Commentary

S-1: changing the facets of adjuvant chemotherapy in pancreatic cancer?

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From an oncologists view the treatment progress in curatively resected patients for pancreatic cancer (PDAC) has been frustrating so far. Although, the implementations of new standard of care chemotherapies in metastatic PDAC such as FOLFIRINOX (1) or Gemcitabine/Nab-Paclictaxel were a great advancement (2), adjuvant treatment efforts remained static. The use of adjuvant therapy is recommended by several medical societies (3-5) and is based on numerous trials: the CONKO-001 (6), ESPAC-1 (7) and ESPAC-3 (8) trials defined to start gemcitabine or infusional 5-FU monotherapy as the standard of care within 12 weeks post-operative, only differing in their respective toxicity profiles. These regimens have been a breakthrough at the time. However, novel and more tailored treatment algorithms are warranted to eventually reach a high response rate in only a subset of PDAC patients as "*one pill fits all*" seems to be an updated goal in PDAC.

A new era of adjuvant treatment?

In that sense, Uesaka and colleagues published a remarkable dataset from an adjuvant phase III trial, the JASPAC-01 trial (9). The study compared S-1, an orally taken fluoropyrimidine, to the standard of care, gemcitabine. Previously, S-1 already confirmed non-inferiority to gemcitabine in metastatic pancreatic cancer in a phase III trial in a Japanese/Taiwanese cohort (10).

The published data is based on a national (Japan), open-label, multi-centre, randomized controlled phase III trial. The primary end-point was overall survival (OS) and the statistical power was set on non-inferiority of S-1.

Patient characteristics were well adjusted between both groups. The per protocol population included 377 patients, randomized 1:1 (190 gemcitabine group, 187 S-1 group). Patients with R1-resection were also included and accounted for 14% and 12% in the gemcitabine and S-1 group, respectively. These numbers are slightly lower as in the CONKO-001 and the ESPAC-3 trial (CONKO-001: 19% R1-resections gemcitabine group; ESPAC-3: 35% R1-resections both treatment groups). Of note, the definition for R1 remains slightly different across these studies. Gemcitabine was used in the recommended standard dose (1,000 mg/m^2 i.v. on d 1, 8, 15 every 4 weeks for six cycles). S-1 was administered according to the body surface area (BSA) (40, 50, 60 mg orally, b.i.d 28 days, followed by 14 days rest every 6 weeks for four cycles).

Using such treatment algorithm, the JASPAC-01 trial defines so far unreached numbers for relapse free survival (RFS) and OS (*Table 1*). The median OS was 25.5 months for gemcitabine and 46.5 months for S-1 treated patients (HR of 0.57 for mortality in favour of S-1). The estimated 5-year survival rate was 24.2% in the gemcitabine group and 43.6% in the S-1 group with a median RFS time of 11.3 months for gemcitabine and 22.9 months for S-1. Of note, the median OS times for gemcitabine in the JASPAC-01 trial was in the published range from 22.8 to 26.5 months (*Table 1*). Besides the nearly doubled survival time, subgroup analysis revealed a favourable outcome for patients with advanced T-stages (T3) and positive lymph nodes (N1) in the S-1 arm.

What about side effects? Indeed, both treatment regimen

Table 1 Randomized controlled trials for adjuvant chemotherapy in pancreatic cancer

Trial	Treatment	No. of patients	mDFS (ms)	P value	mOS (ms)	P value	5-yr OS (%)	Ref.
EORTC	Observation	54	NR	NR	12.6	0.099	10	(11)
	5-FU/RT	60			17.1		20	
RTOG 9704	5-FU/RT	230	NR	NR	17.1	0.08	18	(12)
	Gemcitabine/RT	221			20.5		22	
ESPAC-1	CRT *vs.* no CRT*	145/144	10.7/15.2	0.04	15.9/17.9	0.05	10/20	(13)
	CTx *vs.* no CTx**	147/142	15.3/9.4	0.02	20.1/15.5	0.009	21/8	
ESPAC 3	5-FU/LV	551	14.1	0.53	23	0.39	15.9	(7)
	Gemcitabine	537	14.3		23.6		17.5	
ESPAC 4***	Gemcitabine	366	NR	NR	25.5	0.032	16.3	(14)
	Gemcitabine/Capecitabine	364			28.0		28.8	
CONKO-001	Observation	175	6.7	<0.001	20.2	0.01	10.4	(6)
	Gemcitabine	179	13.4		22.8		20.7	
CONKO-005	Gemcitabine	217	11.6	0.291	26.5	0.406	19	(15)
	Gemcitabine/Erlotinib	219	11.6		24.6		28	
JSAP	Observation	44	8.6	NR	12.5	NR	14.9	(16)
	Cisplatin/5-FU	45	10.2		15.8		26.4	
JSAP-02	Observation	60	5.0	0.01	18.4	0.19	10.6	(17)
	Gemcitabine	58	11.4		22.3		23.9	
JASPAC 01	S-1	187	22.9	<0.001	46.5	<0.001	44.1	(9)
	Gemcitabine	190	11.3		25.5		24.4w	

EORTC, European Organization for Research and Treatment of Cancer; CONKO, Charité Onkologie; RTOG, Radiation Therapy Oncology Group; ESPAC European Study Group for Pancreatic Cancer; JASPAC, Japan Adjuvant Study Group of Pancreatic Cancer/JSAP Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer; S-1, oral fluoropyrimidine; 5-FU/LV, 5-fluorouracil/leucovorine; NR, not reported; No., number; mDFS, median disease free survival time; mOS, median overall survival time; Ref, reference; 2-yr OS, 2 years overall survival; 5-yr OS, 5 years overall survival; ms, months. *, CRT Chemoradiotherapy (5-FU/LV + RT); **, CTx 5-FU/LV; ***, not full published.

were comparable in most grade 3 and 4 adverse event besides more haematotoxicity in the gemcitabine group (Gem: neutropenia grade 3, 45% and grade 4, 27% of patients; S-1: neutropenia grade 3, 11% and grade 4, 2% of patients). Also, grade 3 and 4 infections were increased with gemcitabine. Anyhow, febrile neutropenia remained similar in both study arms as fatigue, anorexia, nausea and vomiting did. Not surprisingly S-1 was associated with increased gastrointestinal adverse events, mainly diarrhoea (grade 3, 4% and grade 4, 1% of the patients) but also stomatitis. Not named are side effects like rash or palmar-plantar erythrodysesthesia that have been previously described for S-1. Furthermore, tolerability was underpinned via a subgroup analysis for patients aged ≥65 years and by progressing quality of life improvement over time. In the gemcitabine group only 35% of the patients completed the planned treatment without dose reduction, compared to 59% in the S-1 group. Thus, S-1 outperforms gemcitabine not only in terms of efficiency but also tolerability at least in an Asian patient cohort.

In turn, one would expect that the JASPAC-01 trial fundamentally changes the field of adjuvant treatment to define S-1 as the new standard of care worldwide. However, a big question mark flanks "worldwide" as S-1 can only be announced for Asians as a standard and here in particular for Japanese. Thus, a potential weakness of the trial is,

albeit the good design with a heterogeneous multi-centre distribution, the single nation realisation. The conclusions cannot be globally transferred, moreover even within Asia the transferability may be limited due to lacking data. But what may be the reasons for population limited effects? The key is probably the metabolism of S-1 by the cytochrome machinery having different genotypes at the CYP2A6 locus in Caucasians and East Asians. This in turn leads to higher toxicity due a faster conversion of tegafur to 5-FU, resulting in an increased area under curve for 5-FU, in the latter groups compared to the East Asian population (18-20). Furthermore, the tolerability of fluoropyrimidines seems to be generally reduced in Caucasians compared to Asians, maybe also due to diet (21). Such side effects limit dose escalation in Caucasians. In a small phase II trial with 27 metastatic PDAC patients S-1 (reduced to 30 mg/m^2!, b.i.d. for 2 weeks, repeated every 3 weeks) showed an acceptable tolerability and even though comparison is not suitable median progression free survival and median OS were similar to the phase III GEST study (10,22). The recommended dosage for Caucasians is reduced to a far below range as it has been used and was well tolerated in the JASPAC-01 trial. In fact dosage according to the BSA would require even higher doses than used in the JASPAC-01 trial in most Caucasians based on their physique. Another hurdle to be taken is the limited availability of S-1 outside the Asian market resulting in restricted use and missing medical approval in several countries. At least in Europe S-1 is approved for gastric cancer in combination with cisplatin and teaches lessons on tolerability and effectiveness in a broader set of Caucasian patients. Anyhow, maybe upcoming subgroup analysis of the JASPAC-1 trial complemented with genetic analysis and biomarkers screened to predict a favourable S-1 metabolism for dose escalation will allow the identification and stratification of patients that primarily profit from S-1 independent of their ethnical background. As far as these data are lacking, the use of adjuvant S-1 in Caucasians has to be with caution and limited to clinical trials.

Moreover new treatment strategies tailored for a more Caucasian population are upcoming, having the capacity to change the standard of care such as the ESPAC-4 trial, propagating the combination of gemcitabine and capecitabine (*Table 1*). Furthermore, several trials are investigating even more intense treatment strategies like adjuvant FOLFIRINOX or Gemcitabine/Nab-Paclitaxel in the APACT trial (23,24), most of these studies have an adjacent biomarker project to define permissive subgroups. This probably will change our standard of care in the near future, in particular should allow more personalized strategies. Also combination approaches with S-1 have to be taken in account and may improve the efficacy as recently shown for the combination with oral leucovorin in metastatic PDAC, with altered application intervals (25). If these data is transferable remains elusive as far as combinations like S-1/gemcitabine did not improve efficacy but increased toxicity (10).

In summary, the data presented in the JASPAC-1 trial is remarkable and indeed changes the facets of treatment at least in an East Asian population. Recent studies identified several genetic subtypes differing not only in their molecular profile and morphology but also in their response to various treatments in metastatic PDAC (26-29). In turn, a biomarker being as simple as the affiliation of a patient to a certain population such as being East Asian is much more desirable than a molecular profile. In addition, we can anew learn from the trial that gemcitabine may not be the right player in the adjuvant treatment, in particular as it is associated with relatively high toxicity (only 35% of the patients completed the planned dosage). Furthermore, we can learn that the formulation of a drug within the same pharmacological group is of high importance, even more when thereby the bioavailability is prolonged or tolerability is improved resulting in higher total doses. Thereby the efficacy of S-1 may be driven by a higher potency against micrometastasis as shown in gastric cancer (30,31). The treatability of a subset of PDAC patients has improved by this study and gives hope that the running trials in this field may give us similar results and improve the landscape for the treatment of patients that are literally cured. But again a "*one pill fits all*" scenario moves further away and calls for more tailored approaches.

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