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Monotherapy vs doublet chemotherapy vs Folfirinox: who and why

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Introduction

Pancreatic cancer (PC) is a particularly aggressive cancer, responsible annually for approximately 50,000 deaths in Europe and 36,800 in the United States and represents the 4th leading cause of death-related cancer. Additionally, unlike the rates of deaths for more frequent cancers (lung, colon, prostate, and breast) are declining in the last decade, the mortality for PC remained relatively stable, and it indicates that there were limited progress in the treatment of this pathology in the last years (1).

The majority of pts are diagnosed with advanced disease and have a median survival of 6 months with chemotherapy. Due to its particular aggressive biology, to the difficulties in diagnosis, associated at lack of effective systemic therapy, the prognosis of PC at 5 years is particularly severe (<5%), so that the mortality rate for this tumor equals its incidence. Palliative treatments PC play a very important role in PC as 80% to 90% of newly diagnosed tumors are not resectable due to local invasion or presence of distal metastasis (2).

Gemcitabine has been considered standard of care for treatment of advanced PC since 1997. Multiple phase III trials have been attempted to improve outcome using gem as a backbone chemotherapy.

A meta-analysis was undertaken to investigate the efficacy of gem-based combination treatment compared with gem monotherapy in locally advanced or metastatic PC. Twenty-six studies were included in the analysis, with a total of 8808 pts recruited. The studies were divided into four subgroups based on the different kinds of cytotoxic agents, including platinum, fluoropyrimidine, camptothecin and targeted agents. Patients treated with gem monotherapy had significantly lower objective response rate (ORR) [risk ratio (RR), 0.72; 95% confidence interval (CI): 0.63-0.83; P<0.001], and lower 1-year overall survival (RR, 0.90; 95% CI: 0.82-0.99; P=0.04). Gemcitabine monotherapy caused fewer complications, including fewer grade 3-4 toxicities: including vomiting (RR, 0.75; 95% CI: 0.62-0.89; P=0.001), diarrhea (RR, 0.66; 95% CI: 0.49-0.89; P=0.006), neutropenia (RR, 0.88; 95% CI: 0.72-1.06; P=0.18), anemia (RR, 0.96; 95% CI: 0.82-1.12; P=0.60), and thrombocytopenia (RR, 0.76; 95% CI: 0.60-0.97; P=0.03) compared with gem combination therapies (3).

There has been some evidence suggesting that maintaining a constant dose rate of Gem with a fixed dose rate regimen (FDR) may improve outcomes (4, 5). An initial trial was done by Tempero and colleagues to test this hypothesis. Patients were administered either 2200 mg/m2 Gem over 30 min (standard arm) or 1500 mg/m2 Gem over 150 min (FDR arm) on days 1, 8 and 15 of every 4-wk cycle. Patients treated with FDR had a trend towards improved survival (OS) (8 mo vs 5 mo, P=0.013) but more severe adverse events, namely hematological toxicity (6). However, a subsequent phase III Eastern Cooperative Oncology Group (ECOG) trial failed to demonstrate a statistically significant improvement in OS of Gem FDR regimen over the standard administration (6.2 mo vs 4.9 mo) (4).

Moreover, Gem monotherapy had an almost 30% lower ORR than combination therapy regimens, but only had a 10% lower 1-year OS than associations. According to the present data, 1-year OS in advanced or metastatic PC was low (less than 20%) after Gem monotherapy; therefore, the combination therapy options studied did not improve outcome in a substantial way, and the prognosis still being poor. Gemcitabine combination therapy provides a modest improvement of survival, but is associated with more toxicity compared with gemcitabine monotherapy (7,8,9).

In 2005, Conroy et al evaluated the RR and toxicity of Folfirinox in 46 chemotherapy-naive advanced pancreatic adenocarcinoma pts. The Folfirinox regimen comprised oxaliplatin 85 mg/m2 and irinotecan 180 mg/m2 plus leucovorin 400 mg/m2 followed by bolus FU 400 mg/m2 on day 1, then FU 2400 mg/m2 as a 46-h continuous infusion. This report showed promising results with an ORR of 26%, a time to progression (TTP) 8.2 mo, and an OS of 10.2 mo. Despite the fact that grade 3/4 neutropenia occurred in 52% of cases, pts had improvement in all functional scales of the EORTC QLQ-C30 (10) . Based on these data, Conroy and colleagues conducted a phase III trial comparing Folfirinox with Gem as first-line treatment for metastatic pancreatic adenocarcinoma in 342 pts with good PS (0-1). The median OS was 11.1 mo in the Folfirinox group compared to 6.8 mo in the Gem group (HR: 0.57; 95% CI: 0.45-0.73; P<0.001). Median progression-free survival (PFS) was 6.4 mo vs 3.3 mo (HR: 0.47; 95% CI: 0.37-0.59, P<0.001). The ORR was 31.6% vs 9.4% (P<0.001). At 6 mo, 31% of the pts in the Folfirinox group had a definitive degradation of the QOL vs 66% in the Gem group (HR: 0.47; 95% CI: 0.30-0.70; P<0.001). Grade 3/4 toxicities were more common in the Folfirinox, diarrhea 12.7% vs 1.8%, nausea 15.6% vs 6.3%, vomiting 14.5% vs 8.3%, fatigue 23.6% vs 17.8%, neutropenia 45.7% vs 21%, and febrile neutropenia 5.4% vs 1.2%. In the Folfirinox arm, 42% of pts received support with granulocyte colony-stimulating factor. Two pts died from treatment-related causes: one from febrile neutropenia in the Folfirinox group and one from cardiac decompensation in the Gem group. This trial was highly selective: only 39% of pts had a primary tumor in the head of the pancreas; whereas in clinical practice, about two-thirds of pts present with a primary tumor in the pancreas, possibly requiring biliary stents. Therefore, for pts with a good PS, normal bilirubin, and a good supportive care system, Folfirinox could be a viable option (11).

On the side of targeted agents, including bevacizumab, cetuximab, and erlotinib, there was described only a modest benefit with erlotinib. A phase III trial using combination of erlotinib plus gemcitabine showed very modest improvement over gemcitabine alone. Though statistically significant, this difference was not considered clinically significant (12).

In the first line setting, european guidelines recommend single agent gemcitabine in metastatic pts with poor performance status and Folfirinox, gemcitabine/erlotinib, or gemcitabine alone for those with good performance status (13).

Recently, Von Hoff et al. conducted a phase III study in 861 pts with advanced PC to compare the combined use of Nab-paclitaxel (Nab-p, 125 mg/m2) administered with Gem (1000 mg/m2) vs. Gem (1000 mg/m2) monotherapy. The primary endpoint was OS; secondary endpoints included PFS and ORR based on independent review. A significant difference was demonstrated in the combination arm vs the Gem arm, respectively with a mOS of 8.5 months vs 6.7 months (P<.001), a median PFS of 5.5 months vs 3.7 months (P<.001) and ORR of 23% vs 7% (P<.001), respectively. The most common grade ≥3 adverse events were neutropenia (38% vs 27%), leukopenia (31% vs 16%), fatigue (17% vs 7%), and peripheral neuropathy (17% vs 1%) in the Nab-p plus Gem and Gem arms, respectively(14) .

A Phase II study by Ramanathan et al investigated the induction with Nab-p (125 mg/m2) plus Gem (1000 mg/m2) on days 1, 8, and 15 of a 28-day cycle followed by consolidation with a modified Folfirinox (irinotecan 180 mg/m2, oxaliplatin 85 mg/m2, 5-FU 2400 mg/m2, leucovorin 400 mg/m2; no 5-FU bolus) regimen every 2 weeks in 31 pts with previously untreated metastatic pancreatic cancer. In 16 evaluable pts, 5 achieved a confirmed partial response (PR), 10 had stable disease (SD) (3 confirmed), and 1 patient progressed. The most

common grade 3/4 AEs reported during induction therapy included fatigue (32%), neutropenia (32%), and anemia (23%). Among the 20 pts treated with the induction phase, 75% have had a significant decrease in CA 19-9 levels and there has been a 50% partial response rate (15).

In conclusion, recent validations that combinations of conventional chemotherapy drugs, the Folfirinox regimen and Gemcitabine plus Nab-p, significantly improves clinical outcomes in patients with metastatic PC. However, in PC there is always a strong need to better understanding tumor biology to develop solid biomarkers to select patients and to predict response.

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