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A New Era in the Adjuvant Treatment of Pancreatic Adenocarcinoma

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Abstract

Pancreatic adenocarcinoma is currently a major public health problem, being the 7th cause of death worldwide. Incidence is increasing and unfortunately nowadays the incidence is almost overlapping to mortality. The cornerstone of curative treatment is still surgery, but adjuvant treatment is critical to decreasing the risk of recurrence.

Keywords

Pancreatic Adenocarcinoma, Adjuvant Chemotherapy, Positive Clinical Trials

1. Introduction

Most malignant pancreatic tumors (95%) arise from the exocrine pancreas and of these 85% are adenocarcinomas. Currently, the only treatment considered curative is surgical resection. Yet, at diagnosis, only 10% - 20% of patients are suitable for surgery and even in these rare patients, the 5-year survival is <10%; the recurrence rate at the 2-year is ~69% - 75%. Clearly, these high-risk patients warrant adjuvant treatment [1] [2] [3].

For over a decade, the standard adjuvant treatment has been chemotherapy (ChT), with Gemcitabine (GEM) monotherapy, 5-Fluorouracil (5-FU)/Leucovorin (LV), or in Asia, S1.

In recent years, after the results of phase III trials, ESPAC-4 and PRODIGE 24/CCTG PA.6, the standard for adjuvant chemotherapy became modified FOLFIRINOX (mFOLFIRINOX), or in some cases, GEM associated to Capecitabine (GEM/CAP).

2. Materials and Methods

The authors have conducted a qualitative systematic review, using the PubMed search engine, of all phase III prospective randomized trials in the adjuvant setting using chemotherapy for pancreatic adenocarcinoma. The trial selection consisted of both statistically significant and clinically relevant works, from January 2007 to October 2019. Negative trials were excluded. We focused mainly on reports of overall survival, disease free survival, objective response rate and impact on quality of life.

3. Article

Among the worldwide causes of death, pancreatic adenocarcinoma ranks in 7th place, in both men and women and its incidence is increasing [1], possibly concerning an ageing population and lifestyle changes.

Surgical resection is the only potentially curative treatment; nevertheless only 15% - 20% of the patients are suitable to surgery, and yet this small group experiences a very high recurrence rate (>80%) and dismal prognosis, with 5-year overall survival of only 9% - 10%, and 45,750 estimated deaths in 2019 [2] [3] [4] [5].

Such disappointing numbers lead to different strategies that should be discussed in a multidisciplinary scenario: adjuvant chemotherapy, adjuvant radiotherapy or both.

Here, the authors will highlight the positive randomized trials evaluating adjuvant chemotherapy.

4. Results/Discussion

The clinical trials RTOG 9704, CONKO-001, ESPAC 3 and JASPAC 1 demonstrated improvement in overall survival (OS) and in progression free survival (PFS) [6].

Up to 2016, the adjuvant standard treatment was 6 months of GEM in monotherapy, or 5FU/LV, or in Asian patients, S1. However, in these trials, even patients who received adjuvant chemotherapy, experienced 2-year recurrence rate of 75%.

More recently, two practice-changing trials established the new adjuvant treatment following resection of pancreatic cancer: ESPAC-4 and PRODIGE 24/CCTG PA.6.

In the CONKO-001 trial, 368 operated patients with R0 and R1 resections were randomized in 2 groups: ChT with GEM (1000 mg/m^2, in a 30 min infusion, days 1, 8 and 15 every 38 days, 6 cycles; n = 179) vs observation (n = 175). The primary objective of the trial was DFS, which was clearly superior in the treatment arm (13.4 vs 6.7 m; Hazard ratio (HR) 0.55; $p < 0.001$). The same was observed in the OS, which was 22.8 months in the GEM group vs 20.2 months (HR 0.76; $p = 0.01$) [7] [8].

In another trial (ESPAC 3), 1088 patients with pancreatic adenocarcinoma

were randomized after surgery (R0 and R1 resections) in 2 adjuvant ChT groups: GEM (1000 mg/m^2, in a 30 min infusion, days 1, 8 and 15 every 38 days, 6 cycles, n = 537) vs AF (20 mg/m^2 day 1) and 5-FU (425 mg/m^2 in bolus, days 1 and 5) every 28 days, 6 cycles. OS was similar in both groups (23.6 vs 23 months; HR 0.94; p = 0.39) and so was the DFS (14.3 vs 14.1 months, HR 0.55, P < 0.001) [9].

In the non-inferiority phase III trial JASPAC 01, which included 385 operated patients with pancreatic adenocarcinoma, with R0 and R1 surgeries in 33 hospitals in Japan, the randomization was carried out in 2 groups of adjuvant ChT: S-1 (80/100/120 mg/day according to BSA *per os* twice a day, days 1 to 28, every 42 days, 4 cycles, n = 192) and GEM (1000 mg/m^2, in a 30 min infusion, days 1, 8 and 15 every 38 days, 6 cycles, n = 193). The relapse free survival was 22.9 months in the S-1 group vs 11.3 months in the GEM group (HR: 0.60; p < 0.0001), with a 5-year DFS of 33.3 vs 16.8%. OS was also superior in patients treated with S-1 (46.5 vs 25.5 months; HR: 0.57; p < 0.0001) with 5-year OS of 44.1% vs 24.4%. Some experts justified this advantage with S-1 with the arguments that all patients were from Asian ethnicity. There was a higher exposure (dose/intensity) in the S-1 treatment (28 consecutive days) and presumably a better absorption of S-1 after a pancreatic resection [10].

In recent years, two studies changed the standard of care in adjuvant treatment of pancreatic adenocarcinoma.

In 2016, the ESPAC 4 phase III trial was published. It randomized, in 1:1 way, 732 patients, after surgical resection (either R0 or R1) and performance status (PS) ≤ 2, within 12 weeks after surgery, to two arms:

- GEM (1000 mg/m^2, 30 minutes infusion, days 1, 8 and 15) associated to CAP (1660 mg/m^2 per day, twice daily, oral, for 21 days), in 28 days cycle, 6 cycles.
- GEM (1000 mg/m^2, 30 minutes infusion, days 1, 8 and 15), in 28 days cycle, 6 cycles.

The primary endpoint was OS, while PFS was a secondary endpoint. Toxicity and quality of life were evaluated. With a median 43.2 months follow-up, there was a survival benefit in the combination arm vs monotherapy (OS 28 months vs 25.5 months, respectively, with HR 0.82; p = 0.032). In the R0 subgroup, the difference was even striking: 39.5 months vs 27.9 months; on the other hand, in R1 resection, the survival was similar: 23.7 months vs 23 months. The PFS was similar (13.9 months vs 13.1 months; HR 0.86, P = 0.082). Not surprisingly, toxicity was higher in the combination arm, but considered manageable. The study was criticized because there was no cut-off for CA 19.9 tumor marker, namely only 662/730 patients (90.7%) the value was actually known. Additionally, the baseline CT scan was allowed up to 12 weeks before randomization, the follow-up protocol was not standardized (variation between centers) and the population was considered very high risk for recurrence (61% R1 resections and 80% N+) [11].

In the multicenter, randomized, phase 3 trial PRODIGE 24-ACCORD and CCTG PA 6, a mFOLFIRINOX regimen was compared to GEM among resected pancreatic cancer patients [12]. In this trial, 493 patients were included: 247 to

mFOLFIRINOX (oxaliplatin 85 mg/m^2, leucoverin 400 mg/m^2, irinotecan 180 mg/m^2, and fluorouracil 2400 mg/m^2 continuous infusion in 46 h, every 14 days for 24 weeks) vs GEM 1000 mg/m^2 D1, 8, 15 every 28 days for 24 weeks. After a safety analysis, the dose of irinotecan was reduced to 150 mg/m^2 and omission of fluorouracil bolus.

The primary endpoint was disease free survival (DFS), which was superior in the mFOLFIRINOX arm: 21.6 vs 12.8 months in GEM arm (HR 0.58; $p < 0.001$), and this benefit occurred across all groups, including with adverse prognostic characteristics, like positive lymph nodes, R1 surgery, and T3 or T4 tumours.

The overall survival (median: 54.4 vs 35 months, HR 0.64, $p < 0.003$), metastasis free survival (median: 30.4 vs 17.7 months; HR 0.59, $p > 0.001$) and cancer-specific survival (not reached vs 36.4 months; HR 0.63, $p = 0.003$) were also improved in the mFOLFIRINOX group compared with GEM, however there were more adverse effects G3 or 4 in the mFOLFIRINOX arm (75.9%) than in the GEM arm (52.9%).

Regarding these impressive outcomes in efficacy, and the longest overall survival ever reported in a trial, we have completely changed our practice in many patients with resected pancreatic adenocarcinoma and good performance status.

5. Conclusions

The ESPAC-4 and PRODIGE 24/CCTG PA.6 led to changes in the standard of care in the adjuvant treatment in pancreatic adenocarcinoma. Currently, in patients successfully resected and with good performance status, the preferred regimen is mFOLFIRINOX. Meanwhile, in frail or older patients, particularly in R0 resections, the GEM/CAP (in some cases even GEM monotherapy) is an option to consider.

The treatment decision should always consider the specific patient, in particular the comorbidities and expectations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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