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Update on chemotherapy for advanced pancreatic cancer

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Advanced ductal pancreatic adenocarcinoma (aPDAC) has a median overall survival (mOS) of about 6 months (mos), with a survival rate of 6% at 5 years (1) .

In 90's gemcitabine (gem) became standard regimen for aPDAC , with a mOS ranged from 5.0 to 7.2 mos when used as a single agent. Gemcitabine- based combination failed to improve mOS over gem alone (4). Only Erlotinib, in a phase III study, demonstrated a prolongation of mOS, statistically but not clinically significant, in association with gem over gem alone (5).

In 2012 as compared with gem, the intensive regimen FOLFIRINOX (oxaliplatin, 85 mg/m^2, irinotecan, 180 mg/m^2, leucovorin, 400 mg/m^2 and fluorouracil, 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 given as a 46-hour continuous infusion, every 2 weeks) was associated with an increased survival with a major toxicity in a randomized phase III trial. FOLFIRINOX is an option for the first line treatment of patients with metastatic PDAC with a good performance status (6).

Although first line FOLFIRINOX is considered one of the standards of care for aPDAC, some concerns emerged with regard to the safety profile in clinical practice. Dose/schedule modifications and additional supportive measures were investigated in a retrospective Italian analysis and the results demonstrated that the minimal differences in toxicity and efficacy obtained with mFolfirinox require additional investigation (7).

Nab-paclitaxel (nab-P) has demonstrated both single-agent activity and synergy with gem in preclinical models of pancreatic cancer, and the association showed efficacy in a phase I/II study (8). MPACT study, a randomized phase III trial comparing nab-P 125 mg/m^2 plus gem 1000 mg/m^2 days 1, 8, and 15 every 4 weeks vs gem 1000 mg/m^2 weekly for 7 weeks followed by 1 week of rest and then days 1, 8, and 15 every 4 weeks in 861 pts with metastatic PDAC, demonstrated that nab-P plus gem was superior to gem in terms of mOS (8.5 vs. 6.7 mos- HR 0.72; 95% CI, 0.617 - 0.835; p = 0.000015), median progression free survival (PFS) (5.5 vs. 3.7 mos - HR 0.69; 95% CI, 0.581 - 0.821; p = 0.000024), and overall response rate (ORR) (23% vs. 7%, p= 1.1 × 10–10). Grade ≥ 3 adverse events (AEs) with nab-P + gem vs. gem included neutropenia (38% vs. 27%), fatigue (17 % vs. 7%), diarrhea (6% vs 1%), and febrile neutropenia (3% vs. 1%). Grade ≥ 3 peripheral neuropathy (PN) occurred in 17% vs. 1% of pts who received nab-P + gem vs. gem. An updated survival analysis revealed a sustained difference in OS over time between the 2 arms (9, 10).

In MPACT study, pts were stratified by region, presence of liver metastases, and Karnofsky performance status. In a recent analysis of MPACT trial, the most important predictors of longer OS and PFS were higher Karnofsky performance status, age < 65 years, absence of liver metastases, and region of North America. A lower number of metastatic sites predicted longer OS but not PFS (10, 11).

No data are available about the comparation of FOLFIRINOX vs nab-p + gem.

There is no standard of care for aPDAC pts who have progressed to first line treatment. The second-line treatment depends mainly on the first-line treatment and clinical evaluation of the patient at the time of progression.

A recent retrospective Italian survey evaluated pts who received off-label combination of nab-p 125 mg/m^2 and gem 1000 mg/m^2 on days 1, 8, and 15 of a 28 day cycle as 2nd or further line of treatment. 34 pts (M/F: 20/14) with median age of 60 (range 41-83) and ECOG Performance Status of 0/1/2: 8/17/9 respectively, were evaluated. Nab-p plus gem was administered as 2nd/3rd/4th/5th line of therapy in 18/12/2/2 pts respectively for a median number of 4 cycles (range 1-14). Median PFS was 4.5 mos (95% CI 1-8). Median OS was 6.5 months (95% CI 1.5-11.5. Treatment was mildly tolerated, so authors concluded that Nab-p plus gem is active, efficacious and mildly tolerated and it could be considered as a valid therapeutic option also in pretreated pts. Activity, efficacy and safety of Nab-P + G have not been established in elderly patients and clinical trials on aPDAC treatment contain fewer elderly patients compared with everyday clinical practice (12).

Another Italian retrospective analysis investigated outcomes and toxicities of elderly pts with aPDAC treated with the combination of nab-P plus gem at classic schedule. Authors evaluated 61 pts aged ≥65 receiving nab-P and gem as first (39 pts, 64%) or further (22 pts, 36%) line of CT. 14 SD, 9 PR (DCR: 59%) were observed in first line CT pts and 9 SD, 2 PR (DCR 50%) were recorded in pretreated pts. Median PFS was 6 mos (95% CI 3.9-8.1) and 3.5 mos (95% CI 1.6-5.4) in first line and pretreated pts, with median OS of 9.5 (95% CI 7.3-11.7) and 6 mos (95% CI 4.2-7.8) in first line and pretreated pts respectively. Age ≥70 was not significantly associated to PFS and OS at univariate and multivariate analysis (13).

At this time, novel association of drugs are under evaluation for aPDAC, and some studies are testing the best ways to combine chemotherapy with radiation therapy or newer targeted therapies.

At present, FOLFIRINOX and Nab-p plus gem are new standard options in first line chemotherapy for aPDAC pts with good PS . Gemcitabine remains the standard first-line in pts with poor PS.

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