Perspective

Locally advanced versus metastatic pancreatic cancer: two different diseases with two different treatment approaches?

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Abstract: The results of the SCALOP trial were reviewed and interpreted at the light of previous trials and of the more recent LAP-07 trial. In this latter trial the role of radiotherapy after an induction chmeotherapy has been questioned. Based on these findings data from the SCALOP trial loose most of their value. In fact, while it showed that capecitabine may be combined with radiotherapy more safely than gemcitabine and it could be a standard regimen as a consolidation regimen after an induction chemotherapy, the LAP-07 trial showed that radiotherapy in combination with chemotherapy does not add any valuable effect to chemotherapy alone.

Keywords: Pancreatic cancer; locally advanced disease; chemoradiotehrapy

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Locally advanced unresectable disease represents around one third of the cases of pancreatic cancer at diagnosis. Although locally advanced pancreatic cancer has a poor prognosis, it is clearly better than that of metastatic disease, with a median survival of 9 months compared with the 3-month survival of the metastatic disease. However, in a few months the majority of patients with locally advanced disease develop metastastes (1). This natural history of disease is probably one of the reasons for the controversies about the optimal management of these patients (2). In fact, after two decades of clinical research, a debated issue is still the contribution of a local regional treatment such as radiotherapy in a disease, apparently localized, but in reality already metastatized. While in US most of the patients receive chemoradiotherapy upfront, in Europe radiotherapy is generally reserved to patients not progressing after 2 or 3 months of chemotherapy. This latter approach is based on the previous considerations but mainly on a retrospective analysis by GERCOR and a systematic overview (2,3). It was shown in fact that patients receiving radiotherapy after an induction chemotherapy seems to have a better survival in comparison with patients receiving only chemotherapy (15 *vs.* 11.7 months) (2,3). These clinical results are supported also by biological findings. Recently, it was demonstrated that EMT and dissemination are early events in pancreatic cancer and precede even tumor formation (4). Obviously, these new biological insights question the role and efficacy of a local treatment such as radiotherapy, in a disease only apparently localized. This has been shown, clinically, in the Chauffert's study where patients with locally advanced disease were randomised to receive gemcitabine or radiotherapy plus 5fluorouracil followed by gemcitabine (5). In the chemoradiotherapy arm survival was significantly worse: 8.6 versus 13 months. It seems to confirm that a local treatment is not a good therapeutic approach for locally advanced pancreatic cancer. Furthermore, radiotherapy or chemoradiotherapy may produce higher rates of toxicity affecting the patients quality of life and even contributing to a worst prognosis since treatment may be delayed or discontinued. On the contrary, reserving radiotherapy as a consolidation treatment in only patients not progressing after 2-3 months of treatment may spare an useless upfront locoregional treatment in several patients showing an early systemic progression of disease. This leads to a significant reduction of severe side effects and costs for patients and health system.

Another debated issue has been which drug is preferable to combine to radiotherapy. Fluorouracil is commonly associated with radiotherapy in several different cancer types. Gemcitabine is a potent radiosensitizer but it is often associated with an increased toxicity.

Three small randomised trials and a meta-analysis suggested a survival advantage of gemcitabine in comparison with fluorouracil when combined to radiotherapy in locally advanced pancreatic cancer (6-9).

The paper by Mukherjee *et al.*, published in the *Lancet Oncology*, reports the results of an interesting trial exploring the role of gemcitabine or capecitabine, combined with radiotherapy, as consolidation treatment in patients with locally advanced unresectable pancreatic cancer not progressing after an induction chemotherapy. Although there were no differences in activity and efficacy, the authors suggested that a capecitabine-based regimen might be preferable in terms of toxicity in the context of a consolidation chemoradiotherapy after an induction chemotherapy (10).

This may be an useful information for the clinical practice since most of the pancreatic cancer patients receive radiotherapy after chemotherapy and it was not completely clear in spite of the previous trials which drug should be better combined with radiotherapy. Gemcitabine is not a "friendly" drug when combined with radiotherapy and, although gemcitabine is popular in metastatic pancreatic cancer more than for its favourable toxicity profile than for its efficacy, it is not reccomandable to combine it with radiotherapy since toxicity may represent a clinical relevant problem.

Can we learn something else from this study? It seems to support the strategy of giving firstly chemotherapy and only in the case of a not progressing disease to deliver radiotherapy. In fact, a minority of patients were candidated to receive radiotherapy: only 74 patients out of the 216 patients assessed for eligibility were randomized in this study. Most of the patients were considered not eligible because of progressive disease or an early deterioration of the clinical conditions.

A critical point in this trial is the regimen chosen as induction chemotherapy. A combination of gemcitabine and capecitabine does not represent a standard therapy in advanced pancreatic cancer worldwide. In fact, the combination of gemcitabine and capecitabine is not clearly superior to gemcitabine alone while other regimens such as FOLFIRINOX or nab-paclitaxel/gemcitabine are more effective in the control of the micrometastatic disease (11,12). In reality, we do not know if a better induction chemotherapy may improve the overall results, by decreasing the rate of metastatic dissemination, and therefore to give some value to radiotherapy in the control of the local disease. Several trials with these new regimens are exploring this hypothesis and we have to wait these results before planning future clinical studies (13,14).

Another problem limiting the potential clinical value of this trial is the results of the LAP-07 trial, presented at the last ASCO meeting (15). In the French trial, 269 patients not progressing after 4 cycles of gemcitabine were randomised to receive gemcitabine alone or capecitabine plus radiotherapy. Surprisingly, there were no differences in survival (16.4 *vs.* 15.2 months). These unexpected results question the role of radiotherapy and suggest that chemotherapy alone could be the standard approach even for locally advanced pancreatic cancer patients. Once again caution should be recommended since the induction chemotherapy regimen does not represent the potentially best chemotherapy in pancreatic cancer.

The SCALOP trial is also of some merit because it allows to interpretate and to put in the right context the LAP-07 trial results. In fact, one of the possible doubts in the interpretations of the negative results of the LAP-07 trial could be the non optimal combination of chemoradiotherapy. Data from the SCALOP trial showed that it could not be the reason since a capecitabine-based regimen is the preferable regimen in this setting.

If we look at the results of the SCALOP trial on the basis of the LAP-07 trial we can learn another important lesson. SCALOP trial was designed on the basis of the results of retrospective data. It is a well designed and conducted trial but it has no clinical value since the assumption of the trial, a consolidation chemoradiotherapy is better than chemotherapy alone, was not demonstrated by the LAP-07 trial. In fact, now we know that capecitabine may be the preffered drug to be combined with radiotherapy but, unfortunately, we know also that the role of radiotherapy in the management of locally advanced pancreatic cancer is marginal. Therefore, the SCALOP trial is completely devoid of any clinical utility and, even, most patients receive a toxic and ineffective regimen raising ethical concerns.

Retrospective analyses can give us relevant informations but they should be prospectivelly confirmed before to be regarded as standard in the clinical practice or as a reference arm in clinical trials. The risk is that several trials, designed on the basis of retrospective findings, can give controversial results by treating several patients with a non optimal

regimen or strategy. Even from an ethical point of view these approaches are not reccomandable.

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