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HIGHLIGHT ARTICLE

New Therapeutic Strategies in the Second Line Setting of Advanced or Metastatic Pancreatic Adenocarcinoma

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

Pancreatic cancer is a lethal disease and its prognosis remains dismal. The modest results of existing available treatments in the second line setting reveal the need of new therapeutic strategies. In this year's American Society of Clinical Oncology (ASCO) Annual Meeting two remarkable trials and one retrospective analysis were presented regarding this vulnerable group of patients. According to the published results, docetaxel plus oxaliplatin (Abstract #4034), selumetinib plus erlotinib (Abstract #4014) and nab-paclitaxel (Abstract #e15057) have shown promising efficacy and manageable toxicity that should be elucidated and confirmed by new prospective, large, randomized trials.

What Did We Know Before the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

Pancreatic cancer is a lethal disease and its prognosis remains dismal. Despite the progress that has been achieved the last years, patients with metastatic disease have a five-year relative survival rate of approximately 2% [1].

Concerning the second line treatment, the standard approach for patients who have already received gemcitabine-based chemotherapy is fluopyrimidine-based chemotherapy [2, 3, 4] and more specifically capecitabine, 5FU/leucovorin/ oxaliplatin [2], and capecitabine plus oxaliplatin (CapeOx) [3]. These are acceptable options but the only established therapeutic choice should be considered the combination of 5-flouorouracil, leucovorin and oxaliplatin (FOLFOX), according to the Charité Onkologie (CONKO)-003 trial [2]. Radiation in combination to chemotherapy should also be considered in this setting, if it has not been administrated in the past in cases of locally advanced unresectable disease.

Key words Antineoplastic Agents; Drug Therapy; Pancreatic Neoplasms

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What Have We Learnt from the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

In this year's ASCO Annual Meeting, three remarkable abstracts about metastatic pancreatic cancer were presented, concerning second line therapy. The purpose of this paper is to dispose the data and the main findings of these studies as shown collectively in Table 1. The incorporation of the new data on a patient approach algorithm is illustrated in Figure 1 and the recommended treatment according to clinical and epidemiological features is disposed to Table 2.

DOCOX: A New Potential Option in Second Line Therapy (Abstract #4034 [5])

Etterich *et al.* (Abstract #4034) conducted a prospective, single arm, non-randomized, multicenter, phase II trial after first line treatment with gemcitabine in patients with advanced or metastatic pancreatic adenocarcinoma. The 44 enrolled patients were scheduled to receive docetaxel plus oxaliplatin (DOCOX). Among them, 4 did not receive treatment. The primary endpoint of response rate was 7 patients (16%) with partial response and disease control rate after 2 cycles was achieved by 21 patients (48%). The secondary endpoint of progression free survival was 7 weeks and of median overall survival after starting second line chemotherapy was 9 months.

Table 1. Clinical studies in the second line setting presented in the 2013 ASCO Annual Meeting.

Abstract	Trial design	No. of patients	Treatment arms	Endpoints	Results
#4034 [5] Etterich *et al.*	Phase II	44	Docetaxel plus oxaliplatin	Primary: response rate Secondary: progression free survival, median overall survival	Partial response: 16% PR Disease control rate: 48% Median progression free survival: 7 weeks Median overall survival: 9 months
#4014 [6] Ko *et al.*	Phase II	46	Selumetinib plus erlotinib	Primary: overall survival Secondary: progression free survival, CA19-9 biomarker response rate, response rate, safety and toxicity profile	Median overall survival: 7.5 months Median progression free survival: 2.6 months CA19-9 decline: 29% Disease control rate: 51% Manageable toxicity profile
#e15057 [8] Vaccaro *et al.*	Retrospective analysis	29	Monotherapy with nab-paclitaxel	Efficacy and safety	Stable disease: 4 patients Partial response: 2 patients Median progression free survival: 8 weeks Median overall survival: 13weeks Manageable toxicity

Selumetinib Plus Erlotinib and Their Role in Second Line Setting (Abstract #4014 [6])

MEK and EGFR have been suggested as pivotal pathways for malignant progression in pancreatic carcinogenesis [7]. Selumetinib, an inhibitor of MEK, in combination with erlotinib, an EGFR inhibitor, seem to have a role in the management of pancreatic cancer according to a non-randomized, multicenter, phase II study by Ko *et al*. [6]. A total of 46 patients were recruited and 41 were finally evaluable to receive both selumetinib and erlotinib as second line treatment. The median overall survival was 7.5 months, progression free survical was 2.6 months, disease control rate was 51% and 29% of the patients have CA 19-9 decline over 50%. Finally, the toxicity profile of the combination was acceptable and manageable.

Nab-Paclitaxel in the Second Line Setting of Pancreatic Cancer (Abstract #e15057 [8])

One remarkable abstract was selected for publication but not presentation at the 2013 ASCO Annual Meeting concerning the second line setting of pancreatic cancer and the efficacy of nab-paclitaxel (nab-P). The abstract was referred to a multicenter, retrospective analysis and the use of nab-paclitaxel in heavily pretreated patients in the second or further line setting. Two of the 29 enrolled patients that received the regimen had partial response, 4 stable disease and 5 had not been yet evaluated by the time of publication of the abstract. Median progression free survival was 8 weeks and median overall survival was 13 weeks.

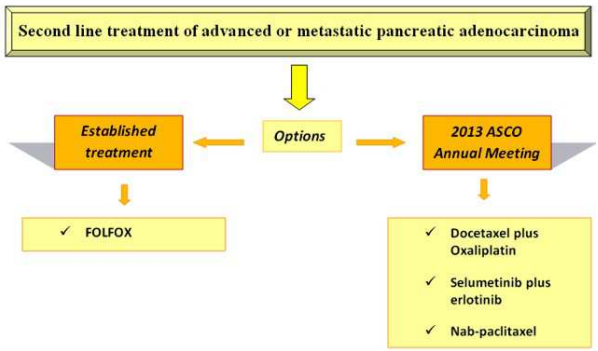

Figure 1. Therapeutic strategies in second line setting of advanced or metastatic pancreatic adenocarcinoma.

Discussion

Despite the enormous advances in clinical research in oncology the prognosis of pancreatic cancer patients remains poor and the therapeutic options in this type of cancer are still limited. That reveals the need of approaching these patients with new strategies and agents.

It is clear that current chemotherapy has reached a plateau of activity and newer more active approaches are needed in order to improve prognosis of this devastating disease.

In this year ASCO Annual Meeting, the efficacy of docetaxel plus oxaliplatin was examined with promising results in terms of disease control rate and progression free survical that need further investigation in large, prospective, randomized trials. MEK and EGFR inhibitors, selumetinib and

Table 2. Recommended treatment according to clinical and epidemiological features based on 2013 ASCO Annual Meeting studies.

	Prior chemotherapy		Performance status			Elderly	Pre-existing peripheral neuropathy
	Gemcitabine based	FOLFIRINOX	0-1	2	>2		
Docetaxel plus oxaliplatin	+	-	+	+	*	*	-
Selumetinib plus erlotinib	+	+	+	-	*	+	+
Nab-paclitaxel	+	+	+	+	*	+	-

*Need further investigation

erlotinib respectively, have also been examined regarding their efficacy and toxicity in the second line setting. Although, it was a small trial, the results showed that this combination could be an alternative option to our therapeutic quiver, since there was a group of patients that benefited. The molecular characteristics of this group of patients remain to be elucidated. Finally, the third abstract was a multicenter retrospective analysis of efficacy and toxicity profile of nab-paclitaxel in heavily pretreated pancreatic cancer patients. Nab-paclitaxel was reported with manageable toxicity and efficacy that has to be proved in future studies.

Improving further the understanding of molecular biology of pancreatic cancer and the mechanisms of tumorigenesis, may allow for the identification of other potential molecular targets and development of novel therapeutic strategies. One major challenge is to find out the way to most effectively combine conventional therapies to targeted agents. We need to find out the best way to combine or sequence cytotoxic therapies, radiotherapy and targeted therapies, in order to achieve the maximum clinical benefit. In order to develop more efficient and less toxic treatments and successfully tailor targeted therapies to individual tumor and patient characteristics we need to further improve our understanding regarding molecular alterations in pancreatic cancer.

Conflicts of interest The authors have no conflicts to disclose

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan;63(1):11-30. doi: 10.3322/caac.21166. Epub 2013 Jan 17.

2. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, Riess H, Oettle H. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer. 2011 Jul;47(11):1676-81. doi: 10.1016/j.ejca.2011.04.011. Epub 2011 May 10.

3. Xiong HQ, Varadhachary GR, Blais JC, Hess KR, Abbruzzese JL, Wolff RA. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. Cancer. 2008 Oct 15;113(8):2046-52. doi: 10.1002/cncr.23810.

4. Maisey N, Chau I, Cunningham D, *et al*. 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

5. Ettrich T, Goetz von Wichert, Gress T, Michl P, Geissler M, Hebart H, *et al*. DOCOX: A phase II trial with docetaxel and oxaliplatin as a second-line systemic therapy for patients with advanced and/or metastatic adenocarcinoma of the pancreas. J Clin Oncol 31, 2013 (suppl; abstr 4034)

6. Ko A, Tempero M, Bekaii-Saab T, Kuhn P, Courtin R, Ziyeh S, *et al*. Dual MEK/EGFR inhibition for advanced, chemotherapy-refractory pancreatic cancer: A multicenter phase II trial of selumetinib (AZD6244; ARRY-142886) plus erlotinib. J Clin Oncol 31, 2013 (suppl; abstr 4014)

7. Diep CH, Munoz RM, Choudhary A, Von Hoff DD, Han H. Synergistic effect between erlotinib and MEK inhibitors in KRAS wild-type human pancreatic cancer cells. Clin Cancer Res. 2011 May 1;17(9):2744-56.

8. Vaccaro V, Bria E, Reni M, Sperduti I, Gelibter A, Nuzzo C, *et al*. Activity of nab-paclitaxel (nab-P) monotherapy in heavily pretreated pancreatic cancer (aPDAC) patients (pts): A multicenter retrospective analysis. J Clin Oncol 31, 2013 (suppl; abstr e15057)