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EDITORIAL

Neoadjuvant treatment for resectable pancreatic cancer: Time for phase Ⅲ testing?

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Abstract

This paper discusses the rationale for phase Ⅲ testing of neoadjuvant therapy in patients affected by resectable pancreatic adenocarcinoma. The therapeutic management of patients affected by resectable pancreatic cancer is particularly troublesome due to the aggressiveness of the disease and to the limited efficacy and sometimes unfavourable risk-benefit ratio of the available therapeutic tools. Conflicting data on the role of adjuvant chemoradiation have been reported, while adjuvant single-agent chemotherapy significantly improved overall survival (OS) when compared to surgery alone. However, the OS figures for adjuvant chemotherapy remain disappointing. In effect, pancreatic cancer exhibits a prominent tendency to recur after a brief median time interval from surgery and extra-pancreatic dissemination represents the predominant pattern of disease failure. Neoadjuvant treatment has a strong rationale in this disease but limited information on the efficacy of this approach is available from single arm trials with low levels of evidence. Thus, in spite of two decades of investigation there is currently no evidence to support the routine use of pre-surgical therapy in clinical practice. To foster knowledge on the optimal management of this disease, and to produce evidence-based treatment guidelines, there is no alternative to well designed randomized trials. Systemic chemotherapy is a candidate for testing because it is supported by a more robust rationale than chemoradiation. Combination chemotherapy regimens with elevated activity in advanced disease warrant investigation. Caution would suggest the running of an exploratory phase Ⅱ randomized trial before embarking on a large phase Ⅲ study.

Key words: Pancreatic cancer; Neoadjuvant therapy; Phase Ⅲ trial; Chemotherapy

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INTRODUCTION

Pancreatic cancer represents the fourth most common cause of cancer death, bears the worst prognosis among solid tumors and has seen very limited progress over the last 30 years. Due to intrinsic chemo- and radio-resistance, surgical resection is considered the only therapy that may have an impact on the natural history of the disease and may increase chance for cure. However, 5-year overall survival (OS) rates of less than 20% can be expected even after a curative resection, which is related to a non-negligible risk of mortality and morbidity. Therefore, the therapeutic management of patients affected by resectable pancreatic cancer is particularly troublesome due to the aggressiveness of the disease and to the limited efficacy and, sometimes, unfavourable risk-benefit ratio of the available therapeutic tools.

STANDARD TREATMENT IN RESECTABLE PANCREATIC CANCER

Adjuvant fluorouracil-based chemoradiation followed[1,2] or not[3] by maintenance systemic chemotherapy with 5-fluorouracil has been tested against surgery alone in a few phase Ⅲ trials with conflicting results, ranging from a significant improvement[1] to a detrimental impact on OS[2]. Accordingly, the use of this strategy is a highly controversial topic in the management of patients with resected pancreatic adenocarcinoma.

More recently, randomized trials have suggested that both adjuvant 5-fluorouracil and gemcitabine may obtain an improvement in median survival of 2.6-4.5 mo and in 2-year OS of 6%-10% over pancreatic resection alone[2,4], with no significant difference between the two drugs[5,6].

It is noteworthy that the OS benefit achieved by adjuvant chemotherapy, in addition to being modest, does not apply to the whole population of patients submitted to pancreatic resection. In fact, up to 25% of patients have a complicated course after surgery and are unable to receive the planned treatment in due time[3,7]. Also, patients with evidence of persistent local disease or metastatic disease at the first post-operative radiological assessment are ineligible for prospective trials on adjuvant chemotherapy, whose results are, consequently, not fully generalizable.

PATTERN OF DISEASE RECURRENCE AFTER STANDARD TREATMENT

In the subset of patients receiving postoperative treatment, pancreatic cancer exhibits a prominent tendency to recur locally and to metastasize after a brief median time interval of about 13 mo from surgery[4]. Early relapse after curative surgery may be explained by the presence of micro-metastases or minimal residual disease not detectable at the time of surgery, or by the spread of cancer cells into the portal vein, lymphatic vessels, and the peritoneal cavity due to surgical manipulation of the tumor. In spite of adjuvant systemic chemotherapy, extra-pancreatic dissemination represents the predominant pattern of disease failure, affecting 63%-83% of patients, and occurs earlier than isolated local failure, which can be observed in 17%-37% of cases[2,4-6,8,9].

RATIONAL FOR NEOADJUVANT THERAPY

In this scenario, the administration of neoadjuvant systemic chemotherapy may offer several theoretical advantages. Firstly, micro-metastatic disease may be immediately treated, thus avoiding the harmful delay of at least 2 mo which occurs for patients submitted to upfront surgery. Second, a larger proportion of patients may receive an active systemic treatment compared with the adjuvant setting. Third, the treatment itself may be better tolerated, resulting in a higher rate of treatment compliance and improved dose-intensity. Fourth, neoadjuvant chemotherapy potentially reduces intraoperative tumor spillage. Fifth, the delivery of treatment before surgical manipulation may be favored by better tissue oxygenation, facilitating the distribution of chemotherapy agents into the tumor, and increasing normal tissue tolerance. Moreover, the administration of chemotherapy before surgery allows an *in vivo* assessment of tumor chemo-sensitivity. Finally, neoadjuvant chemotherapy may also lead to more definitive surgical resections by reducing the risk of tumoral infiltration of lymph nodes and of resection margins in the surgical specimen.

On the other hand, the neoadjuvant approach is subject to hypothetical risks such as (1) inaccurate staging and the consequent overtreatment of very early disease; (2) erroneous histology; (3) diagnostic inaccuracy due to difficulties in distinguishing between intra-pancreatic bile duct adenocarcinoma and pancreatic adenocarcinoma; (4) increase in operative morbidity and mortality; and (5) the possibility that the disease might metastasize or become unresectable during the course of induction therapy. The first topic appears to be of little relevance in pancreatic cancer since systemic treatment administration is warranted at virtually any stage of disease, aside from, perhaps, stage I , which is exceedingly rare. Similarly, the risk of yielding an inaccurate pathological diagnosis is limited as the widespread and systematic use of endoscopic ultrasound and fine needle aspiration considerably reduces the possibility of errors. As regards surgical complications, no increase in morbidity or mortality after neoadjuvant therapy has been reported in prior trials[10-12]. Conversely, the topic of disease progression during pre-surgical treatment is of considerable concern because, among patients whose disease was deemed resectable at the time of trial enrolment, only 45%-74% were actually submitted to surgical resection after induction chemoradiation[12-16] and 38%-70% after induction chemotherapy followed[10] or not[11] by chemoradiation. Proponents of neoadjuvant therapy consider these figures another advantage of this strategy, claiming that patients who experience disease progression during induction treatment suffer from an extremely aggressive tumor, which cannot be cured by extensive surgery. In fact, avoiding the risk of surgical mortality and morbidity in this subset of patients may be appealing. However, this is not necessarily true for patients who experience only local progression during neoadjuvant therapy, and in any case, no comparative information from randomized trials on the impact of the different management strategies is available in order to rule out a detrimental impact of delaying surgery. Furthermore, the proper aim for pre-surgical therapy should be that of downstaging disease and of improving both disease control and, ultimately, cure rate, rather than improving patient selection for surgery. Overall, the balance between the theoretical advantages and disadvantages of neoadjuvant therapy in pancreatic cancer appears uncertain.

PRIOR EXPERIENCE WITH NEOADJUVANT THERAPY

There have been no large randomised controlled studies

on the use of neoadjuvant therapy in resectable pancreatic cancer and the sample size of prospective series has usually been limited. In addition to the abovementioned disappointing resection rates, reported median OS and 2-year OS in this single arm selected series ranged from 8 to 23 mo and from 27% to 40%[10-17]. Altogether, these figures do not appear to represent a remarkable improvement when compared to those of patients submitted to surgery alone (median OS 11-17 mo; 2-year OS 15%-31%)[1-3], or to compare favorably with those of adjuvant therapy (median OS 14-25 mo; 2-year OS 29%-55%)[1-4,6,7]. It is noteworthy that prior experiences with adjuvant combination chemotherapy reported more promising results (median OS 27-44 mo; 2-year OS 53%-58%)[9,18,19]. However, inter-trial comparisons, which already have several limitations, are in this case subject to an additional bias due to the different enrolment timing. In fact, the typical population enrolled in a prospective adjuvant trial is better selected than the typical population enrolled in a neoadjuvant trial because it does not include patients with intraoperative or postoperative detection of metastases, patients who die due to surgical complications or those who experience severe morbidity and delayed surgical recovery.

Thus, in spite of two decades of investigation of neoadjuvant therapy in resectable pancreatic cancer, there is currently no evidence to support its routine use in clinical practice, and even a detrimental effect on outcome cannot be ruled out.

TRIAL DESIGN TO ASSESS THE ROLE OF NEOADJUVANT THERAPY

Single arm trials with historical or literature comparison, and divergent study designs and entry criteria have produced modest therapeutic progress and do not allow a proper assessment of the role of neoadjuvant therapy in resectable pancreatic cancer. To foster knowledge regarding the optimal management of this disease and to produce evidence-based treatment guidelines, there is no alternative to well designed randomized trials. Since timing and sequencing of treatments appears to be a crucial and as yet unanswered issue, patients in the ideal trial should be randomly allocated to receive exactly the same treatment for the same period of time before and after surgery. Otherwise, the attribution of any potential outcome improvement to treatment type, timing or duration will be irremediably confounded and trial interpretation inconclusive.

CANDIDATES FOR PROSPECTIVE ASSESSMENT

As mentioned above, pancreatic cancer has an elevated risk of both local and systemic failure after surgery. In this perspective, local therapy represents a poor chance of considerably improving cure rates while the concomitant administration of radiotherapy and systemic chemotherapy may simultaneously address both troubles. The main radiosensitizing antitumor agents available for pancreatic cancer are gemcitabine and 5-fluorouracil. Unfortunately, gemcitabine has to be administered at suboptimal doses which are unlikely to achieve any effect against systemic disease, due to the overlapping toxicity with radiotherapy and both drugs yield scarce activity. In fact, gemcitabine and 5-fluorouracil obtained objective response rates around 10% in advanced disease[20-26]. Any chemotherapy with a low rate of tumor shrinkage is clearly unable to provide any major advantage in terms of either micro-metastatic or local disease control for the majority of patients and may therefore be assumed to have a limited role in the neoadjuvant setting. More active combination chemotherapy regimens appear to be more promising candidates for testing but have feasibility limitations with concomitant irradiation. Furthermore, the value of radiotherapy in this disease is controversial and, at the moment, does not represent the most burning question, while the rational endorsement of the assessment of the role of combination chemotherapy as pre-surgical therapy is more convincing. Among several regimens with conventional or target agents that have been assessed for use against advanced pancreatic cancer, objective response rates over 20% have rarely been reported, while gemcitabine-cisplatin and gemcitabine-oxaliplatin doublets obtained a response rate of 26%[22] and 28%[23], respectively. Unfortunately, these figures were not reproduced in larger trials where partial plus complete response rate was in the range of 10% to 13% with gemcitabine-cisplatin[24,25] and 9% with gemcitabine-oxaliplatin[26]. Response rates with triplets including gemcitabine, a fluoropyrimidin and either a platinating agent (18%-33%)[27-29] or docetaxel (29%)[30], FOLFOXIRI (5-fluorouracil-oxaliplatin-irinotecan; 26%)[31] and G-FLIP (gemcitabine-5-fluorouracil-irinotecan-cisplatin; 26%)[32] regimens have shown promise in single phase Ⅱ series, but no phase Ⅲ or confirmatory trials are available. A PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) regimen was proven, in a phase Ⅲ trial, to be both clinically and statistically more effective than single agent gemcitabine as upfront treatment in advanced pancreatic cancer[33]. It is noteworthy that this combination chemotherapy had manageable toxic effects and the significant survival improvement was not achieved at the cost of impaired quality of life[34]. Four consecutive trials with the PEFG regimen and its variants reproduced a radiological response rate in the range of 38.5%-51%[33,35-37]. The substitution of infusional 5-fluorouracil by oral capecitabine originated the PEXG regimen that further confirmed the activity figures[38] and rendered the schedule more suitable for clinical use. The reliability of the response rate was also endorsed by the biochemical response rate. In effect, a major biochemical response (i.e. CA19.9 reduction at nadir relative to baseline value reduction $\geqslant$ 90%) was observed in 30% of patients treated with quadruplets *vs* 7% with single agent gemcitabine[39]. The superiority of this four-drug combination over other regimens was also suggested by a recent survey on treatment trends and outcomes of 650 patients with stage Ⅲ pancreatic adenocarcinoma[40]. Based on these data and

considerations, the PEXG regimen appears to be the most deserving candidate for a prospective assessment in the neoadjuvant setting.

CONCLUSION

The topic of treatment sequencing for patients affected by resectable pancreatic adenocarcinoma is of paramount importance and warrants further investigation. Time is mature for the running of a randomized prospective study, which is the only approach capable of providing evidence-based answers. To date, on the basis of activity data from trials on advanced pancreatic cancer, the most robust candidate for testing is the PEXG regimen. However, the lack of a large randomized trial confirming survival improvement over single agent gemcitabine in advanced disease suggests caution before embarking on a phase Ⅲ study in the neoadjuvant setting. An exploratory phase Ⅱ randomized trial seems to embody the optimal approach to avoid the risk of wasting resources and time. Accordingly, a clinical trial involving more than 20 Italian institutions has been designed as a three-arm calibrated study[41] and is currently underway. Patients are randomly allocated to receive either an adjuvant treatment with gemcitabine for 6 mo (calibration arm) or an adjuvant treatment with PEXG for 6 mo or a perioperative treatment (3 mo before and 3 mo after surgery) with PEXG. After completion of recruitment for the phase Ⅱ part of the study, an analysis of the results will be performed to decide whether to continue to the subsequent phase Ⅲ part of the study. It is hoped that this trial will contribute to an expansion of knowledge on the optimal therapeutic management of resectable pancreatic cancer.

REFERENCES

1 **Kalser MH**, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985; **120**: 899-903

2 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210

3 **Klinkenbijl JH**, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, Arnaud JP, Gonzalez DG, de Wit LT, Hennipman A, Wils J. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999; **230**: 776-782; discussion 782-784

4 **Oettle H**, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; **297**: 267-277

5 **Neoptolemos J**, Büchler M, Stocken DD, Ghaneh P, Smith D, Bassi C, Moore M, Cunningham D, Dervenis C, Goldstein D. ESPAC-3(v2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma. *J Clin Oncol* 2009; **27**: A4505

6 **Regine WF**, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, Benson AB, Macdonald JS, Kudrimoti MR, Fromm ML, Haddock MG, Schaefer P, Willett CG, Rich TA. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA* 2008; **299**: 1019-1026

7 **Spitz FR**, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, Cleary KR, Janjan NA, Goswitz MS, Rich TA, Evans DB. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 1997; **15**: 928-937

8 **Van den Broeck A**, Sergeant G, Ectors N, Van Steenbergen W, Aerts R, Topal B. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. *Eur J Surg Oncol* 2009; **35**: 600-604

9 **Reni M**, Passoni P, Bonetto E, Balzano G, Panucci MG, Zerbi A, Ronzoni M, Staudacher C, Villa E, Di Carlo V. Final results of a prospective trial of a PEFG (Cisplatin, Epirubicin, 5-Fluorouracil, Gemcitabine) regimen followed by radiotherapy after curative surgery for pancreatic adenocarcinoma. *Oncology* 2005; **68**: 239-245

10 **Palmer DH**, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, Buckels JA, Bramhall SR. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol* 2007; **14**: 2088-2096

11 **Varadhachary GR**, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Abdalla E, Wang H, Staerkel GA, Lee JH, Ross WA, Tamm EP, Bhosale PR, Krishnan S, Das P, Ho L, Xiong H, Abbruzzese JL, Evans DB. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008; **26**: 3487-3495

12 **Evans DB**, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Wang H, Cleary KR, Staerkel GA, Charnsangavej C, Lano EA, Ho L, Lenzi R, Abbruzzese JL, Wolff RA. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008; **26**: 3496-3502

13 **Hoffman JP**, Lipsitz S, Pisansky T, Weese JL, Solin L, Benson AB 3rd. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. *J Clin Oncol* 1998; **16**: 317-323

14 **Pisters PW**, Wolff RA, Janjan NA, Cleary KR, Charnsangavej C, Crane CN, Lenzi R, Vauthey JN, Lee JE, Abbruzzese JL, Evans DB. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 2002; **20**: 2537-2544

15 **White RR**, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, Gottfried MR, Baillie J, Branch MS, Jowell PS, McGrath KM, Clary BM, Pappas TN, Tyler DS. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001; **8**: 758-765

16 **Moutardier V**, Magnin V, Turrini O, Viret F, Hennekinne-Mucci S, Gonçalves A, Pesenti C, Guiramand J, Lelong B, Giovannini M, Monges G, Houvenaeghel G, Delpero JR. Assessment of pathologic response after preoperative chemoradiotherapy and surgery in pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2004; **60**: 437-443

17 **Yeung RS**, Weese JL, Hoffman JP, Solin LJ, Paul AR, Engstrom PF, Litwin S, Kowalyshyn MJ, Eisenberg BL. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A Phase II Study. *Cancer* 1993; **72**: 2124-2133

18 **Reni M**, Cereda S, Passoni P, Rognone A, Mazza E, Nicoletti R,

Arcidiacono PG, Zerbi A, Balzano G, Di Carlo V. A randomized phase II trial of PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG (docetaxel) regimen in advanced pancreatic adenocarcinoma. *J Clin Oncol* 2007; **25**: A4628

19 **Picozzi VJ**, Kozarek RA, Traverso LW. Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am J Surg* 2003; **185**: 476-480

20 **Burris HA 3rd**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413

21 **Maisey N**, Chau I, Cunningham D, Norman A, Seymour M, Hickish T, Iveson T, O'Brien M, Tebbutt N, Harrington A, Hill M. Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. *J Clin Oncol* 2002; **20**: 3130-3136

22 **Colucci G**, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, Cigolari S, Testa A, Maiello E, Lopez M. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002; **94**: 902-910

23 **Louvet C**, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005; **23**: 3509-3516

24 **Heinemann V**, Wilke H, Mergenthaler HG, Clemens M, König H, Illiger HJ, Arning M, Schalhorn A, Possinger K, Fink U. Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. *Ann Oncol* 2000; **11**: 1399-1403

25 **Colucci G**, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, Dapretto E, Manzione L, Piazza E, Sannicolò M, Ciaparrone M, Cavanna L, Giuliani F, Maiello E, Testa A, Pederzoli P, Falconi M, Gallo C, Di Maio M, Perrone F. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010; **28**: 1645-1651

26 **Poplin E**, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson AB 3rd. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; **27**: 3778-3785

27 **Correale P**, Montagnani F, Miano S, Sciandivasci A, Pascucci A, Petrioli R, Testi W, Tanzini G, Francini G. Biweekly triple combination chemotherapy with gemcitabine, oxaliplatin, levofolinic acid and 5-fluorouracil (GOLF) is a safe and active treatment for patients with inoperable pancreatic cancer. *J Chemother* 2008; **20**: 119-125

28 **Novarino A**, Chiappino I, Bertelli GF, Heouaine A, Ritorto G, Addeo A, Bellone G, Merlano M, Bertetto O. Phase II study of cisplatin, gemcitabine and 5-fluorouracil in advanced pancreatic cancer. *Ann Oncol* 2004; **15**: 474-477

29 **Wagner AD**, Buechner-Steudel P, Wein A, Schmalenberg H, Lindig U, Moehler M, Behrens R, Kleber G, Kuss O, Fleig WE. Gemcitabine, oxaliplatin and weekly high-dose 5-FU as 24-h infusion in chemonaive patients with advanced or metastatic pancreatic adenocarcinoma: a multicenter phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Ann Oncol* 2007; **18**: 82-87

30 **Fine RL**, Fogelman DR, Schreibman SM, Desai M, Sherman W, Strauss J, Guba S, Andrade R, Chabot J. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother Pharmacol* 2008; **61**: 167-175

31 **Conroy T**, Paillot B, François E, Bugat R, Jacob JH, Stein U, Nasca S, Metges JP, Rixe O, Michel P, Magherini E, Hua A, Deplanque G. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol* 2005; **23**: 1228-1236

32 **Goel A**, Grossbard ML, Malamud S, Homel P, Dietrich M, Rodriguez T, Mirzoyev T, Kozuch P. Pooled efficacy analysis from a phase I-II study of biweekly irinotecan in combination with gemcitabine, 5-fluorouracil, leucovorin and cisplatin in patients with metastatic pancreatic cancer. *Anticancer Drugs* 2007; **18**: 263-271

33 **Reni M**, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005; **6**: 369-376

34 **Reni M**, Bonetto E, Cordio S, Passoni P, Milandri C, Cereda S, Spreafico A, Galli L, Bordonaro R, Staudacher C, Di Carlo V, Johnson CD. Quality of life assessment in advanced pancreatic adenocarcinoma: results from a phase III randomized trial. *Pancreatology* 2006; **6**: 454-463

35 **Reni M**, Passoni P, Panucci MG, Nicoletti R, Galli L, Balzano G, Zerbi A, Di Carlo V, Villa E. Definitive results of a phase II trial of cisplatin, epirubicin, continuous-infusion fluorouracil, and gemcitabine in stage IV pancreatic adenocarcinoma. *J Clin Oncol* 2001; **19**: 2679-2686

36 **Reni M**, Cereda S, Bonetto E, Viganò MG, Passoni P, Zerbi A, Balzano G, Nicoletti R, Staudacher C, Carlo VD. Dose-Intense PEFG (Cisplatin, Epirubicin, 5-Fluorouracil, Gemcitabine) in Advanced Pancreatic Adenocarcinoma: A Dose-Finding Study. *Cancer Invest* 2007; 1-5

37 **Reni M**, Cereda S, Bonetto E, Viganò MG, Passoni P, Zerbi A, Balzano G, Nicoletti R, Staudacher C, Di Carlo V. Dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* 2007; **59**: 361-367

38 **Cereda S**, Rognone A, Ghidini M, Rezzonico S, Passoni P, Mazza E, Nicoletti R, Zerbi A, Villa E, Reni M. A randomized phase II trial of two different four-drug combinations in advanced pancreatic adenocarcinoma: Cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel. *J Clin Oncol* 2009; **27**: A4614

39 **Reni M**, Cereda S, Balzano G, Passoni P, Rognone A, Fugazza C, Mazza E, Zerbi A, Di Carlo V, Villa E. Carbohydrate antigen 19-9 change during chemotherapy for advanced pancreatic adenocarcinoma. *Cancer* 2009; **115**: 2630-2639

40 **Reni M**, Sartori N, Mambrini A, Berardi R, Passardi A, Milella M, Cereda S, Tronconi MC, Aprile G, Cordio S, Pasetto LM, Rognone A, Pederzoli P, Falconi M. An Italian study on treatment trends and outcomes of patients with stage III pancreatic adenocarcinoma in the gemcitabine era: is it time to change? *Anticancer Drugs* 2010; **21**: 459-464

41 **Herson J**, Carter SK. Calibrated phase II clinical trials in oncology. *Stat Med* 1986; **5**: 441-447

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