Opinion

Neoadjuvant treatment in non- metastatic pancreatic cancer, an option to be considered

Abstract

Adenocarcinoma of the pancreas is a high lethal malignancy. Metastatic and unresectable patients have a very poor expectative of survival. For resectable patients and borderline resectable patients surgery is the only chance of cure, however early recurrence and distant metastasis are very frequent and rarely these patients will live longer than 3 years despite a complete tumor resection. Neoadjuvant treatments have been explored in order to improve R0 resection rates and survival. Despite a lack of phase 3 trials there is some evidence that supports the use of neoadjuvant chemotherapy with or without sequential radio chemotherapy in borderline resectable pancreatic cancer patients.

Keywords: pancreatic cancer, borderline resectable pancreas cancer, neoadjuvant chemotherapy

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Opinion

Pancreatic adenocarcinoma is one of the malignancies with worse prognosis among all solid tumors. It is the third cause of death due to cancer in the United States, with an estimated incidence of 48.960 new cases by 2015 and 40.560 deaths during the same year. Incidence and mortality are slightly higher in men than in women.[1]

In some developing Latin American countries, for several reasons such as the increase in life expectancy and changes in alimentary styles, pancreatic cancer is becoming a more frequent malignancy. For example, in Chile where the population is almost 17million inhabitants the annual mortality for adenocarcinoma of the pancreas was 5.8 for 100.000 in men and 5.6 for 100.000 in women by 2012, nevertheless, curiously due to a problem in registers in Chile, but also in some other countries, the reported mortality is higher than the reported incidence for this malignancy.[2] In order to define the upfront treatment, non-metastatic pancreatic cancer patients have been classified into 3 subgroups using radiological criteria: resectable patients, borderline resectable patients and unresectable patients.

Non- metastatic unresectable patients and metastatic patients have a similar bad prognosis and in the case that they have a good performance status then they should be considered to be treated with palliative systemic chemotherapy with the aim of improving quality of life and overall survival. Regardless of the relative poor 5-years survival, resectable and borderline pancreatic cancer patients should be considered for curative intention treatments.

Until today surgery is the only treatment that can offers a potential cure to pancreatic cancer patients, however less than the 20% of patients might be considered as resectable at diagnosis, and even worse, several patients that might undergo a R0 resection will have a recurrence before two years after surgery.[3] From the total of patients that undergo surgery, 75% of them will have a recurrence due to microscopic metastatic disease that was undetectable at diagnosis, or due to a resistance of residual tumor cells to adjuvant treatments, and also in some cases due to a non achieved R0 resection during surgery,[4,5] therefore the median overall survival in well resected patients is not greater than 11 to 20months in different reports.[6,7]

The current standard of care treatment for early stages-resectable pancreatic adenocarcinoma patients is surgery followed by adjuvant chemotherapy.[8–10] Concurrent radiotherapy plus chemotherapy combination have shown disparities in results and its use is not a standard of care, however it can be considered in some well selected patients for adjuvant treatment.[11–15]

The use of adjuvant chemotherapy can be delayed or affected by postoperative complications but also by the appearance of early recurrences that can be found before that systemic treatment starts or during early images control. Prospective observational trials have shown that up to 38% of resected pancreatic cancer patients did not achieve to receive chemotherapy due to those reasons.[16,17] Recently, modified FOLFIRINOX regimen became the new standard of care in the adjuvant setting for resected pancreatic cancer patients.[18] Considering the bad prognosis of this disease despite of a complete resection when feasible, neoadjuvant treatments have been explored in order to improve survival curves. Theorically, treating patients with neoadjuvant chemotherapy might favor to eliminate microscopic metastatic disease looking forward to get better results in terms of overall survival, but also it can allow selecting patients for surgery because if they have disease progression during treatment an unnecessary surgery could be avoid in patients that otherwise would have a rapid disease progression after surgery, procedure that is also not free of comobirdities and mortality.[19]

Nevertheless, to date there are not phase 3 clinical trials that support the use of neoadjuvant treatments in pancreatic cancer patients. Most of the available evidence is limited to retrospective evidence or to one arm design-prospective clinical trials.[20] Phase 2 clinical trials have evaluated the use of neoadjuvant treatment for resectable and borderline resectable pancreatic cancer patients, either with chemotherapy or with chemo radiotherapy combination.[21–23] These trials have been hard to interpret at because included different types of patients such as resectable, borderline resectable and unresectable patients at diagnosis, but also have used different modalities of radiotherapy and different schedules of chemotherapy as well. In general one third of the patients that underwent neoadjuvant chemo radiotherapy had disease progression after the upfront treatment and surgery was not performed. Patients that underwent surgery achieved a R0 resection between 68 to 96% of the total of resected patients. Patients that had recurrence after treatment did it mainly with distance

metastasis (59 to 73%), most of them located at the liver, and with a lower local recurrence rate that was seen between 0 to 25% in different reports. Reported overall survivals show also heterogenecety, patients that only received neoadjuvant treatment with chemoradiation but did not undergo surgery had survival between 9 and 22months, however patients that underwent surgery after neoadjuvant treatment that included radiotherapy with or without chemotherapy achieved survivals up to 31months.

The use of neoadjuvant FOLFIRINOX followed by chemoradiation as a multimodality treatment has shown promising results. In a small multicenter trial that included 22 borderline resectable pancreatic cancer patients, Katz et al assayed the use of 4 cycles of neoadjuvant modified FOLFIRINOX followed by 5.5weeks of radiation therapy with a total dose of 50,4 Gy in 28 fractions with concurrent capecitabine twice daily during radiation.[24] Grade 3 toxicity was reported in 64% of patients. 15 patients underwent pancreatectomy, 80% of them required vascular resection and R0 resection was achieved in the 93% of the resected patients, the reached median overall survival was 21,7months.

Prospective trials are currently ongoing and their aim is to find out the real impact of neoadjuvant treatment in resectable pancreatic cancer patients.[25–27]

Recently Mokdad et al.[28] reviewed the data from a cohort of 15.237 patients (National Cancer Database 2006-2012) with stage I-II adenocarcinoma of the head of the pancreas that were treated with curative intention, comparing neoadjuvant treatment (chemotherapy or chemo radiotherapy combination) with patients that underwent upfront resection with or without adjuvant treatments (chemotherapy or chemo radiotherapy combination) in order to evaluate overall survival. Authors of this manuscript showed that patients that had been received neoadjuvant treatment had better results in terms of survival when compared with patients that underwent surgery as an upfront treatment. Median survival was 26months for the neoadjuvant group and 21months for the group that underwent surgery as an upfront treatment, but also it was seen a higher pathological tumor stage, higher incidence of lymph node compromise and a lesser R0 resection in the group that did not receive neoadjuvant treatment.

Despite that these findings give us some important information about this until recently few explored option of treatment, their designs limit to have a global conclusion and enhance the need to develop well designed phase 3 clinical trials in the neoadjuvant setting for pancreatic cancer patients.

Pancreatic cancer patients with resectable or borderline resectable disease should be always discussed in a multidisciplinary approach in order to define their best options of treatment. This discussion should include but not be limited to a digestive oncological surgeon with expertise in pancreatic oncological surgery, a medical oncologist, a radiologist with expertise in pancreas, a radiotherapist and a pathologist. Upfront resectable patients normally are considered to undergo surgery followed by chemotherapy, and in some exceptional cases or when the patients have a R1 resection, chemo radiotherapy combination as adjuvant treatment become an option. Borderline resectable pancreatic cancer patients are a challenge for the multidisciplinary oncological team, and a neoadjuvant treatment should be always considered in order to attempt a R0 resection, otherwise the chance of cure, that it is just limited for the diagnosis itself it will be similar to metastatic patients.

Chemotherapy without radiation has been explored as an option for neoadjuvant treatment in pancreatic cancer. A phase 2 clinical trial in the neoadjuvant setting using gemcitabine with or without cisplatin showed a resection rate of 54% and a median overall survival of 28 months in resected patients.[29] Unfortunately similar trials using gemcitabine plus cisplatin doublet showed inferior results.[30] A meta analysis, that included several chemotherapy schedules as monodrug or combination drugs in patients with resectable disease but also unresectable at the time of diagnosis, showed that from the total of patients that were initially considered unresectable, after chemotherapy treatment one third of them were able to undergo surgery achieving a complete tumor resection.

Promising results in small trials have been achieved with FOLFIRINOX schedule in patients with borderline resectable pancreatic cancer, that included or not preoperative radiotherapy after the chemotherapy regimen, achieved a 80% of resection rate.[31] Report of a case showed efficacy in order to achieved resection in a patient with unresectable local advanced diseased that was treated with gemcitabine plus nab paclitaxel combination followed by FOLFIRINOX.[32] Current ESMO guidelines support the use of FOLFIRINOX followed by chemo radiotherapy in borderline resectable patients as a main option in pancreas cancer.[33]

Due to a lack of strong data based on phase 3 clinical trials, it is not possible to talk about a gold standard treatment in the neoadjuvant setting of pancreatic cancer patients. Most of the groups support the idea to perform surgery as an upfront treatment in resectable patients followed by adjuvant chemotherapy. Patients that are clearly unresectable or metastatic should be considered for palliative treatments that may include systemic treatments as a part of a global approach. The most difficult approach to define the best treatment is in the borderline resectable patients subgroup. There are disparities of opinions, that´s why the importance to get a consensus of treatment. At SLAGO 2015 (Latin American Gastro-Enterology Cancer Symposium) congress,[34] a meeting held every two years in Latin America that focuses on digestive malignancies, specialists from different Latin American countries met to discuss about pancreatic cancer. Concerning borderline resectable pancreatic cancer patients, SLAGO´s main recommendation is to consider FOLFIRINOX schedule as the best choice for neoadjuvant treatment, then after selected patients that do not have disease progression after chemotherapy could be consider for radiotherapy with capecitabine as radio sensibilizer before surgery. For patients that have contraindication to receive FOLFIRINOX and in older than 76 years old neoadjuvant treatment with gemcitabine plus nab- paclitaxel combination can be an option to use.[35]

As final remarks, we would like to emphasize that there is not strong evidence to have final conclusions in order to define the best upfront treatment in non- metastatic resectable and borderline resectable pancreatic cancer patients. For resectable patients at diagnosis upfront surgery is the standard of care followed by adjuvant chemotherapy. In this subgroup of patients radiotherapy and radio chemotherapy do not seem to be the best choice, by other hand neoadjuvant chemotherapy has not been explored in well designed clinical trials just limited to this subset of patients. Borderline resectable pancreatic cancer patients is a subgroup where upfront surgery has a low chance of achieve a R0 resection, therefore these patients must be considered to receive neoadjuvant treatments in order to improve complete tumor resection and as a consequence the overall survival. As in resectable subset of patients, radiotherapy or radio chemotherapy have not shown a real impact in this group. Folfirinox followed or not of chemo radio radiotherapy seems to be the best option in terms to improve respectability, ensure a best chance of complete resection, a pathological down staging and overall survival in resected patients.

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However all this information has been obtained from small trials and must be explored in well designed phase 3 clinical trials to obtain a knowledge that confirms us the best option of treatment in borderline pancreatic patients.

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Conflict of interest

Author declares that there is no conflict of interest.

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