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HIGHLIGHT ARTICLE

Advancements in the Management of Pancreatic Cancer

Highlights from the "2009 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 15-17, 2009

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Summary

Management of pancreatic cancer remains the most challenging work in oncology. Though pancreatic cancer represents only 2-3% of all cancers, it is the most fatal one accounting for the 6% of all cancer death. It remains the 4th cause of death by cancer since 1970s in the U.S.. Gemcitabine remains the only standard of care for this disease. More and more combination therapies containing gemcitabine have been tested or undergoing investigation. The interest in treating pancreatic cancer is apparently global. Over 75 abstracts were presented in the 2009 ASCO Gastrointestinal Cancers Symposium at San Francisco in the field of pancreatic cancer. In this highlights article, authors summarize the critical studies in the management of pancreatic cancer. A large retrospective study evaluated the role of post-operative adjuvant radiation (Abstract #181) and correlated the receipt of radiation with survival benefit. Borderline resectable pancreatic cancer remains an area that requires multi-disciplinary approach. Neo-adjuvant therapy very likely plays a role to downstage to a resectable state in these subgroup patients (Abstracts #197 and #248). In advanced or metastatic setting, studies aiming at the gemcitabine-based triplet or doublet combinations are still the mainstream. FFCD 0301 trial (Abstract #180), the only large phase III trial presented in the first-line setting, failed to demonstrate any survival advantage of either 5-FU and leucovorin plus cisplatin followed by gemcitabine or *vice versa*. Biologic agents containing regimens were also presented. Of note, gemcitabine and oxaliplatin plus bevacizumab achieved a high response rate of 39% (Abstract #182) while gemcitabine with dual monoclonal antibody regimen was disappointing (Abstract #183). The clear benefit of all other combinations over gemcitabine alone remains questionable given most studies are small. Newer agents, especially S-1 (Abstracts #213 and #251), are very promising, and further studies are warranted. In a nut shell, pancreatic cancer continues to pose an enormous challenge to clinicians and cancer scientists. With a more affluent world the global incidence of pancreatic cancer is rising. This meeting again emphasizes us that it is urgent to make big inroads into what still remains the most lethal of the common.

Introduction

Management of pancreatic cancer remains the most challenging work in oncology. American Cancer Society has estimated cancer related death in 2008-pancreatic cancer 34,290 in men and women [1]. Though pancrea tic cancer represents only 2-3% of all cancers, it is the most fatal one accounting for the 6% of all cancer death. It remains the 4th cause of death by cancer after lung, prostate (breast in women) and colorectal cancer since 1970s in the U.S. in spite of tremendous effort from clinical and experimental points [1]. Its aggressive features include insidious presentation, unresectablity due to early involvement of major vessels, debilitating symptoms at late stage, and *de novo* chemo-resistance.

Keywords Adenocarcinoma; Carcinoma, Pancreatic Ductal; Fluorouracil; gemcitabine; oxaliplatin; Pancreatic Neoplasms; Radiotherapy; Salvage Therapy; Treatment Failure

Abbreviations RTOG: Radiation Therapy Oncology Group

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The discouraging features of this disease did not retard the effort of investigating the disease mechanism and development of newer agents. Extensive research in the past two decades have revealed that pancreatic cancer is a genetic disease involving multiple levels of abnormalities: oncogenes, tumor suppressor genes, and DNA mismatch genes [2, 3, 4, 5]. The interest in conquering pancreatic cancer is apparently global, from cellular biology to molecular biology, from surgery to medicine, from orthodox approaches to alternative ways. We gladly saw over 75 abstracts presented in the 2009 ASCO Gastrointestinal Cancers Symposium at San Francisco in the field of pancreatic cancer. In this highlights article, we will focus on the management of pancreatic cancer in all stages.

I. Adjuvant Therapy for Resectable Disease After Surgical Resection

Options of adjuvant therapy for pancreatic cancer remain to be controversial, dividing between chemo-radiotherapy and chemotherapy alone. After the Gastrointestinal Tumor Study Group (GITSG) study

Table 1. Role of adjuvant radiation (n=4,410).

Independent predictors of overall survival	Significance
Early stage	P<0.01
Small tumor size T1-2	P<0.01
Well-differentiated tumor	P<0.01
N0 nodal status	P<0.01
Receipt of radiotherapy	P<0.01
Receipt of radiotherapy after adjustment	P<0.0001 (HR: 0.793; 95% CI: 0.729-0.864

showing a survival advantage of postoperative chemo-radiotherapy using bolus 5-FU [6], more trials were designed to confirm this benefit. The European Organization of Research and Treatment of Cancer (EORTC) study was not able to show a statistically significant benefit, but the trend towards chemoradiotherapy was emerging [7]. However, the role of chemoradiotherapy in adjuvant setting was questioned in the European Study Group for Pancreatic Cancer (ESPAC-1) trial which demonstrated chemo-radiotherapy could be detrimental, but surprisingly chemotherapy only arm achieved significant benefit over observation in median survival (20.1 months *vs*. 15.5 months; P=0.009) [8]. The Radiation Therapy Oncology Group (RTOG-9704) evaluated gemcitabine combined with radiotherapy [9]. However, a survival benefit of gemcitabine over 5-FU (18.8 months *vs*. 16.7 months; P=0.047) was only seen in adenocarcinoma of the pancreatic head only. The Charité Onkologie (CONKO-001) was the first trial showing gemcitabine alone suitable in the adjuvant setting to prolong disease free survival without the sacrifice of intolerable toxicities [10].

In the adjuvant setting, basically no breakthrough abstract was presented on this year's symposium. As mentioned earlier, the role of post-operative adjuvant radiation remains controversial in the U.S. while gemcitabine as a monotherapy has become the standard across the Atlantic. A retrospective large national database univariate analysis using Cox proportional hazards and propensity-adjusted scoring system was conducted by McDade *et al*. (Abstract #181) [11]. More than forty-four hundred patients with pancreatic adenocarcinoma resection were analyzed, 42.5% received adjuvant radiation. Receipt of radiation therapy was revealed as one of the independent predictors of survival in addition to early age, smaller tumors, well-differentiated histology and negative nodal status. This is one of the largest studies on the role of adjuvant radiation therapy; the signif icance of survival benefit should shed light on this field (Table 1).

On another poster, Piperdi *et al*. presented the data of a modified Radiation Therapy Oncology Group (RTOG-9704) regimen (Abstract #229) [12]. RTOG-9704 proved survival benefit of gemcitabine before and after concurrent chemoradiation with 5-FU. In this retrospective study, 5-FU was substituted with capacitabine. The assumption of this design is capacitabine is exchangeable with 5-FU based on previous trials [13]. Total 14 patients were reviewed. Capacitabine was given at a dose of 825 mg/m^2 *bid* Monday to Friday concurrent with radiation. With a median follow-up of 18 months, more than half of the patients had relapse d disease either locally (n=1) or systemically (n=7). The median disease free survival was 18.2 months. This result is promising in that capacitabine offers convenience and less toxicity to the patients. Our group has performed the first study employing capecitabine [14] and found it to be an acceptable, less toxic and equally effective radiosensitizer compared to historical control.

II. Borderline Resectable Pancreatic Cancer

Management of borderline resectable pancreatic cancer remains a challenging field without a defined approach and requires multi-disciplinary effort. This subgroup of pancreatic cancer patients are determined to be potentially resectable if they have good response with pre-operative chemotherapy or combined modality with radiation. Five abstracts were presented in an effort of defining a "standard" neoadjuvant regimen (Table 2).

Study presented by Chaudhary *et al*. (Abstract #197) [15] is the only prospective one in which 32 patients with locally advanced disease were enrolled. Patients received gemcitabine and oxaliplatin plus cetuximab regimen consisting of gemcitabine at 1,000 mg/m^2 on day 1, oxaliplatin at 100 mg/m^2 on day 2 every 2 weeks for 6 cycles with weekly cetuximab at 400 mg/m^2 loading dose then 250 mg/m^2 maintenance dose. Restaging was performed after completion of neoadjuvant therapy by CT scan and EUS. Patients who were considered surgically resectable underwent

Table 2. Neo-adjuvant regimens for borderline resectable pancreatic cancer.

Abstract	Author	Study	Title
#191 [41]	Stokes *et al*.	Retrospective	Outcome following neoadjuvant therapy for borderline resectable pancreatic cancer
#197 [15]	Chaudhary *et al*.	Phase II trial	Preliminary results of a phase II neoadjuvant trial with gemcitabine and oxaliplatin plus cetuximab followed by surgery or concurrent intensity modulated radiation therapy with capecitabine for patients with borderline resectable and unresectable pancreatic cancer.
#224 [42]	Masui *et al*.	Retrospective	Gemcitabine and S-1 combined neoadjuvant chemotherapy for patients with locally advanced pancreatic cancer
#228 [43]	Cardenes *et al*.	Follow-up of a pilot study	Long-term follow-up of a pilot study using neoadjuvant gemcitabine, erlotinib and hypofractionated radiation therapy for potentially resectable pancreatic cancer.
#248 [16]	Rifkind *et al*.	Retrospective	Neo-adjuvant chemoradiotherapy for pancreatic cancer: The Dartmouth experience.

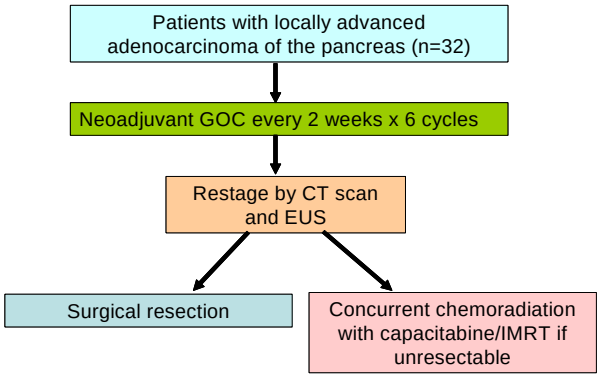

Figure 1. Treatment schema of phase II study by Chaudhary *et al.* [15]. GOC: gemcitabine plus oxaliplatin plus cetuximab; IMRT: intensity modulated radiation therapy

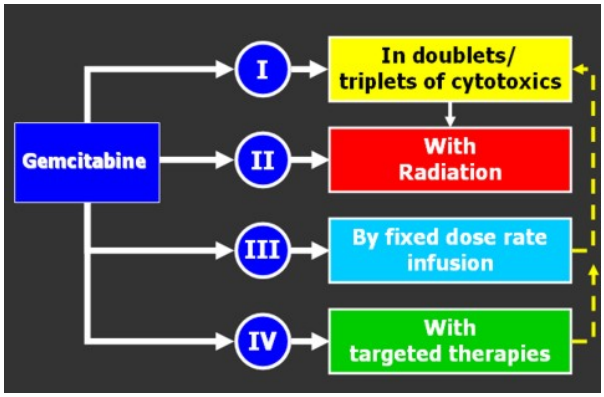

Figure 2. Study designs to improve outcome with gemcitabine (adapted from Saif MW [25]).

surgery, while unresectable patients received concurrent capacitabine and intensity modulated radiation therapy (Figure 1).
The results are summarized in Table 3.
Chaudhary *et al*. offered an interesting approach based on the studies performed in the metastatic setting. However, no conclusions can be drawn from small phase II study. Moreover, role of K-*ras* testing before cetuximab in pancreatic cancer also needs to be elucidated.
Dartmouth investigators (Abstract #248) [16] presented their retrospective result on 113 patients who received one of three gemcitabine-based neoadjuvant chemoradiotherapy regimens: gemcitabine and cetuximab plus intensity modulated radiation therapy, or gemcitabine plus external beam radiation therapy, or gemcitabine and docetaxel plus external beam radiation therapy. Among 113 patients, only 18% were initially determined to be resectable, 34% were defined as borderline resectable, and 49% were unresectable. More than half patients (56%) underwent resection and achieved medial survival of 21 months. These results encourage a larger prospective study to explore the role of neoadjuvant in each specific subgroup.
Whether neoadjuvant has a role in resectable pancreatic cancer remains an unanswered question. However, as illustrated in Table 2, most neoadjuvant studies are retrospective and small studies. There remains no standard approach for this category nowadays. One can at least conclude that approaches involving gemcitabine and targeted therapy definitely need further attention to improve the outcome in this disease and surgery remains the only potential cure.

III. Locally Advanced Unresectable, Recurrent or Metastatic Pancreatic Cancer

Gemcitabine remain to be the only drug of choice for the treatment of advanced pancreatic cancer [17]. Numerous combinations with gemcitabine were created over the last decade, multiple cytotoxic (5-FU, oxaliplatin, irinotecan, capecitabine, cisplatin, etc.) [18, 19, 20, 21, 22], and targeted agents (bevacizumab, cetuximab, erlotinib) [23, 24] have been combined with gemcitabine in clinical trials (Figure 2) [25].
Gemcitabine and platinum combination showed promising result in phase II level which led to phase III Groupe d'Etude et de Recherche en Cancreologie Onco-Radiotherapic (GERCOR) trial [21]. The gemcitabine and oxaliplatin arm demonstrated higher response rate (26.8%), longer progression-free survival (5.8 months), and clinical benefit (38.2%) compared with the gemcitabine alone arm (17.3%, 3.7 months and 26.9%, respectively); however, the overall survival benefit was not reached statistically.
In first-line setting, most effort is still focusing on gemcitabine-based combinations as shown in Table 4.

1. Cytotoxic Agents Containing Gemcitabine Based Triplets

Gemcitabine plus leucovorin/5-FU plus cisplatin

Of note, FFCD 0301 is the only phase III trial in the first-line metastatic setting (Abstract #180) [26]. The study design of FFCD 0301 is depicted in Figure 3.
Total 202 patients with advanced pancreatic cancer were enrolled in this large randomized trial. Half of the patients received leucovorin, 5-FU, cisplatin followed

Table 3. Result of phase II neo-adjuvant therapy with gemcitabine and oxaliplatin plus cetuximab.

	No. of patients
Patients completed neo-adjuvant therapy	29
Borderline resectable disease	10
Unresectable disease	19
Patients undergo surgical resection	6 (5 had R0 resection, 1 is pending)
Patients regained respectability after chemoradiation	2
Resectability	**8/29 (28%)**

Table 4. Gemcitabine-based phase II-III studies presented at the 2009 ASCO GI Symposium.

Abstract	Author	Study	Combination
#180 [26]	Ychou *et al*.	Phase III	Gemcitabine + leucovorin + 5-FU (FFCD 0301)
#196 [27]	Ghosn *et al*. ù	Phase II	Gemcitabine + FOLFOX
#182 [28]	Fogelman*et al*.	Phase II	Gemcitabine + oxaliplatin + avastin
#183 [29]	Ko *et al*.	Phase II	Fixed dose rate gemcitabine + cetuximab + avastin
#LBA120 [35]	Lohr *et al*.	Phase II	Gemcitabine + taxel
#277 [44]	Sakamoto *et al*.	Phase II	Gemcitabine + 5-FU
#214 [45]	Li *et al*.	Retrospective	Single day gemcitabine + oxaliplatin
#189 [46]	Richards *et al*.	Phase II	Gemcitabine + enzatraurin
#192 [36]	Kindler *et al*.	Phase Ib	Gemcitabine + AMG 655
#213 [32]	Zang *et al*.	Phase II	Gemcitabine + S-1
#251 [33]	Nakamori *et al*.	Phase II	Gemcitabine + S-1
#195 [38]	Strumberg *et al*.	Phase II	S-1

FOLFOX: folinic acid plus 5-FU plus oxaliplatin

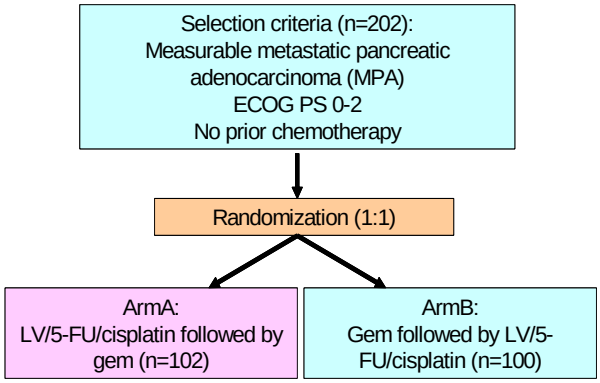

Figure 3. Study design of the FFCD 0301 study.
Dosage. leucovorin (LV): 200 mg/m^2; 5-FU: bolus 400 mg/m^2 and 46-hour infusion at 2,400 mg/m^2 every 2 weeks; cisplatin: 50 mg/m^2 on day 1 or 2; gemcitabine (gem): 1,000 mg/m^2 7 out of 8 weeks and then 3 out of 4 weeks.
ECOG: Eastern Cooperative Oncology Group; PS: performance status

by gemcitabine, the other half received the opposite sequence. Survival data are listed in Table 5.
After a median follow-up of 44 months, majority of the patients (n=192) died. No statistically significant difference in terms of survival between the two arms. This trial failed to demonstrate any superiority of one arm over the other, however given no gemcitabine alone arm in this trial, it is hard to draw the conclusion if this combination is better or worse compared with gemcitabine alone.
All other studies in the first line setting either triplets or doublets are at phase II level. Two triplets combined gemcitabine with cytotoxic agents, while the other two combined gemcitabine with one or two biologic agents. These studies deserve a discussion here.

Gemcitabine plus FOLFOX

This phase II trial investigated the efficacy of sequential use of FOLFOX-6 (folinic acid plus 5-FU plus oxaliplatin) regimen followed by gemcitabine in first line setting for advanced pancreatic cancer (Abstract #196) [27]. The schedule of the regimen is illustrated in Figure 4.
Thirty-two patients were included in this trial, only 28 were evaluated for response. The results are listed as following (Table 6).
This triplet achieved some clinical benefit; however, it is hard to draw any definite conclusion from such a small phase II trial without an arm of gemcitabine monotherapy.

2. Biologic Agent Containing Gemcitabine Based Triplets

Two phase II trials were presented on this meeting to evaluate the efficacy of gemcitabine plus biologic agents (Abstracts #182 and #183) [28, 29].

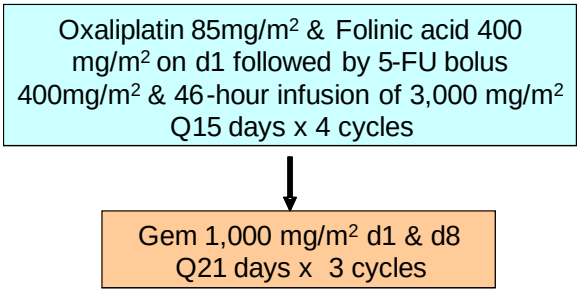

Figure 4. Schedule of regimen of FOLFOX-6 plus gemcitabine.
FOLFOX: folinic acid plus 5-FU plus oxaliplatin; Gem: gemcitabine

Table 5. Results of the phase III FFCD 0301 study (n=202).

Survival	Arm A Leucovorin + 5-FU + cisplatin followed by gemcitabine (n=102)	Arm B Gemcitabine followed by leucovorin + 5-FU + cisplatin (n=100)	P value (B *vs.* A)
Median overall survival (months)	6.6 (95% CI: 5.3-8.4)	8.0 (95% CI: 5.9-9.8)	0.85
Median progression free survival (months)	3.4	3.5	0.67

Table 6. Efficacy and survival data of phase II trial of FOLFOX-6 followed by gemcitabine (n=28).

Complete response	0
Partial response	6 (18.7%)
Median progression free survival (months)	5.2
Median overall survival (months)	11.1

FOLFOX: folinic acid plus 5-FU plus oxaliplatin

Gemcitabine and oxaliplatin combination has achieved the highest progression free survival in advanced pancreatic cancer among all combinations. Fogelman *et al*. reported final results from two institutes including M.D. Anderson Cancer Center of a 3-drug combination consisting of gemcitabine, oxaliplatin and a VEGFR monoclonal antibody: bevacizumab (Abstract #182) [28]. Fifty patients met with the selection criteria and were enrolled onto this trial (Figure 5, left). Ko *et al*. designed another phase II trial to evaluate the efficacy of dual EGFR/VEGFR monoclonal antibodies cetuximab and bevacizumab with or without gemcitabine (Abstract #183) [29]. Total 57 patients were enrolled into this randomized trial; half patients received gemcitabine plus dual antibodies, while the other half received just dual antibodies (Figure 5, right).

The toxicity and efficacy results of these two trials are listed in Tables 7 and 8.

Gemcitabine and oxaliplatin plus bevacizumab regimen demonstrated a higher response rate, longer median survival compared with previously reported gemcitabine and oxaliplatin study [21]. A head-to-head comparison is absolutely warranted in a larger randomized trial. However, the toxicity remains an issue like other 3-drug regimens. Fogelman *et al*. in this abstract also incorporated CA 19-9 value into survival. The lower CA 19-9 value correlates with the longer median survival length, which suggests the predictive role of CA 19-9 in addition to a response surrogate.

The unique feature of Abstract #183 is in that gemcitabine was combined with dual EGFR/VEGFR monoclonal antibodies cetuximab and bevacizumab. This dual monoclonal antibody approach had previously been tested in BOND-2 trial in metastatic colorectal cancer [30]. However, we have learned a lesson from PACCE trial that we should be extremely careful when putting two biologic target therapies together [31]. More consistent with BOND-2 result, this dual EGFR/VEGFR antibody regimen did not cause overwhelming toxicity in the combination with gemcitabine. However, the response rate was disappointing. The information derived from this presentation tells us that gemcitabine remains the key element in the metastatic setting in order to achieve any survival benefit.

3. Gemcitabine Based Doublets

Seven doublets in the metastatic setting use gemcitabine as a backbone to combine with either conventional cytotoxic agents or newer agents such as S-1, AMG 655, enzatraurin, and a novel formulation of paclitaxel (Table 9).

None of the three studies on cytotoxic agent combination reached overall response rate of 20%; however, the newer agents are much more promising (Table 10). Interestingly, two relatively small trials investigated a same combination (gemcitabine plus S-1) but the dosage and schedule are slightly different (Abstracts #213 and #251) [32, 33]. S-1 is an oral fluoropyrimidine consisting of 1 M tegafur, 0.4 M gimeracil and 1 M oteracil potassium. S-1 has been extensively studied and currently used as a standard adjuvant therapy for gastric cancer in Japan [34]. The efficacy of S-1 in pancreatic cancer is under investigation. Both trials achieved overall response rate above 30% which is historically higher than any other trials in the literature. The results are consistent with each other and seem to be very promising. However, both trials are small and underpowered with only approximately 30 patients. A larger trial to compare with gemcitabine monotherapy should be considered in the near future.

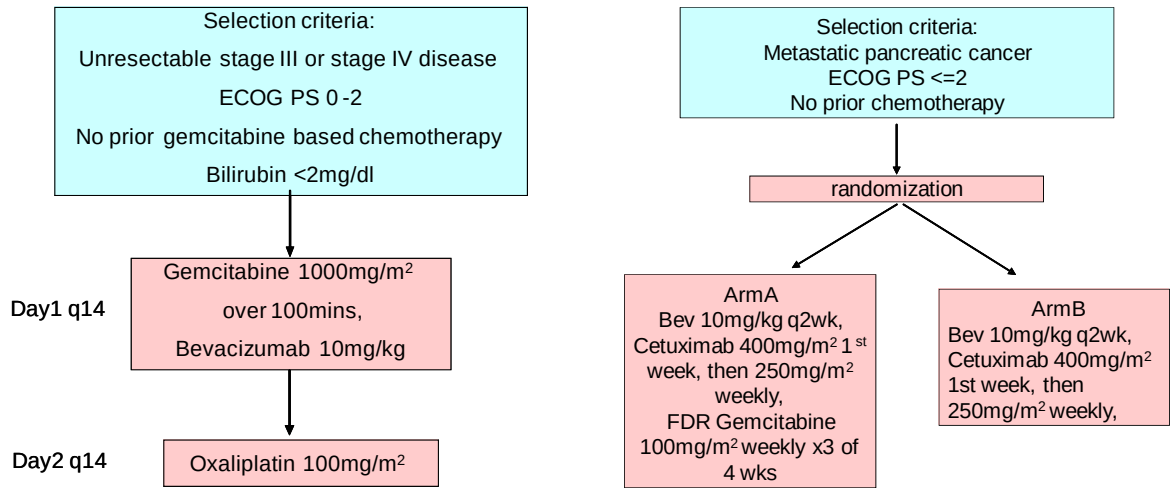

Figure 5. Trial design of Abstract #182 (left) [28] *vs*. Abstract #183 (right) [29].
Bev: bevacizumab; ECOG: Eastern Cooperative Oncology Group; PS: performance status

Table 7. Toxicity of gemcitabine and oxaliplatin plus bevacizumab (n=50) *vs*. gemcitabine plus cetuximab plus bevacizumab (n=57).

Toxicity	Frequency		
	Gem/Ox/Bev (n=50)	Gem/Cet/Bev (arm A, n=28)	Cet/Bev (arm B, n=29)
Severe toxicity	86.0%	39.3%	20.7%
Cutaneous toxicity	Not presented	78.6%	58.6%
Infusion reaction	Not presented	7.1%	0
Hematological	16% (neutropenia)	3.6%	0
Pulmonary embolism	Not presented	0	3.4%
Shortness of breath	38.0%	Not presented	Not presented

Bev: bevacizumab; Cet: cetuximab; Gem: gemcitabine; Ox: oxaliplatin

Table 8. Efficacy of gemcitabine and oxaliplatin plus bevacizumab (n=50) *vs*. gemcitabine plus cetuximab plus bevacizumab (n=57).

Response	Gem/Ox/Bev (n=50)	Gem/Cet/Bev (arm A, n=28)	Cet/Bev (arm B, n=29)
Overall response rate (%)	39.0%	10.7%	0%
Median overall survival (months)	12.1	Not presented	Not presented
Median progression free survival (months)	Not presented	3.5	1.8
12-month survival rate	40.0%	Not presented	Not presented
18-month survival rate	16.0%	Not presented	Not presented

Bev: bevacizumab; Cet: cetuximab; Gem: gemcitabine; Ox: oxaliplatin

EndoTAG-1 is a novel cationic liposomal formulation of paclitaxel. The combination of gemcitabine plus liposomal paclitaxel was tested in 200 patients with metastatic pancreatic cancer. This regimen achieved disease control rate of 53-69% depending on the dosage of paclitaxel, however response rate was not reported. It is unclear if this combination is superior to gemcitabine alone (Abstract LBA120) [35]. We are expecting the final result of this large trial.

Another newer agent, AMG 655, also showed some clinical benefit (Abstract #192) [36]. AMG 655 is a fully humanized monoclonal antibody that targets human death receptor 5 (DR5), activates caspases, and induces apoptosis in sensitive tumor cells. The data suggested the synergistic effect of gemcitabine and AMG 655, however, the true benefit of AMG 655 needs to be studied more.

4. Single Agent (Non-Gemcitabine)

Like mentioned above, S-1 is a new oral formulation of 5-FU combining tegafur (FT) with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate. S-1 was developed by the scientific theory of both potentiating antitumor activity of 5-FU and reducing gastrointestinal toxicity induced by 5-FU (Figure 6) [37].

The CESAR study group presented very interesting result of S-1 in the first line treatment of metastatic pancreatic cancer. S-1 was administered to 22 patients at 30 mg/m^2 twice daily for 14 days followed by 7 day rest. Overall median survival was 9.1 months. Two patients achieved confirmed partial response.

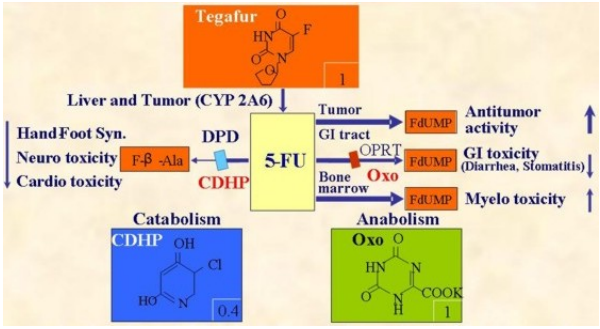

Figure 6. Composition and mode of action of S-1 (adapted from Saif MW [37]).

Table 9. Gemcitabine-based doublets presented at the 2009 ASCO GI Symposium.

Abstract	Author	Study	Combination/dose/schedule	No. of patients
#LBA120 [35]	Lohr *et al*.	Phase II	Gemcitabine: 1,000 mg/m^2 weekly Liposomal paclitaxel: 11, 22 or 44 mg/m^2 twice weekly	200
#277 [44]	Sakamoto *et al*.	Phase II	Gemcitabine: 800 mg/m^2 weekly x3, every 4 weeks 5-FU: 125 mg/m^2/day on days 1-5 weekly as continuous arterial infusion	86
#214 [45]	Li *et al*.	Retrospective	Gemcitabine: 1,000 mg/m^2 on day 1 every 2 weeks Oxaliplatin: 85-100 mg/m^2 on day 1 every 2 weeks	31
#189 [46]	Richard *et al*.	Phase II	Gemcitabine: 1,000 mg/m^2 over 30 min on days 1, 8, 15 every 4 weeks Enzatraurin: 500 mg *po* daily (1,200 mg loading dose on day 1 of cycle 1)	130
#192 [36]	Kindler *et al*.	Phase Ib	Gemcitabine: 1,000 mg/m^2 on days 1, 8, 15 every 4 weeks AMG 655: 3mg/kg or 10 mg/kg on day 1 and 15 every 4 weeks	13
#213 [32]	Zang *et al*.	Phase II	Gemcitabine: 1,000 mg/m^2 on days 1 and 8 every 3 weeks S-1: 60-80 mg/m^2 *po* on days 1-14 every 3 weeks	29
#251 [33]	Nakamori *et al*.	Phase II	Gemcitabine: 1,000 mg/m^2 over 30 min on days 6 and 13 every 3 weeks S-1: 80 mg/m^2/day on days 1-5 and days 8-13 every 3 weeks	34

Table 10. Results of gemcitabine-based doublets presented at the 2009 ASCO GI Symposium.

Abstract	Combination	Overall response rate	Toxicity
#LBA120 [35]	Liposomal paclitaxel	Disease control rate: 53-69% [a]	Mild chills, pyrexia
#277 [44]	5-FU	14%	Marrow suppression
#214 [45]	Oxaliplatin	17.4%	Hypersensitivity reaction marrow suppression
#189 [46]	Enzatraurin	8% *vs*. 5% (gemcitabine alone)	Marrow suppression
#192 [36]	AMG 655	23%	Marrow suppression
#213 [32]	S-1	30.4%	Marrow suppression
#251 [33]	S-1	35%	Marrow suppression

[a] Overall response rate was not presented

Unfortunately, escalation to the next stage was held due to unable to meet the predefined aim; however, this trial deserves another look given the comparable survival advantage and very minimal toxicity of S-1 (Abstract #195) [38].

Single agent S-1 was also investigated in the second line setting. Total 45 patients were enrolled into a phase II study to evaluate the role of S-1 in gemcitabine-refractory metastatic pancreatic cancer. No objective response was seen in, however a trend of survival benefit with median survival of 5 months was found in the patients with very good performance status (Karnofsky performance status 90-100%, n=27) which suggested only selective patients would derive further benefit from more chemotherapy after gemcitabine (Abstract #243) [39].

Discussion

Options for pancreatic cancer in either adjuvant setting or advanced/metastatic setting are still limited despite so much effort we put in this disease. Gemcitabine remains the standard of care for this aggressive disease since its approval in 1997. Over the last 12 years, we have already investigated numerous combinations with gemcitabine; the benefit over gemcitabine monotherapy is minimal and somewhat controversial. Gemcitabine and erlotinib combination was the only one approved by FDA for metastatic disease; however, its true clinical value is always questionable [40]. More triplets and doublets were presented on this meeting; one impression was gemcitabine does seem to be the key elements in the treatment of pancreatic cancer.

The major question that must be answered before this field can move forward is that: “Should we stop further discovery and just rely on gemcitabine?”. Or: “Should we explore non-gemcitabine agents/regimens and then evaluate them with biologics?”

Newer agents including biologic target therapy and newer forms of conventional cytotoxic agents appear very encouraging. Among the ones presented at the symposium, S-1 outshines as an agent that draws some hope. Meanwhile, we should not stop searching for novel agents and combinations and quickly apply them in clinical trials.

Conflict of interest: The authors have no potential conflicts of interest

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