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Minireview

Chemotherapy in Palliative Metastatic Pancreatic Adenocarcinoma: A Review of the Existing Literature

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Abstract

Pancreatic cancer is increasing and unfortunately most patients are diagnosed in advanced stages, when surgery is not possible. Nowadays, pancreatic cancer represents only 2,5% of all malignant neoplasms diagnosed annually in the world, but it is the 4th leading cause of cancer death in both sexes.

keywords: metastatic pancreatic adenocarcinoma. palliative chemotherapy, positive phase III clinical trials

Introduction

The term pancreatic cancer includes two distinct entities: pancreatic adenocarcinoma and neuroendo-crine tumour of the pancreas. The adeno-carcinoma of the pancreas is the eleventh most common cancer in the world, comprising 2,5% of all cancers. It usually only exhibits symptoms in an advanced stage of the disease. Consequently, it is frequently diagnosed as already inoperable and therefore carries a reserved prognosis. It represents the seventh deadliest cancer globally, with higher impact in developed countries, namely Europe. According to the SEER database from 2008 to 2014, its 5 years overall survival was 8,5% [1-3]. Incidence seems to be rising, but mortality might finally be slowing down since 2005 [4].

Risk factors for pancreatic adenocarcinoma include old age (incidence increases after 60 years of age) [3], male sex, family history, type 1 and type 2 diabetes mellitus, cigarette smoking, alcohol abuse, obesity, certain foods (such as red meat, processed meats, high cholesterol intake) and occupational exposures. [1, 5, 6] Better therapies for pancreatic adenocarcinoma are needed and in recent years there has been some development on this front. In this article we aim to review the published trials on the subject.

Methods

A PubMed search was performed, and the authors selected phase III clinical trials on palliative chemotherapy (ChT) for pancreatic adenocarcinoma with positive results.

Discussion

Initial clinical trials for adenocarcinoma of the pancreas found a small benefit in the treatment with 5-Fluorouracil (5-FU), but were later criticized due to measuring response rates depending on clinical reduction of hepatomegaly and palpable lesions, with little gain regarding Overall Survival (OS). The first real advancement, albeit modest, in the treatment of pancreatic adenocarcinoma was accomplished in 1997, in the clinical trial using the novel drug (at the time) gemcitabine against 5-FU, the standard treatment until then. The trial included 126 patients, with a Karnofsky performance status of 50 or above, 63 of which were randomized to treatment with gemcitabine 1000mg/m^2 weekly x 7 with 1 pause week, then weekly for 3 weeks with 1 rest week, and 63 patients to 5-FU 600 mg/m^2 once weekly. The trial was single blinded (treatment allocation was known by the physicians, but not the patients). The primary endpoint was clinical benefit, measured by improvement in at least one of the following: pain control, Karnofsky performance status and weight.

On the gemcitabine arm, 23.8% of patients experienced clinical benefit, opposed to 4,8% of the 5-FU treated patients (p=0,0022). The median OS was

5,65 months for gemcitabine and 4,41 months for 5-FU and the OS at 12 months was 18% and 2% for emcitabine and 5-FU, respectively (p=0,0025). Both drugs were well tolerated, with higher incidence of grade 3 or 4 neutropenia with gemcitabine, as well as nausea and vomiting. Thus, a new standard of care was established [7].

In 2007 a phase 3, double blind clinical trial was published comparing gemcitabine/placebo (gemcita-bine 1000mg/m^2 weekly x 7 with 1 pause week, then weekly for 3 weeks with 1 rest week) with gemcitabine/erlotinib (gemcitabine 1000mg/m^2 weekly x 7 with 1 pause week, then weekly for 3 weeks with 1 rest week and erlotinib orally 100 or 150 mg/d) until progression or unmanage-able toxicity. The primary end point was OS. The treatment with the doublet is associated with a statistically significant increase in OS SG (6,24vs 5,4 months; HR 0,.82; p:0.088) and in Progression Free Survival (PFS). Adverse events such as rash and diarrhea were increased in the group of patients treated with the doublet, and the occurrence of grade 2 or higher skin rash was associated with better responses and OS in patients treated with erlotinib [8-10].

One of the successes to date in this pathology was obtained in a multicenter phase 2/3 clinical trial (PRODIGE) with the schedule FOLFIRINOX. The trial included 342 patients without previous ChT and ECOG 0-1. No patients over the age of 76 were contemplated in this study, nor were patients with cardiac disease or elevated bilirubin levels. Patients were randomized to treatment with FOLFIRINOX (85mg/m^2, 2-hour intraven-ous infusion, then leucovorin 400mg/m^2 in a 2-hour intravenous infusion, adding irinotecan 180mg/m^2 after 30 minutes, as a 90-minute intravenous infusion, followed by 5-FU 400mg/m^2, by intravenous bolus and finally 5-FU 2400mg/m^2 in continuous intravenous infusion over a 46-hour period every 2 weeks) or gemcitabine (1000mg/m^2, in a 30-minute intravenous infusion weekly for 7 weeks, followed by a 1-week rest, then weekly for 3 weeks every 4 weeks). In the phase 3 trial, the primary end point was OS.

Median OS was improved to 11,1 months with FOLFIRINOX versus 6,8 months with gemcitabine (HR 0,57, 95% CI 0,45-0,73). OS at 12 months was 48,4% with the triplet and 20,6% with gemcitabine, whereas OS at 18 months 18,6% in the former group and 6% in the latter. Median PFS was 6,4 months in the FOLFIRINOX group, opposed to 3,3 months in the gemcitabine one; PFS at 12 months was 12,1% and 3,5% for FOLFIRINOX and gemcitabine, respectively. Objective response rate (ORR) was 31,6% for FOLFIRINOX and 9,4% for gemcitabine (statistically significant difference).

The FOLFIRINOX group experienced more cases of grade 3-4 neutropenia and febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, as well as alopecia. Despite this fact, in the performed questionnaires, the analysis of the interval of time to quality of life deterioration was in favor of FOLFIRINOX [11].

In 2013, a multi-center, randomized phase III clinical trial compared gemcitabine with gemcitabine in combination with albumin-bound paclitaxel particles (nab-paclitaxel). Inclusion criteria consisted of patients with a Karnofsky performance status of 70 or above, chemotherapy naïve for metastatic pancreatic adenocarcinoma (it allowed previous adjuvant chemotherapy, including with gemcitabine); 10% of patients were older than 75 years. The trial included 861 patients, who were randomized to intravenous infusion of nab-paclitaxel at a dose of 125mg/m^2, followed by infusion of 1000mg/m^2 of gemcitabine (days 1, 8, 15, 29, 36, and 43) or gemcitabine alone (1000 mg/m^2) weekly for 7 of 8 weeks, after which all treatments were given on days 1, 8, and 15 every 4 weeks. The primary efficacy endpoint was OS.

The patients in the gemcitabine/nab-paclitaxel arm achieved a median OS of 8,5 months and the patients in the gemcitabine arm 6,7 months (hazard ratio 0,72; confidence interval 95% 0,62-083); OS at 12 months was 35%vs22% with gemcitabine/nab-paclitaxel and gemcita-bine, respectively (statistically significant difference). ORR was also improved with gemcitabine/nab -paclitaxel, from 7% to 23%. PFS was 5,5 months in the combination arm and 3,7 months in the monotherapy arm; PFS at 1 year was 16% and 9% with gemcitabine/nab-paclitaxel and gemcitabine. Decrease in Ca 19-9 was more evident with the combination treatment. The reported rate of serious adverse events was akin in both groups, (50% with nab-paclitaxel and 43% without). Patients treated with nab-paclitaxel had more neutropenia, peripheral neuropathy (all grade 3 or lower), fatigue, sepsis and pneumonitis. Therefore, gemcitabine with nab-paclitaxel is a viable treatment option in patients with adenocarcinoma of the pancreas[12].

It is clear that patients in the FOLFIRINOX trial were younger and fitter on average than the ones in the gemcitabina/nab-paclitaxel trial. The FOLFIRINOX trial patients also presented a smaller percentage of tumours of the pancreatic head. The current literature is lacking a trial with a direct comparison of these two ChT regimens.

We consider that gemcitabine, gemcitabine /nab-paclitaxel and FOLFIRINOX are appropriate first line (1st L) choices of palliative ChT of pancreatic adenocar-cinoma, to be selected according to the indivi dual patient characteristics (such as age, performance status and comorbidities).

Although in patients who were treated with prior fluoropyrimidine based ChT, 2ndL therapy with gemcita-bine based therapy is acceptable and vice versa also, only two phase 3 clinical trials in second line were positive. In the CONKO-0003 trial published in 2014, 46 patients without previous exposure to fluropyrimidine based chemotherapy were randomized between best supportive care (BSC) and ChT with oxaliplatin plus 5FU and leucoverin (LV) (OFF: LV

200 mg/m^2 in 30 minutes infusion followed by 5 FU 200 mg/m^2 in a 24 hours infusion on days 1,8, 15 and 22 and oxaliplatin 85 mg/m^2 in 2-4 hours infusion prior to leucoverin/5 FU on days 8 and 22; cycles every 6 weeks). The OS was superior on the arm of OFF treatment (5.9 vs 3.3 months). The most frequent toxicities in the OFF arm were sensory diarrhea and emesis, but no grade 4 of non haematologic toxicities.nor grade 3 or 4 of haematologic toxicities were reported in the OFF treatment arm.The best response obtained was stable disease [13,14].

In the NAPOLI-1 trial, a double blind phase III trial, 228 patients with metastatic pancreatic adenocarcinoma previously treated with gemcitabine based therapy were randomized between three arms: nanolipossomalirinotecan (nal-IRI) monotherapy (nal-IRI 120 mg/m^2 every 3 weeks) or 5FU/LV (5-Fluorouracil 2000 mg/m^2 IV and Leucovorin 200 mg/m^2 IV for 4 weeks followed by 2 weeks of rest every 6 weeks). A third arm consisting of nal-IRI 80 mg/m^2, with 5-Fluorouracil 2400 mg/m^2 IV and folinic acid 400 mg/m^2 IV every 2 weeks was added later (1:1:1), in a protocol amendment. Median PFS, objective response rate and disease control rate were all in favor of thenal-IRI/5FU/LV treatment arm; the estimated one-year overall survival rate was also superior (25% vs 16%)[15].

Emphasizing that there are only two phase 3 clinical trials in 2nd line, in clinical practice in patients with good performance status in 2nd L the patients who did 1st L ChT based on gemcitabine should performed therapy based in fluoropyrimidine (nal-IRI/ 5FU/LV, FOLFIRINOX, FOLFOX, OFF, FOLFIRI, CAPOX, Capecitabine, FOLFIRI) and in patients who did 1st L based in fluoropyrimidine, usually ChT based in gemcitabine (gemcitabine / nab-paclitaxel, gemcitabine/ erlotinib, gemcitabine/cisplatin, gemcitabine in mono-therapy) should be chosen.In patients with microsatellite instability (MSI) or mismatch repair deficiency (dMMR) tumors pembrolizumab can also be an option in patients with good performance status.

Conclusion

Currently opinions are divided when consider-ing the best chemotherapy option for 1st line: FOLFIRINOX vsgemcitabine / nab-paclitaxel, without the answer being linear. Several factors must be taken into account, such as comorbidities, patient preference, among others. Although only two positive clinical trials in the 2nd L occurred (CONKO-003 and Napoli-1) it is accepted that patients with good PS that did 1st L ChT based in fluoropyrimidine in 2nd L should do Cht based on gemcitabine and vice versa.

References

1. Rawlaa P. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors.World J Oncol. 2019; 10(1):10-27.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
3. SEER Database, on https://seer.cancer.gov/statfacts/html/ pancreas.html, consulted in 28.03.19
4. Wenrui Wu. Rising trends in pancreatic cancer incidence and mortality in 2000-2014, Clinical Epidemiol.2018; 10: 789-797.
5. Bosetti C. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4), Ann Oncol. 2012; 23(7): 1880-1888.
6. Lowenfels AB. Risk factors for pancreatic cancer J Cell Biochem. 2005;95(4):649-56.
7. Burris HA, Moore M J, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. JClinOncol.1997; 15(6): 2403-2413.
8. Moore MJ, Goldstein D, Hamm J, et al.Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25:1960-1966.
9. Aranda E, Manzano JL, Rivera F, etal. Phase II open-label study of erlotinib in combination with gemcitabine in unresectable and/or metastatic adenocarcinoma of the pancreas: relationship between skin rash and survival (Pantar study). Ann Oncol 2012;23:1919-1925.
10. Stepanski EJ, Reyes C, Walker MS, etal. The association of rash severity with overall survival: findings from patients receiving erlotinib for pancreatic cancer in the community setting. Pancreas.2013; 42:32-36.
11. Conroy T, Desseigne F, Ychou M,*et al*. for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup, FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer, N Engl J Med 2011; 364:1817-1825.
12. Von Hoff D, Ervin T, Arena T. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine, N Engl J Med. 2013; 369:1691-1703.
13. Pelzer U, Kubica K, Stieler J, etal. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study [abstract]. J ClinOncol. 2008;4508.
14. Saif MW. New developments in the treatment of pancreatic cancer. Highlights from the 44th ASCO Annual Meeting& quot; Chicago, IL, USA. May 30 - June 3, 2008.JOP . 2008; 9:391-397.
15. Wang-Gillam A, Li CP, Bodoky G, et al.Nanoliposomalirinote can with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1):

a global, randomised, open-label, phase 3 trial. Lancet. 2016;
387:545-557

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