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EDITORIAL

Role of taxanes in pancreatic cancer

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Abstract

Pancreatic cancer is one of the most deadly cancers and is characterized by a poor prognosis. Single agent gemcitabine, despite its limited activity and modest impact on disease outcome, is considered as the standard therapy in pancreatic cancer. Most of the combination regimens used in the treatment of this disease, also including the targeted agents, did not improve the outcome of patients. Also, taxanes have been tested as single agent and in combination chemotherapy, both in first line and as salvage chemotherapy, as another possible option for treating pancreatic cancer. The inclusion of taxanes in combination with gemcitabine as upfront therapy obtained promising results. Accordingly, taxanes, and above all, new generation taxanes, appear to be suitable candidates for further testing to assess their role against pancreatic cancer in various clinical settings.

Key words: Pancreatic cancer; Advanced disease; Metastatic disease; Chemotherapy; Taxanes; Drug combinations; Radiotherapy; ABI-007

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INTRODUCTION

Pancreatic cancer has a very poor prognosis and it still remains as one of the most deadly cancers. At diagnosis, only 10%-20% of patients are considered candidates for a curative resection that is possible only in the absence of distant metastases, peritoneal carcinomatosis, and lack of any involvement of celiac axis and superior mesenteric artery[1]. Around 80% of patients have advanced or metastatic disease and median overall survival (mOS) of this group is very poor ranging from 3 to 6 mo[2]. The first drug used in the treatment of advanced pancreatic cancer was 5-fluorouracil (5-FU) that provided a palliative benefit with a significant improvement in mOS compared to best supportive care (6 mo *vs* 2.5 mo, $P < 0.01$)[3]. When compared to bolus 5-FU, gemcitabine yielded a significantly better response rate (RR) (5.4% *vs* 0%), survival (mOS 5.65 mo *vs* 4.41 mo, $P = 0.0025$) and clinical benefit, which is a composite measure consisting of reduction of pain, analgesic drugs intake and weight loss (23.8% *vs* 4.8%)[4]. Given the modest and disappointing impact on overall survival (OS) achieved with single agent gemcitabine, other agents or drug combinations are continuously tested in advanced pancreatic cancer[5-7]. Among others, taxanes (docetaxel and pacli-

taxel) were tested as single agents or in combination with other chemotherapeutic agents in pancreatic cancer[8-10] because they showed promising activity in other solid tumours[11,12]. Mechanism of action of these drugs consists in enhancing microtubule assembly and inhibiting the depolymerization of tubulin responsible for the formation of bundles of microtubules blocking cell proliferation[13].

This article summarises the main clinical studies conducted in pancreatic cancer with taxanes as first or second line chemotherapy, both as monotherapy and combination therapy, in order to clarify the potential role of this class of drugs for further investigations.

DOCETAXEL

First-line therapy

Single agent: Docetaxel gained researchers' attention for the treatment of pancreatic cancer after a preclinical study showed its effectiveness in a murine model of pancreatic ductal adenocarcinoma[14]. Docetaxel activity as single agent was assessed in phase Ⅱ trials in chemonaïve patients affected by pancreatic cancer at two different dosages, 60 mg/mq[8] and 100 mg/mq[9,15], showing promising activity when used at higher dose (Table 1). With higher doses[9,15], the overall RR ranged from 5% to 15%, the median time to progression (mTTP) was 2.1-5.0 mo, and the mOS was 7-8.5 mo. Neutropenia was the most frequently observed grade 3/4 toxicity in both studies (36%-95%)[9]. Grade 3-4 anemia (9%-16%) and fatigue (9%-23%) were also commonly reported[9]. Given the phase Ⅱ nature of the trials, the small sample size and the selection of patient population, including stage Ⅱ and Ⅲ disease and patients who mainly had a performance status of 0-1, these results should be interpreted with caution. Nevertheless, these trials showed that docetaxel has some activity in the treatment of pancreatic cancer, and warrant further exploration. Docetaxel administered at lower dose failed to demonstrate any activity in pancreatic cancer[8]. In fact, no objective response was observed and both mTTP and mOS were shorter when compared to higher doses[9,15]. Moreover, grade 3-4 toxicity was remarkable with nearly 80% of the patients developing neutropenia, 7% anaemia, and 27% fatigue[8].

Combination chemotherapy: Docetaxel role was also addressed in combination with other drugs (Table 1). *In vitro* and *in vivo* studies have demonstrated that docetaxel yields a synergism with other drugs like capecitabine[16,17], 5-FU[18], gemcitabine[19,20], and cisplatin[21] .

The rationale for the combination of an oral fluoropyrimidine with docetaxel is based on the ability of taxanes to increase the activity in the tumoral tissue of thymidylate phosphorylases, which are key enzymes in the transformation process of capecitabine into its active metabolite 5-FU. The synergism of docetaxel with gemcitabine was observed *in vitro* in several cancer cell lines, but the biological mechanism is not clear. Hypothetically, the combination of these two agents could regulate the apoptotic process by increasing the apoptotic index. Finally, the synergism of docetaxel and cisplatin, observed in cell lines of gastric cancer, could be due to the down-regulation of multi drug resistant proteins by docetaxel thereby increasing cytotoxic index of cisplatin[21].

Several phase Ⅱ clinical trials assessed the activity of these combinations against advanced pancreatic cancer as an upfront therapy[19,20,22-26]. Docetaxel and gemcitabine yielded promising RR ranging from 12% to 40% and mOS ranging from 6 to 9 mo[19,20,23,25]. However, these single arm findings cannot be considered conclusive. Interestingly, the European Organization for Research and Treatment of Cancer (EORTC) group conducted a phase Ⅱ trial in which 96 patients were randomized to receive gemcitabine plus docetaxel or cisplatin plus docetaxel[24]. In 70 patients who were assessable for response, the RR was 19.4% with gemcitabine-docetaxel combination and 23.5% with cisplatin-docetaxel combination. Conversely, survival figures were better in 49 patients treated by the gemcitabine-docetaxel combination [median progression free survival (mPFS) 3.9 mo, mOS 7.4 mo; 1-year OS 30%] compared to those receiving cisplatin-docetaxel (mPFS 2.8 mo, mOS 7.1 mo; 1-year OS 16%). Toxicity was not negligible, consisting of grade 3-4 neutropenia in 47% and 55%, and febrile neutropenia in 9% and 16%, respectively. Altogether, safety profile and survival analysis favoured gemcitabine-docetaxel combination for further evaluation. Another phase Ⅱ trial randomized 259 patients with metastatic pancreatic cancer to receive fixed dose gemcitabine or gemcitabine combined with either docetaxel, cisplatin, or irinotecan[27]. The primary end point of this study was the six months OS that was similar in all four treatment arms: 57% for fixed gemcitabine dose, 53% for gemcitabine plus cisplatin, 54% for gemcitabine plus docetaxel, and 57% for gemcitabine plus irinotecan. The mOS and mTTP were similar in the treatment groups and ranged between 6.4-7.1 mo and 3.3-4.5 mo, respectively. The RRs were also indistinguishable among treatment groups and ranged between 12% to 14%. The cisplatin and docetaxel combination tested in this study gave similar results, in terms of mOS and TTP, to that reported in the EORTC trial[24].

Another drug tested in combination with docetaxel was liposomal doxorubicin starting from preclinical study conducted on xenografted human pancreatic carcinoma in which this drug demonstrated to reduce tumor growth with a low toxicity[28]. In a phase Ⅱ clinical trial, this combination was studied on twenty-one locally advanced and metastatic pancreatic cancer patients[29]. The results in terms of RR (21%) and mOS (10 mo) were similar to those observed with combination of docetaxel with other drugs[19,20,22-26].

The activity of docetaxel, gemcitabine, capecitabine regimen (GTX) was also tested in 43 patients with metastatic disease yielding a RR of 22% and a mOS of 14.5 mo[30]. These results were echoed in a recent retrospective study on 79 chemonaïve patients with locally advanced or metastatic pancreatic cancer who had a mOS

Table 1 Clinical trials of docetaxel in pancreatic cancer

Trial	CT agent	Line CT	No. of patients	RR %	mPFS (mo)	mOS (mo)	Toxicity %
Okada *et al*[8]	Doce	I	21	CR 0 PR 0 SD 33	1[1]	6	Neutropenia 86, anemia 10, thrombocytopenia 5, asthenia 33, nausea-vomiting 29
Androulakis *et al*[9]	Doce	I	33	CR 3 PR 3 SD 58	5[1]	8.5	Neutropenia 36, febrile neutropenia 6, anemia 9, asthenia 9, neuropathy 6
Rougier *et al*[15]	Doce	I	43	CR 0 PR 15 SD 3	2.1[1]	7	Neutropenia 95, febrile neutropenia 9, anemia 16, asthenia 23, vomiting 7
Stathopoulos *et al*[23]	Doce + GEM	I	54	CR 0 PR 13 SD 33	8[1]	6	Neutropenia 31, febrile neutropenia 11, thrombocytopenia 7, asthenia 13, diarrhea 6
Ryan *et al*[25]	Doce + GEM	I	33	CR 0 PR 18 SD 39	3.8	8.9	Neutropenia 49, febrile neutropenia 12, asthenia 27, nausea-vomiting 12, diarrhea 12, neuropathy 9
Lutz *et al*[24]	Doce + GEM Doce + CDDP	I	96	CR 0/2.9 PR 19.4/20.6 SD 36.1/35.3	3.9/2.8	7.4/7.1	Neutropenia 40/50, febrile neutropenia 9/16, anemia 20/9, thrombocytopenia 8/5, diarrhea 8/5, stomatitis 8/10
Kulke *et al*[27]	GEM + CDDP GEM FDR GEM + Doce GEM + CPT-11	I	259	CR 2/0/0/2 PR 11/14/12/12 SD 54/58/53/55	4.5/3.3/4.1/4.0	6.7/6.4/6.4/7.1	Neutropenia 46/48/31/25, febrile neutropenia 2/3/5/2, anemia 16/12/16/5, thrombocytopenia 49/25/9/14, asthenia 16/14/21/19, nausea-vomiting 41/26/17/25, diarrhea 80/2/8/8
Fine *et al*[30]	GTX	I	43	CR 0 PR 21.9 SD 41.5	6.9[1]	14.5	Neutropenia 29.2, thrombocytopenia 12.2, mucositis 7.5
Reni *et al*[22]	PDXG PEXG	I	105	CR 2/4 PR 58/33 SD 19/46	7.4/7.6	10.7/11	Neutropenia 4/13, thrombocytopenia 2/4, anemia 4/4, asthenia 6/3
Cereda *et al*[35]	Doce	II	10	CR 0 PR 0 SD 20	1.5	4	Not observed
Katopodis *et al*[37]	Doce + X	II	31	CR 0 PR 9.7 SD 22.6	2.4	6.3	Neutropenia 32.2, febrile neutropenia 3.2, anemia 3.2, thrombocytopenia 3.2, stomatitis 3.2, asthenia 6.5
Reni *et al*[39]	MDI	II-III	15	CR 0 PR 0 SD 20	1.7	6.1	Phase I study Neutropenia 23, fatigue, diarrhea, and vomiting 10

[1]mTTP: Median time to progression; CT: Chemotherapy; RR: Response rate; mPFS: Median progression free survival; mOS: Median overall survival; Doce: Docetaxel; GEM: Gemcitabine; CDDP: Cisplatin; CPT-11: Irinotecan; GTX: Gemcitabine + Taxotere + Xeloda; PDXG: Cisplatin + Docetaxel + Gemcitabine + Xeloda; PEXG: Cisplatin + Epirubicin + Xeloda + Gemcitabine; X: Xeloda; MDI: Mitomycin + Docetaxel + Irinotecan; CR: Complete response; PR: Partial response; SD: Stable disease.

of 25.0 and 11.3 mo, respectively[31].

A four drug combination of cisplatin, docetaxel, capecitabine, and gemcitabine (PDXG) was tested in a randomized phase II trial in which a cisplatin, epirubicin, capecitabine, and gemcitabine (PEXG) regimen was chosen as calibration arm[22]. This choice was based on the fact that a PEFG regimen (cisplatin, epirubicin, fluorouracil, and gemcitabine) was previously shown to be superior to gemcitabine monochemotherapy in terms of progression free survival [PFS; hazard ratio (HR) 0.51; range 0.33-0.78] and OS (HR 0.65; range 0.43-0.99) in a phase III trial of first line therapy of pancreatic cancer[32] and that the use of oral capecitabine was shown to be equivalent to 5-FU in other tumors[33]. Both the radiological and the biochemical RR[34] were better for 53 patients treated with PDXG (60% complete plus partial radiological responses; 41% major biochemical responses; 39% minor biochemical responses) than for 52 patients receiving PEXG (37% complete plus partial radiological responses; 32% major biochemical responses; 32% minor biochemical responses). However, OS and PFS were very similar in the two arms (mOS 10.7 mo *vs* 11.0 mo and mPFS 7.4 mo *vs* 7.6 mo, with PDXG and PEXG regimens, respectively). The safety profile of PDXG regimen was more favourable than that of PEXG regimen in terms of grade 3-4 neutropenia (4% in PDXG group *vs* 13% in PEXG arm).

Overall, these studies suggest that multi-drug associations, in particular triplets and quadruplets, are more active in pancreatic cancer when compared to monochemotherapy.

Salvage therapy

Single agent and combination chemotherapy: Docetaxel was also tested as salvage treatment in pancreatic cancer both as single agent and in combination[31,35-40]

Table 2 Clinical trials of paclitaxel as single agent or in combination chemotherapy in pancreatic cancer

Trial	CT agent	Line CT	No. of patients	RR %	mPFS (mo)	mOS (mo)	Toxicity %
Whitehead *et al*[10]	PTX	I	45	CR 3 PR 5 SD 13	NR	5	Neutropenia + leukopenia 92 , anemia 23, thrombocytopenia 20, asthenia 23, nausea-vomiting 18, neuropathy 7
Saif *et al*[46]	GPM	I	56	CR 1.7 PR 3.5 SD 54.8	2.8	6.5	Neutropenia 40, asthenia 17.8, neuropathy 13.3
Löhr *et al*[48]	GEM GEM + ET 11 mg/mq GEM + ET 22 mg/mq GEM + ET 44 mg/mq	I	212	CR 0/0/0/0 PR 14/14/14/16 SD 30/46/51/35	2.7/4.1/4.6/4.4	6.8/8.1/8.7/9.3	Neutropenia 18/12/16/22, anemia 4/0/4/8, thrombocytopenia 2/8/16/14, nausea + vomiting 2/2/0/10
Von Hoff *et al*[50]	Nab-PTX + GEM	I	67	CR 4 PR 42 SD 18	7.9	12.2	Neutropenia 67, thrombocytopenia 23, asthenia 21, neuropathy 15
Hosein *et al*[51]	Nab-PTX	II	19	CR 0 PR 5.3 SD 31.6	1.6	7.3	Neutropenia 32, febrile neutropenia 11, anemia 11
Kim *et al*[52]	PTX + 5-FU	II	28	CR 0 PR 10 SD 20	2.5[1]	7.6	Leukopenia 6, diarrhea 2, neuropathy 1

[1]mTTP: Median time to progression; CT: Chemotherapy; RR: Response rate; mPFS: Median progression free survival; mOS: Median overall survival; PTX: Paclitaxel; NR; Not reported; GPM: Paclitaxel loaded polymeric micelle, ET: Paclitaxel embedded in cationic liposomes; Nab-PTX: Paclitaxel protein-bound particles; 5-FU: 5-fluorouracil.

(Table 1). In a phase II trial conducted on 10 patients, no response was obtained, mPFS was 1.5 mo and mOS was 4.0 mo[35].

Combination chemotherapy with taxanes as salvage treatment gave disappointing results with a significant toxicity[37-39]. In these trials, docetaxel combined with capecitabine[37], with irinotecan[38], and with mitomycin plus irinotecan[39] resulted in a RR ranging between 0% to 9.7%, and mOS between 4.5-6.3 mo. The most common toxicity in these studies was grade 3-4 neutropenia observed in around 30%-32% of patients[37-39]. Two retrospective series reported the results of GTX regimen as salvage therapy in patients affected by pancreatic cancer[31,40]. The RR was 12%-15% and mOS was 5.7-6.7 mo[31,40]. Altogether, the response and survival figures observed with docetaxel-based combinations as salvage therapy in advanced pancreatic cancer were in the range reported with other regimens[41-45]. These drug combinations tested in the second line gave RR between 0%-24% and mOS between 3.7-6.2 mo[41,42,44,45]. The PEFG combination was the only regimen that reported a better mOS in second line therapy (8.3 mo) with an acceptable toxicity[43].

PACLITAXEL AND NEW PACLITAXEL FORMULATIONS

First-line therapy

Single agent: Single agent paclitaxel yielded a RR of 3% and a mOS of 5 mo in a series of 45 patients with advanced pancreatic cancer (Table 2)[10], while paclitaxel loaded with polymeric micelle obtained an overall RR of 6.7%, mPFS of 2.8 mo, and mOS of 6.5 mo in 56 patients with advanced pancreatic cancer[46].

Combination chemotherapy: EndoTAG™-1 (ET) is a cationic liposome membrane charging paclitaxel. This particular structure promotes the delivery of the drug in the tumor mass. Tumor endothelium lacks glycocalix which normally covers endothelial cells, so negative charges are exposed on the cell surface. Thus, the positive charges carried by liposomes is exposed and interact with the negative charges present on tumoral cells favouring the internalization of the drug into the tumor[47].

Löhr *et al*[48] tested ET in combination with gemcitabine *vs* gemcitabine alone in a four-arm randomized phase II trial on 212 patients affected by locally advanced or metastatic disease (Table 2). The treatment consisted of seven weekly infusions of standard gemcitabine alone or associated with twice-weekly ET at dosage of 11 (Endo11), 22 (Endo22) or 44 mg/mq (Endo44) for seven weeks. RR was comparable across the four treatment groups (14%-16%), the mPFS was longer in the gemcitabine plus ET arms (4.1, 4.6, and 4.4 for Endo11, Endo22, and Endo44, respectively) compared to gemcitabine group (2.7 mo). Also the mOS appeared to be better in the combination arms (from 8.1 to 9.3 mo) compared to single agent (mOS 6.8 mo). The treatment with gemcitabine and ET was well tolerated with a dose-dependent increase in grade 3-4 thrombocytopenia (from 8% to 14%), neutropenia (from 12% to 22%), and anemia (from 4% to 8%). Grade 3-4 febrile neutropenia was observed in 6% of the patients. No treatment-related neuropathy was observed in this trial. This study suggested that this new formulation of paclitaxel warrants further investigation to define its role in the treatment of pancreatic cancer.

Another paclitaxel formulation known as ABI-007 was tested against pancreatic cancer. ABI-007 (also

known as *nab*-paclitaxel), is a cremophor-free, albumin-bound 130-nm particle form of paclitaxel that does not require the use of cremophor-EL, thus avoiding the severe toxicities associated with this vehicle[49]. The albumin in nab-paclitaxel binds to gp60 (albondin) receptors and to caveolae resulting in the formation of caveoli transporting the drug across the endothelial cells to the tumor interstitial space. In pancreatic tumor stroma, secreted protein acid and rich in cystein (SPARC) protein, which is also called osteonectin, is overexpressed. SPARC interacts with the albumin of nab-paclitaxel enhancing the concentration of this drug into the tumor, which causes "stromal collapse", a phenomenon of depletion and collapsing of stroma, bringing tumor cells closer to each other and to blood vessel. A phase IB-Ⅱ study of ABI-007 in combination with gemcitabine was performed in metastatic pancreatic cancer (Table 2)[50]. The maximum tolerated dose (MTD) was 125 mg/mq for ABI-007 in combination with standard gemcitabine[50]. The PFS for the whole population of patients enrolled into the trial was 6.9 mo and the mOS was 10.3 mo, while in the group of 44 patients treated with ABI-007 at MTD, the mPFS was 7.9 mo and the mOS was 12.2 mo. A phase Ⅲ clinical trial of gemcitabine and ABI-007 combination *vs* standard gemcitabine is currently ongoing in patients with metastatic pancreatic cancer (NCT00844649).

Salvage therapy

Single agent and combination chemotherapy: ABI-007 at 100 mg/mq weekly for three weeks, out of every 4, was also tested as second line chemotherapy in 19 patients with progressive pancreatic cancer after previous gemcitabine-based therapy (Table 2)[51]. One partial response (5.3%) and six stable disease (31.6%) were reported. The mPFS and mOS were 1.6 mo and 7.3 mo, respectively. Grade 3 or 4 neutropenia, neutropenic fever and anemia occurred in 32%, 11% and 11% of patients, respectively.

Paclitaxel in combination with 5-FU was administered as salvage therapy to 28 patients with advanced pancreatic cancer after gemcitabine failure (Table 2)[52]. The RR was 10%, the mTTP 2.5 mo, and the mOS 7.6 mo. This regimen was well tolerated with grade 3-4 neutropenia in 21.4% of the patients, anemia in 3.6%, grade 4 neuropathy in 3.6%, and grade 3 diarrhea in 7.2% of the patients.

TAXANES PLUS RADIOTHERAPY

Pancreatic cancer is characterized by a high rate of both local and systemic failure. Chemoradiation was tested in stage Ⅲ disease with different drugs yielding a mOS between 8 to 11 mo and 1-year survival rate between 25% to 40%[53-55].

Due to their radiation-sensitizing properties[56], taxanes were also tested in combination with radiotherapy in locally advanced[57,58] and in resectable[59] pancreatic cancer. In locally advanced disease, paclitaxel and radiotherapy obtained RR of 26%, mOS of 8-11.2 mo and 1-year OS of 30%-43%[57,58]. These results were in the range reported with other drugs tested in combination with radiotherapy.

Conversely, paclitaxel-based chemoradiation as neoadjuvant therapy in resectable patients yielded disappointing results[59]. In fact, 46% of the patients suffered grade 3 toxicity (hematological, gastrointestinal, asthenia, anorexia, allergic reaction) and the mOS (19 mo) was inferior than expected with 5-FU based chemoradiation (25 mo)[60].

A phase Ⅱ trial randomized 20 patients with resectable and unresectable disease to receive docetaxel plus either continuous 5-FU or weekly cisplatin concomitant to radiotherapy. The enrolment was prematurely concluded due to poor preliminary results[61].

CONCLUSION

Pancreatic cancer is characterized by a dismal prognosis and limited therapeutic progress has been achieved in the past 30 years. Due to its intrinsic or rapidly acquired chemoresistance, the therapeutic armamentarium against pancreatic cancer is limited and there is an urgent need to individuate new active agents or regimens. Single agent gemcitabine, despite poor activity and modest impact on disease outcome, is still considered the standard treatment both in early and advanced stages of the disease[62]. Most combination regimens using gemcitabine-based doublets and including both conventional and targeted agents failed to significantly improve OS over gemcitabine alone[6,7,33,63,64] or yielded a statistically significant but clinically negligible benefit[65]. Interestingly, two phase Ⅲ trials showed that drug combinations including more than two agents may improve OS when compared with gemcitabine alone[32,66] and two clinical practice surveys suggested that the 4-drug regimens may be superior to gemcitabine/platinating-agent doublets[41,67].

In particular, the PEFG regimen and the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) yielded 1-year OS of 38%-48%[32,66]. The results obtained with these regimens should be generalized with caution due to the lack of confirmatory trials and, in the case of FOLFIRINOX, to the highly selected patients population, which is evident on the basis of the better than expected standard arm outcome and because 4 years occurred to enrol 342 patients in 48 centers (< 2 pts/center per year)[66]. Moreover, while PEFG toxicity profile was favourable[32,68], and the regimen was in fact feasible also in the adjuvant setting[69,70], grade 3-4 toxicity observed with FOLFIRINOX was remarkable particularly in the case of extra-hematological toxicity that may be barely acceptable in the context of a palliative therapy. In fact, the main reason for ending treatment was death in 85 (50%) patients in the FOLFIRINOX arm *vs* 75 in the gemcitabine arm, while fatigue was reported in 24% of the patients, vomiting in 15%, diarrhea in 13%, and neuropathy in 9%[66]. Altogether, these results are encouraging and do suggest that a nihilistic attitude towards pancreatic cancer is no

longer justified and that more aggressive treatment approach may partially overcome chemoresistance. As previously observed with other drugs, like gemcitabine, 5-FU, capecitabine, pemetrexed[4,6,71], the use of taxanes as single agent treatment, both upfront and as salvage therapy, showed moderate activity but did not obtain exciting results[8,9,15,35,36]. Not surprisingly and similarly to fluoropyrimidines and platinating agents, the inclusion of old generation taxanes in doublets with gemcitabine or cisplatin did not appear to produce better results than gemcitabine alone[19,20,23-27,29,37-39]. On the other hand, the inclusion of taxanes in combination with more than 2 drugs[22,30,31,40] seem to be more promising. Worth of note, unexpected radiological and biochemical response was observed in an exploratory subset analysis in patients with stage Ⅲ disease (60% radiological response in PDXG group *vs* 37% in PEXG group and major plus minor biochemical response of 80% *vs* 64%, respectively[22]). Furthermore, more patients in PDXG arm underwent to surgery with radical intent compared to PEXG arm (17% *vs* 6%) and neither resection margin nor nodal involvement was observed in the group treated with docetaxel. Furthermore, the new generation of taxanes, due to their unique chemical structure, are able to penetrate in tumor cell mass in high amount and apparently yields better activity than older taxanes. Accordingly, taxanes, and above all, new generation taxanes, appear to be suitable candidates for further testing to assess their role against pancreatic cancer in various clinical settings.

FUTURE PERSPECTIVES

Apart from the combination of ABI-007 with gemcitabine as first-line therapy in metastatic disease, which is currently being tested in a phase Ⅲ trial (NCT00844649), the role of multiple (i.e., more than two drugs) agents regimens should be addressed. In fact, the hypothesis of stromal depletion induced by ABI-007, if confirmed, may provide a robust rationale for combination polychemotherapy, due to better drug penetration into tumor. Furthermore, a larger effect may be expected in primary tumor where the stroma is more abundant[72-74]. A phase Ⅱ clinical trial is evaluating a combination of ABI-007 with gemcitabine, and GDC-0449, a hedgehog inhibitor, in patients with untreated metastatic pancreatic cancer in order to evaluate the PFS and the safety of this combination (NCT01088815). The hedgehog signalling pathway is involved in embryonic development, but is also activated in pancreatic cancer[75]. In preclinical model the inhibition of this pathway enhanced drug delivery to tumor cells by disrupting the desmoplastic stroma and increasing tumor vascularity[76]. The combination of gemcitabine, ABI-007 and GDC-009 could enhance the stroma collapse and increase the intratumoral concentration of chemotherapeutic drugs. Accordingly, neoadjuvant therapy in patients with stage Ⅲ disease, borderline resectable disease and resectable disease represents a potential field of investigation. Finally, ABI-007 may improve primary tumor oxygenation by inhibiting the formation of novel microvessel and by disrupting established microvessels thus increasing the therapeutic window of concomitant radiation therapy and targeted agents[77,78]. So, the next logical step is to evaluate a combination of anti-angiogenic therapy with ABI-007 in metastatic setting. Furthermore, the identification of new prognostic markers like SPARC could help both in understanding the molecular changes responsible for development and progression of pancreatic cancer and in identifying a subset of patients in which taxane-based therapy may have a more relevant impact on the outcome.

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