Chemotherapy in advanced pancreatic cancer with hyperbilirubinemia

Silvia Noventa, Sara Cherri, Alberto Zaniboni

Department of Medical Oncology, Poliambulanza Foundation, Brescia, Italy
Correspondence to: Alberto Zaniboni, MD. Department of Medical Oncology, Poliambulanza Foundation, via Bissolati 57, 25124 Brescia, Italy. Email: alberto.zaniboni@poliambulanza.it.
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Hyperbilirubinemia (HB) is very common in patients (pts) with pancreatic cancer (PC), often at the onset of the disease. In fact, 60–70% of pancreatic carcinomas are localized in the pancreatic head and in 70–80% of cases occur with jaundice (1), due to distal biliary tract obstruction requiring biliary stent placement, especially if chemotherapy is planned. Most of the other causes of jaundice in PC pts are also cholestatic, caused by obstruction of the biliary tract at other sites, generally caused by metastasis (e.g., compression of perihilar or intrahepatic biliary tract by adenopathies or liver metastases). In a minority of cases, HB is a sign of liver failure, due to massive metastatic liver infiltration. In this case, mechanical palliation is not possible and probably the optimal therapeutic choice is best supportive care. Less frequently, HB is due to concomitant hepatic diseases such as cirrhosis or congenital bilirubin conjugation defects (e.g., Gilbert syndrome).

In cancer pts, alteration of liver function may limit the administration of chemotherapy by interference with both the hepatic metabolism of drugs and with their biliary elimination. So, in PC, after biliary stent placement, it's necessary to wait for the reduction of bilirubin values in order to start chemotherapy. But how long?

The pivotal trials of the main chemotherapy regimens used for the treatment of PC, nab-paclitaxel-gemcitabine (nab-P/G) and FOLFIRINOX, excluded pts with bilirubin above the upper normal limit (2,3). But in clinical practice, waiting up to the normal value of bilirubin can mean waiting for several weeks, with a risk of worsening in the patient's performance status (PS). In fact, we recognize that pts with PC are often symptomatic (e.g., pain, fatigue, anorexia, weight loss, etc.) and that disease has a rapidly evolving trend. Therefore, it's important to start treatment as soon as possible, not only to relieve symptoms earlier but also to avoid losing the therapeutic window in which the patient's PS is still conserved (PS ECOG ≤2), especially in advanced disease. So, in the absence of a response provided by prospective clinical studies, clinicians have managed to reduce doses of drugs or modify the administration schedule based on their experiences. For example, in FOLFIRINOX regimen we could omit irinotecan until bilirubin normalization (4), since FOLFOX chemotherapy is also feasible in patients with severe liver dysfunction (5).

In literature, we can find retrospective cases collecting safety and clinical outcome data in small groups of PC pts starting chemotherapy with HB.

Rogers *et al*. (6), in a retrospective, single-institution study, collected data on safety and efficacy of nab-P/G in pts with pancreatic adenocarcinoma (17% borderline resectable, 25% locally advanced and 58% metastatic) and HB (median baseline bilirubin 2.4 mg/dL, from 2.1 to 5.2). They analyzed 12 pts. The only patient with non-obstructive cause of jaundice (extensive liver metastases) has stopped treatment due to liver failure. According to their institution standard practice, no pts received gemcitabine starting dose at 1,000 mg/mq but 92% at 600 mg/mq and 8% at 500 mg/mq. Only 2 pts received nab-paclitaxel at 125 mg/mq, 6 pts at 100 mg/mq and 4 at 65 mg/mq. Furthermore, 75% of pts received drugs in biweekly schedule of administration and

only 41.7% underwent doses escalation as bilirubin elevation subsided. In overall population median overall survival (OS) was 13.9 months, time on treatment (TOT) 5.2 months and disease control rate (DCR) 58.3%. In pts with metastatic disease, OS was 6.9 months, TOT 2.1 months and DCR 28%. Almost 42% of pts required a dose delay due to chemotherapy adverse effect. The adverse effects of Grade 3 were one case of neuropathy, one of neutropenia (granulocyte growth factors were used) and one of liver enzyme elevation (pts with massive liver metastasis).

In this experience, authors chose to use reduced doses of drugs (on average 100 mg/mq of abraxane and 600 mg/mq of gemcitabine) with a biweekly treatment schedule, not only at baseline justified by high bilirubin values but even after the drop and normalization of bilirubin values, without clear reasons. This could be justified by toxicity, but the adverse events described do not appear so relevant. It is also not clear the need to modify the administration schedule in addition to doses reduction, although this seems to be a standard for their institution. This modality allowed to register low toxicities but does not allow to draw conclusions on the safety of a standard regimen in this subpopulation of patients. Moreover, we could speculate that this choice leads to lower efficacy. Survival, TOT and response rate in the overall population are not evaluable, because pts with both localized and metastatic disease are included. No pts with localized disease went to surgery, but numbers are too small to comment on this. Focusing on metastatic pts, clinical outcomes are lower than in pivotal trial (3) or in real life experiences (7), more similar to those obtained with a monotherapy (e.g., control arms in pivotal trials), but this comparison cannot be made, because populations are not comparable. In fact, we have no data regarding significative prognostic factors of PC such as performance, tumors burden, metastatic sites, etc. Furthermore, probably the most relevant limitation of the study is that the patient sample is very small.

In literature, others retrospective studies tried to answer the same questions. One example is the analysis of Pelzer *et al.* (8) that included 29 pts with PC (90% metastatic disease) and cholestatic HB. They were divided into three groups according to the bilirubin value (A: 1.2–3; B: 3–5, C: >5 mg/dL) and treated with nab-P/G in different lines of treatment. The decision about the starting dose of nab-P/G was taken by the investigator: 85% of pts received first administration at a dose level of 100%, 10% at 75% and 3% at 50%. Median OS was 11.8 months without differences between the three subgroups. Therefore, the basal bilirubin

level seems doesn't seem to influence OS. The authors did not register early severe toxic effects.

Paclitaxel clearance is primarily determined by CYP2C8 and CYP3A4, followed by biliary excretion. Total bilirubin is considered a predictor of paclitaxel elimination capacity and of individual susceptibility to paclitaxel-related myelosuppression (9). However, the distribution and elimination of nab-paclitaxel were different from classical solved-based (sb) paclitaxel since the former causes more rapid and deeper tissue penetration with a shorter duration of high plasma concentration. The meta-analysis by Chen *et al.* (10) analyzed the pharmacokinetics and pharmacodynamics of nab-paclitaxel in patients with different solid tumors, including patients with hepatic impairment. In the covariate analysis, changes in total bilirubin had a limited effect on paclitaxel elimination when administered as nab-paclitaxel. The mean reduction in maximal elimination rate was estimated to be 26% in patients with total bilirubin >3 to ≤5× ULN compared with patients with a normal total bilirubin level. The authors showed that for nab-paclitaxel hepatic impairment was not a significant predictor of neutropenia and absolute neutrophil count (ANC) was correlated with paclitaxel exposure but not total bilirubin. Consequently, simple extrapolation of the hepatic dosages from sb-paclitaxel to nab-paclitaxel is not supported. They concluded that a reduction of 20% in the starting nab-paclitaxel dose may be considered for patients with total bilirubin >1.5 to ≤5× ULN to avoid a potential increase in systemic drug exposure. Regrettably, this analysis does not include PC patients with mechanic obstruction of the bile duct. It is for this reason that European Medicines Agency (EMA) reported the possibility of administering nab-paclitaxel with a 20% reduction in dose for pts with total bilirubin >1.5 to ≤5× ULN and AST ≤10× ULN only for metastatic breast cancer or non-small cell lung cancer, but not for PC. But it is reasonable to think that these considerations also apply to this category of patients, especially if we consider that in PC the weekly treatment schedule provides for a lower dose of drug compared to other tumors and allows constant monitoring of blood values.

As far as it concerns gemcitabine, it is inactivated by cytidine deaminase followed by urinary excretion. Since pts with elevated bilirubin levels have an increased risk of hepatic toxicity and are prone to develop substantial but transient increases in bilirubin and liver transaminases, a reduction of the gemcitabine starting dose was historically recommended (11). However, some experiences showed

that, for the treatment of biliary tract or PCs, an initial dose reduction of gemcitabine as monotherapy is not necessary for patients with HB, provided that obstructive jaundice is well managed (12). The review and German expert opinion published by Vogel *et al.* (13) is potentially useful in clinical practice. The expert panel prefers to use the combination treatment with nab-P/G at a reduced starting dose over gemcitabine monotherapy. They propose a starting dose based on the underlying cause of HB, total bilirubin level and other parameters (13).

In conclusion, there's evidence, deriving from retrospective cases and pharmacokinetic studies in other malignancies, for believing that nab-P/G can be safe in patients with PC and HB. At the beginning it's essential to distinguish the cause of HB, to consider the trend of bilirubin levels, the patient's PS and the purpose of the treatment. We'll probably have more accurate evidence when the results of the ongoing AIO-PAK-0117 trial will be available (14). It's a phase 1, multicenter, open-label, dose-escalation study that Investigates safety and pharmacokinetics of nab-P/G in pts with advanced PC who have cholestatic HB secondary to bile duct obstruction (ClinicalTrials.gov Identifier: NCT02267707). Recruitment status is terminated, but the results are not disclosed. Looking forward to this data, we can continue to rely on the above reported evidence.

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Footnote

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