



Chemotherapy of pancreatic cancer in patients with poor performance

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Pancreatic cancer is the seventh most leading cause of all cancer related deaths, accounting for 4.5% of these (1,2). Less than 20 % of the patients who are diagnosed with pancreatic ductal adenocarcinoma present with a nonmetastatic localized disease and surgery is a potential curative option (3). Another third of the patients present with locally advanced nonmetastatic cancer and may undergo neoadjuvant chemotherapy with or without radiation followed by exploration and resection as a possible curative treatment. In most of the cases however, patients are diagnosed with a metastatic disease and chemotherapy is the only viable option to increase overall survival and improve quality of life by relieving symptoms.

First line chemotherapy in a metastatic pancreatic cancer is well defined for patients with good performance score. The ACCORD trial showed superior outcomes for patients in first line FOLFIRINOX versus gemcitabine (overall survival 11.1 *vs.* 6.8 months, $P < 0.001$) (4). The cohort consisted of a total of 342 patients of which 37.4% patients had ECOG 0, 61.9% were ECOG 1 and 0.6% had ECOG 2 status. In 2013 the results of the MPACT trial established gemcitabine in combination with nab-paclitaxel (Gem/NabPac) as a first line therapy in pancreatic cancer (overall survival 8.5 compared 6.7 months with gemcitabine only, $P < 0.001$) (5). The MPACT trial excluded patients with ECOG equal or higher than 2. To date, there is no head-to-head prospective randomized comparison between first line FOLFIRINOX versus Gem/NabPac. However

retrospective meta-analysis shows little to no difference in overall survival between both regimens (6). Meta-analysis also shows that in treatment with Gem/NabPac versus FOLFIRINOX there is less grade 3–4 toxicity like nausea with an odd ratio (OR) of 0.11 (95% CI: 0.03–0.34), less neutropenia with OR of 0.71 (95% CI: 0.54–0.92) and less febrile neutropenia [OR 0.45 (95% CI: 0.29–0.7)] (6). In contrast there was less grade 3–4 neurotoxicity in FOLFIRINOX with an OR of 2.8 (95% CI: 1.4–5.7) and less anemia (6).

While first line recommendation for good performing patients is well defined, literature on the management of elderly and poor performing patients is sparse. It is generally estimated that only 20% of patients are eligible for clinical trials because of inability to meet inclusion criteria or due to poor performance status (7). As performance score is known to be a prognostic factor in pancreatic cancer (8), recruitment for the major trials exclude these patients to rule out this potential co-founder. The study presented by Macarulla *et al.* provides important information to this unresolved issue (9). In their phase I/II trial, the authors evaluate a combination of Gem/NabPac in pancreatic cancer patients with ECOG 2. In phase I, there are four study arms with six patients per arm. In arm A, a biweekly schedule of NAB-paclitaxel (150 mg/m²) plus gemcitabine (1,000 mg/m²) was administered. Arm C contained also of biweekly schedule of gemcitabine (1,000 mg/m²) with a standard dose NAB-paclitaxel (125 mg/m²). In

Arm D, the authors administered a standard schedule of 3 weeks on and 1 week off of NAB-paclitaxel (125 mg/m²) plus gemcitabine (1,000 mg/m²). Arm B consisted also of a standard schedule gemcitabine (1,000 mg/m²) and a reduced dose of NAB-paclitaxel (100 mg/m²). The authors choose arm B and D for their phase II randomizing a total of 221 ECOG 2 patients. Median age was 69 and the proportion of patients older than 75 years was 27.6%. The most frequent grade 3 or 4 toxicities in arms B versus D were anemia (12% *vs.* 7%), neutropenia (32% *vs.* 30%), thrombocytopenia (7% *vs.* 11%), asthenia (14% *vs.* 16%), and neurotoxicity (11% *vs.* 16%). There was no statistically significant difference in progression free survival rates between both arms (Arm B: 5.7 months, Arm D: 6.7 months, P=0.283). Macarulla *et al.* conclude that Gem/NabPac administered at either 100 or 125 mg/m² on a standard schedule of 3 weeks on and 1 week off is well tolerated and results in acceptable safety and efficacy in patients with ECOG 2.

While in clinical practice FOLFIRINOX is still first choice in younger patients with good performance status, this study demonstrates that Gem/NabPac can be used safely in patients with poor performance (ECOG >1). Thus, this study provides relevant and urgently needed evidence for these underrepresented patients who are usually excluded from phase III trials in this field. And yet more trials are needed to improve outcomes while maintaining quality of life even in these patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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