CASE REPORT

Sustained response with gemcitabine plus Nab-paclitaxel after folfirinox failure in metastatic pancreatic cancer: Report of an effective new strategy

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Summary

Introduction: Folfirinox has shown a benefit in terms of survival and quality of life in first line treatment of metastatic pancreatic cancer. However, efficacy of second line chemotherapy after folfirinox is still limited. Gemcitabine plus Nab-paclitaxel have been recently validated as first line treatment with an increased overall survival compared to gemcitabine. This combination has never been studied as second-line after folfirinox.

Case report: A metastatic pancreatic cancer was diagnosed in a 60-year-old patient with a performance status of 0. After 10 cycles of folfirinox, and an initial objective response, we objectively noted progressive disease according to the RECIST 1.1 criteria together with an increased carbohydrate antigen 19-9. The multidisciplinary team decided to use gemcitabine plus Nab-paclitaxel as second line palliative chemotherapy. After 2 months, we obtained an objective response. After 6 months, this response was maintained with an acceptable tolerability.

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Conclusion: Gemcitabine plus Nab-paclitaxel, as second line palliative chemotherapy, after failure of folfirinox, could be a good strategy for patients with a performance status of 0 and 1. Obviously, this data has to be confirmed in larger patients series and in future comparative clinical studies.

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Introduction

Incidence of pancreatic cancer has been slowly increasing over the past 10 years [1]. Within gastrointestinal cancers, metastatic pancreatic cancer has the worst prognosis [2]. Its median survival without treatment is consistently less than 6 months [3], and it still remains an unresolved therapeutic challenge and therefore new therapeutic options are needed. However, improvements have been seen during the last three years with the results of two positive phase III trials testing folfirinox (5-fluorouracil, oxaliplatin, irinotecan, leucovorin) [4] or gemcitabine plus Nab-paclitaxel [5] versus gemcitabine respectively.

These different efficient therapeutic regimens have however never been tested sequentially to our knowledge. We present here for the first time, the case of a patient successfully treated for a metastatic pancreatic cancer with Nab-paclitaxel plus gemcitabine as second-line chemotherapy after progression with folfirinox.

Patient case presentation

In August 2012, a 60-year-old patient was referred to our institution with epigastric pain and a recent weight loss of 5 kg. His past medical history included a dyslipidemia and cigarette smoking. Performance status (PS) was 0. Biologically, elevated PAL (1.5N) and GGT (5N) were observed with a normal bilirubin level. The carbohydrate antigen 19-9 (Ca 19-9) was over 10000 UI/ml (standard value < 36.5 UI/ml). Computed Tomography scan (CT scan) showed a 46 mm diameter tumour in the pancreatic tail with more than 10 metastatic nodules ranging from a few millimetres to 30 mm in the liver and the coeliac nodes. An ultrasound-guided hepatic biopsy showed a hepatic metastasis of moderately differentiated pancreatic ductal adenocarcinoma. Considering his favourable PS and normal bilirubin level, the multidisciplinary decision is to begin a first line chemotherapy with folfoxirin as described by Conroy et al. [4]. Tolerability was acceptable. However, oxaliplatin was stopped after 6 cycles because of a grade 3 neurotoxicity. Initially after 4 cycles (2 months), the patient experienced a complete regression of his epigastric pain, Ca 19-9 decreased to 2159 UI/ml. The CT scan showed an objective response using RECIST 1.1 criteria on the primary tumour and metastases. After five months (10 cycles), we objectively noted progressive disease according to the RECIST 1.1 criteria (Fig. 1) together with a Ca 19-9 increase to 4300 UI/ml. The patient was still PS 0 and the multidisciplinary team decided to use compassionate Nab-paclitaxel plus gemcitabine as second line palliative chemotherapy. Treatment modalities were similar to those reported in the MPACT trial [5] (three weeks of chemotherapy and one week break). After two months of treatment, abdominal pain disappeared, Ca 19-9 decreased to 64 UI/ml and the CT scan showed an objective response according to the RECIST 1.1 Criteria with a 35% decrease in the sum of maximal target lesions diameters (Fig. 2). Tolerability was good. The grade 2 (NCI-CTC scale v4.03) oxaliplatin neurotoxicity remained unchanged during the Nab-paclitaxel plus gemcitabine treatment. Other side effects were grade 1 asthenia, grade 2 alopecia. No haematological toxicity was reported. After 6 months of treatment, objective response was sustained and Ca 19-9 was at 8 UI/mL.

Discussion

Since 1997, gemcitabine is the standard treatment for metastatic pancreatic cancer with a median survival of 7 months. Since 2011, folfirinox has shown significant benefit compared to gemcitabine in terms of response rate, progression-free and overall survival rate [4]. However, folfirinox is not feasible for all patients, because of its associated high rate of haematological and clinical toxicity. Therefore, it is reserved for patients with PS 0-1 and those with normal serum bilirubin levels. More recently, the MPACT phase III study [5] compared Nab-paclitaxel plus gemcitabine to gemcitabine as first line treatment of metastatic pancreatic adenocarcinoma. Nab-paclitaxel is an albumin-bound paclitaxel. Its target is the secreted protein acid rich in cysteine (SPARC) within a tumoral microenvironment. This protein, which is over-expressed in pancreatic adenocarcinoma, is involved in cell matrix interaction. It plays an important role in tissue remodelling, wound repair, cell migration and has a high affinity for albumin [6]. The MPACT study showed a statistically significant benefit for Nab-paclitaxel plus gemcitabine in terms of overall survival (OS) (8.5 months vs 6.7 months; HR 0.72; P = 0.000015), progression-free survival and objective response rate.

There is no standard care for chemotherapy regimen for second-line therapy in metastatic pancreatic adenocarcinoma [7]. Many drugs have been tested in phase II and III studies. Folfirinox (5-fluorouracil, folinic acid and oxaliplatin), after gemcitabine first line treatment, is the one with the best evidence-based level [8]. The median second-line survival was 4.82 months with folfirinox and 2.3 months with best supportive care. However folfox cannot be administrated as second line treatment after folfirinox.

To keep folfirinox as second line treatment seems sub-optimal because of the expected toxicity profile of this regimen in pre-treated patients. Moreover, patient’s PS and hepatic biology may not allow an aggressive triplet
chemistry containing irinotecan in a significant percentage of patients at this stage.

After 5FU and platinum doublet, second line gemcitabine is well tolerated but allows only limited overall survival (OS). In the FFCD 0301 trial [9], median OS after first and second line chemotherapy is 6.7 months (95% CI 5.4 to 8.6). Assuming the limitation of an indirect comparison, Nab-paclitaxel plus gemcitabine seems to be better tolerated than folfirinox and therefore usable for patients with a less good PS. This regimen has recently being tested as second line treatment with an acceptable toxicity profile in patients pre-treated by gemcitabine-based therapy [10].

With an acceptable tolerability and proven better efficacy than gemcitabine alone as first line treatment, this combination seems, from our point of view, promising for second line treatment after folfirinox failure.

We tested this strategy for our patient. To our knowledge, it has never been reported before. Efficacy of this strategy was good, with an objective response using RECIST 1.1 Criteria and Ca 19.9 normalization, despite failure of folfirinox. One of the major concerns of such a therapeutic sequence is the induction of a severe peripheral chronic sensitive neurotoxicity. However, oxaliplatin and Nab-paclitaxel mechanisms of neurotoxicity are different, especially with regards reversibility. Oxaliplatin induces symmetrical symptoms with paresthesia and distal hypoesthesia that lead to difficulties in writing, buttoning, sewing or driving. This toxicity can increase after treatment is stopped. Nab-paclitaxel also causes paresthesia, and distal burning pain. Symptoms decline most of the time within 4 weeks when treatment is stopped [11]. Therefore, it is not an argument to prevent the use of both drugs sequentially.

An alternative approach could be a sequential strategy as is illustrated in the FIREGEM study [12] testing two months of Folfiri-3 followed by two months of gemcitabine with promising results, but replacing gemcitabine by Nab-paclitaxel plus gemcitabine. Such a sequential approach with folfirinox for two months followed by Nab-paclitaxel plus gemcitabine for two months could also be an interesting option.

Conclusion

In conclusion, Nab-paclitaxel is a new treatment option and SPARC is a pioneer therapeutic target which has led to substantial improvements in survival in metastatic pancreatic adenocarcinoma. However, combining folfirinox and gemcitabine plus Nab-paclitaxel treatment in good performance status patients with metastatic pancreatic cancer is not clear to date for physicians. This case report illustrates that Nab-paclitaxel plus gemcitabine, as a second line of palliative chemotherapy after failure of folfirinox, could be a good strategy for patients in performance status 0-1. Obviously, this data has to be confirmed in larger patients series and in future comparative clinical studies.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


