Treatment of advanced pancreatic cancer

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Metastatic pancreatic cancer afflicts the vast majority of patients diagnosed with this disease: it is calculated that, overall, pancreatic cancer is the fourth most common cause of cancer death, that the overall survival at 5 years is <5% and that at diagnosis more than half of the patients have advanced disease with distant metastases.

In the case of locally advanced disease without distant metastases, there is a possible role for chemoradiation. A systematic review [1] clearly indicated that the combination of chemotherapy and radiotherapy is more effective than best supportive care and than radiotherapy alone, but not better (and more toxic) than chemotherapy alone. Also considering the limits of the studies performed so far, a possible strategy for clinical practice could be the consolidation with radiochemotherapy (or even radiotherapy alone) in patients with a disease well controlled (tumour shrinkage or stabilization) with chemotherapy [2]. This approach is now under evaluation in a prospective phase III trial.

In metastatic disease the life expectancy is limited to a few months and the role of medical treatment is essentially palliative.

The following statements summarize the state of the art in this field:

- Monotherapy with gemcitabine has remained the main option for about 15 years [3]
- The combination of gemcitabine with different drugs generally did not produce any significant advantage in comparison with gemcitabine alone
- Associations of gemcitabine with fluoropyrimidines (i.v. or oral) or platinum derivatives (cisplatin or oxaliplatin) obtained a significant improvement in overall survival only in meta-analyses [4]
- Among the several evaluated targeted drugs, only erlotinib was able to obtain, when combined with gemcitabine, an increase in overall survival, but this advantage is very modest (2 weeks only) [5]
- Among the new drugs there is a particular interest for nab-paclitaxel, which demonstrated high activity (response rate: 48% and median overall survival: 12.2 months) in combination with gemcitabine in a small study [6] and which seems able to overcome the drug resistance related to the large stromal component of this disease

More recently, a combination regimen including conventional agents (FOLFIRINOX: 5-fluorouracil, folinic acid, irinotecan and oxaliplatin), but not gemcitabine, was demonstrated to be more effective than gemcitabine alone in an independent phase III clinical trial [7]. There was a significant improvement in overall survival, progression-free survival and quality of life, even though FOLFIRINOX was more toxic than gemcitabine in terms of diarrhoea, nausea/vomiting, fatigue, neutropenia and febrile neutropenia. However, the study population was favourably selected (performance status [PS] 0–1, metastatic cancer mainly of the pancreatic body, age <76 years etc.) and therefore the translation of this regimen into clinical practice appears to be limited to patients with normal bilirubin, no biliary stent, good PS, no cardiac ischaemia, age <70 years etc. The possible role of the addition of granulocyte-colony stimulating factors (G-CSFs) and the potential optimization/simplification of the administration schedule are the matter of ongoing or future clinical trials.

Another recent achievement is the real possibility of submitting selected patients to a second-line medical treatment [8], with interesting results obtained by a conventional regimen for gastrointestinal cancer such as FOLFIRI [9].

To further improve the dismal prognosis of locally advanced or metastatic pancreatic cancer, a recent paper from an international expert panel proposed, among others, the following recommendations [10]:

- Define in an uniform manner specific groups of patients for various areas of clinical research
- Define uniform criteria to report treatment results and endpoints in clinical studies
- Treat as many patients as possible in the framework of prospective clinical studies
- Collect tumour material and blood samples for translational research
- Set up biobanks using standardized operating procedures

Following this vision, it is conceivable that significant progress in this difficult field could be made in the next few years.
disclosure

The authors have declared no conflict of interest.

references


