advanced and metastasised pancreatic cancer. A few combination studies that included targeted therapy agents were discussed at the ‘Gastrointestinal Cancers Symposium’ held at Orlando. Most of the studies are still in phase I/II, the results of which indicate that the treatment outcomes vary in locally advanced and metastasised pancreatic cancer and future studies should take this into consideration. Two drug combinations of volociximab- gemcitabine and irinotecan- gemcitabine, three drug combination of
gemcitabine - bevacizumab – erlotinib, four drug combination of gemcitabine - capecitabine - bevacizumab- erlotinib are still under study. 5

Conclusion

Chemotherapy has been established as the best option for palliative therapy in advanced pancreatic cancer. The main advantages that chemotherapy offers over other types of supportive care are symptomatic improvement, a better quality of life along with an increase in survival period. The results of meta-analyses advocate the need for further randomised trials to find the optimal chemotherapy regimen. Another important need for evaluating multidrug regimens is because of the relative chemotherapy resistance of pancreatic cancer and the failure of different single-agent and combination regimens to improve survival. When compared to other chemotherapeutic agents gemcitabine not only offers superior clinical effectiveness, but also has a low toxicity profile. However, chemotherapeutic research should explore other novel agents which will inhibit growth of malignant tumors and target those pathways that fail to undergo normal apoptosis.

References


