Current advances and research in the treatment of pancreatic cancer

Pancreatic cancer is one of the most difficult cancers to treat and is associated with a poor prognosis for patients. The latest figures from Cancer Research UK show that pancreatic cancer is the 11th most common cancer in the UK, with an incidence of 7,600 new cases per year. The mortality rate for pancreatic cancer closely matches the incidence rate, with 7,700 people in the UK dying per year and these figures are reflected in the poor survival rate, with only 2 to 3 per cent of pancreatic cancer patients surviving five years.

The best chance of improving survival rates is through surgery, but this is only possible in early limited stage disease. There is, however, an increasing role for adjuvant treatment — the use of chemotherapy following surgery — in reducing the risk of recurrence and improving survival rates. The European Study Group for Pancreatic Cancer (ESPAC)-3 trial compared an adjuvant 5-fluorouracil (5-FU) chemotherapy regimen with single agent gemcitabine and demonstrated an equivalent average survival time (5.6 months) in the two treatment arms, but the safety profile of gemcitabine was better. The Charité Onkologie (CONKO) 001 trial confirmed the improvement in survival rates for adjuvant gemcitabine compared with surgery and, among patients who had undergone complete resection for pancreatic cancer, median progression-free survival was 13.4 months in the gemcitabine group and 6.9 months in the control group.

Gemcitabine: the current gold standard
Gemcitabine, 2',2'-difluorodeoxycytidine (dFdC), is a pyrimidine analogue anti-metabolite. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis through the actions of its two active metabolites, the 5'-diphosphate (dFdCDP) and 5'-triphosphate (dFdCTP) derivatives. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside diphosphates required for DNA synthesis. Inhibition of this enzyme thus leads to a decrease in the concentrations of these pivotal DNA precursors.

Secondly, dFdCTP competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA and, after incorporation, appears to induce programmed cell death. Further, the decreased concentrations of the essential DNA precursors via inhibition of ribonucleotide reductase by dFdCDP augments the efficacy of dFdCTP through reduced competition with natural substrates for incorporation into DNA.

Combination chemotherapy
Although 5-FU has some activity in pancreatic cancer, the results from a recent multicentre UK trial GemCap, which combined gemcitabine with capecitabine, suggest that combination chemotherapy might be more beneficial than gemcitabine monotherapy in advanced pancreatic cancer. The data from this trial indicated a trend towards a median overall survival advantage (7.1 months versus 6.2 months, P=0.08) for patients in the gemcitabine-plus-capecitabine group. The improvement in outcome was marginal, with only five weeks' survival advantage, so the GemCap regimen has yet to be universally adopted.

Other chemotherapeutic agents that have been tested in combination with gemcitabine include irinotecan, cisplatin, oxaliplatin, and pemetrexed. Trials with these drugs all showed some early promise, with improvements in time to disease progression for the combination arms, but none showed a statistically significant survival advantage over gemcitabine alone.

Targeted therapies
As for many other cancers, the focus of research has moved onto using newer, molecularly targeted therapies, with the aim of blocking the pathways that support the development, survival and progression of pancreatic cancer cells. Research has shown that pancreatic cancer has particular biological characteristics that suggest that this class of agents could prove effective. For example, the epidermal growth-factor receptor (EGFR) and vascular endothelial growth-factor (VEGF) pathways are both over-expressed in pancreatic cancer (ie, the cancer cells have a greater number of EGFR and VEGF receptors than normal cells). This over-expression has been shown to stimulate tumour growth, and is linked to poor disease outcomes and decreased sensitivity to chemotherapy.

Erlotinib
Erlotinib (an EGFR tyrosine kinase inhibitor) is licensed for treatment of patients with metastatic pancreatic cancer in combination with gemcitabine, and this combination showed a statistically significant survival benefit over gemcitabine alone in locally advanced or metastatic disease (median overall survival 6.4 months versus six months, P=0.038). Although of scientific interest, the clinical relevance of a survival difference less than two weeks has been questioned. In the US, the results from this trial were seen as ev...
Bevacizumab

Bevacizumab is a novel humanised monoclonal antibody that binds to, and inhibits, VEGF, thereby inhibiting angiogenesis (the growth of new blood vessels). Cancer cells release pro-angiogenic factors (e.g., VEGF) to nearby blood vessels, causing them to develop new “branches” that grow towards the cancer, providing oxygen and nutrients. In addition to its direct antiangiogenic effects, bevacizumab may also help to improve the delivery of chemotherapeutic agents to the tumour by normalising tumour vasculature and decreasing the elevated interstitial pressure within the tumour. Bevacizumab remains an interesting drug, but a combination of high cost and marginal benefit from clinical trials has limited its use in licensed indications in the UK.

Cyclopamine

One compound that may offer future hope in the treatment of pancreatic cancer is cyclopamine, a natural product derived from Veratrum californicum (the corn lily), which provides a perfect illustration of the power and complexity of natural product chemistry.

Origin

Around 50 years ago, sheep ranchers from Idaho noticed that some of their lambs were born with unusual cyclopian-like birth defects. After many years of research into this phenomenon, it was found that, when pregnant ewes ingested Veratrum californicum, characteristic cyclopian-like birth defects resulted in the lambs. The compound that induced these effects was isolated and was found to contain a basic nitrogen (so, an amine) (see Figure above), which led to this alkaloid being named cyclopamine.

Mechanism

Cyclopamine is a potent inhibitor of a cell-signalling pathway, known as the hedgehog signalling pathway. This pathway is normally switched on in healthy adults, but is turned on at certain times, such as during embryonic development, during tissue repair, and also during the tumorigenesis of some cancers. Cyclopamine therefore offers a novel therapeutic strategy in the treatment of some cancers, including pancreatic cancer, and has been shown to induce cell death and block proliferation, both in vitro and in vivo, in some cancer cell lines. Cyclopamine has also been evaluated as an adjuvant treatment for pancreatic cancer with conventional chemotherapy, and initial results appear to be promising, with cyclopamine increasing the cytotoxic effects of both paclitaxel and radiotherapy.

References


Limitations

There are, however, pharmaceutical chemistry barriers to cyclopamine becoming a new blockbuster drug. One problem is that it has a poor solubility profile, while its complex structure, with 10 chiral centres, means that the total synthesis of cyclopamine would be a complex and expensive process. Currently, 1mg of cyclopamine costs in excess of £90. One possible solution to this latter problem would be to extract cyclopamine from the corn lily. Studies have shown that the roots and rhizomes of Veratrum californicum can contain up to 2.34g of cyclopamine per kilogram of dried plant material.

In an attempt to overcome the problems, research is currently under way to develop cyclopamine derivatives, or discover other novel hedgehog pathway inhibitors.

Conclusions

In recent years, we have seen advances in the treatment of many cancers which have poor prognosis. Cancers, such as lung cancer, renal cancer and hepatic cancer, have benefited from the development of novel targeted therapies. Sadly, pancreatic cancer remains a disease with poor patient outcomes and, although there are some promising therapies on the horizon, so far only two agents, capcitabine and erlotinib, have shown any additional benefit over treatment with gemcitabine alone. Single agent gemcitabine remains the mainstay of the palliative treatment of advanced disease.

Research into new signalling pathways, such as the hedgehog pathway, has provided novel therapeutic targets for the treatment of pancreatic cancer. The challenges for the future are to find agents that, after showing initial promise in research, deliver meaningful results for patients as part of therapeutic regimens.