EDITORIAL

Biomarkers for Pancreatic Cancer: Is it Ready for Primetime?

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Pancreatic cancer remains a lethal disease with brief survival especially in patients with advanced disease. Within this decade pancreatic cancer will become the second leading cause of cancer death in the Unites States after lung cancer. It is estimated that 45,220 people will be diagnosed with pancreatic cancer and about 38,460 people will die of pancreatic cancer [1].

Standard treatment for advanced pancreatic cancer has had minimal impact on natural course of the disease. Current standard chemotherapy for healthy, robust patients remains FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) chemotherapy which showed 4-month overall survival benefit compared to gemcitabine alone [2]. Recently MPACT study showed that adding nab-paclitaxel to gemcitabine significantly improved overall survival compared to gemcitabine (8.5 months *vs*. 6.7 months P=0.000015). However, the combination remains more toxic compared to gemcitabine [3].

Also despite extensive investments in targeted therapy trials for pancreatic cancer there has been no meaningful impact on survival. To this date, erlotinib is the only targeted therapy drug which has shown statistically significant (HR=0.81, P=0.025) but only modest improvement in median survival (5.9 to 6.4 months) [4]. Both anti-angiogenic agents and epidermal growth factor receptor (EGFR) antibodies have failed to improve survival in pancreatic cancer patients [5, 6].

Key words Biological Markers; Equilibrative Nucleoside Transporter 1; Osteonectin; Pancreatic Neoplasms

Abbreviations CDHP: 5 chloro-2,4-dihydroxypyridine; DPD: dihydropyrimidine dehydrogenase; hENT1: human equilibrative transporter 1

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Therefore, having a biomarker which is both predictive and prognostic marker may play an important role in treatment of pancreatic cancer. To this date there are no biomarkers available which are used in treatment of pancreatic cancer.

Human equilibrative transporter 1 (hENT1) is a member of nucleoside transporter proteins which mediates cellular entry of cytotoxic chemotherapies such as gemcitabine [7]. HENT1 is the most abundant and the major route for gemcitabine transport. Therefore, hENT1 may potentially be a predictive marker for gemcitabine. There is existing evidence supporting hENT1 as predictive biomarker in pancreatic cancer patients treated with gemcitabine [8, 9, 10]. At the 2013 ASCO Annual Meeting there were two abstracts presented with hypothesis that hENT1 is a predictive marker for gemcitabine.

The first study was the European Study Group for Pancreatic Cancer (ESPAC) study where they looked at hENT1 expression retrospectively (Abstract #4006 [11]). This is a trial randomizing resected pancreatic cancer patients to 5-FU or gemcitabine. In this study there was significant interaction between hENT1 immunohistochemistry expression and the use of gemcitabine. Similar to other studies high hENT1 immunohistochemistry expression was associated with improved survival using gemcitabine. Interestingly, there was suggestion that low hENT1 was associated with improved survival for using 5-FU rather than gemcitabine. However this is only hypothesis generating and further prospective validation must be done.

The second (LEAP study) was randomized phase II study randomizing patients with gemcitabine *vs*. CO-101 (Abstract #4007 [12]). CO-101 is drug with elaidic acid lipid tail which allows passive diffusion and does not depend on hENT1 transport. The primary endpoint of this study was to double the

overall survival in low hENT1 patients treated with combination therapy; however, the primary endpoint was not reached. The possible reason for negative results is unclear. But it is possible that there are more important factors other than hENT1 for drug uptake such as stromal barrier and metabolism of gemcitabine might also be important in this setting. Other hypothesis is that LEAP study was conducted in metastatic disease while other previous studies were done in early resected pancreatic cancer which may account for different biology leading to different outcome.

Overexpression of protein secreted protein acidic and rich in cysteine (SPARC) has been noted in the pancreatic cancer and its peritumoral stroma. SPARC is involved in cell matrix interaction, cell migration, proliferation and angiogenesis [13]. Infante *et al*. investigated 299 cohorts of resected pancreatic cancer at John's Hopkins and showed that stromal SPARC expression is a marker of poor prognosis (15 months *vs*. 30 months) [14]. In contrast, the expression of SPARC in pancreatic cancer cells was not associated with prognosis (P=0.13). In ASCO 2013, Sinn *et al*. examined the patients from Charité Onkologie (CONKO)-001, a prospective randomized phase III study, investigating the role of adjuvant gemcitabine in resected pancreatic cancer patients. Tissue samples of 160 patients were analyzed by immunohisto-chemistry for the expression of SPARC in the peritumoral stroma and in the tumor cell cytoplasm Strong stromal SPARC expression was associated with worse disease free survival and overall survival in the study population (disease free survival: 9.0 *vs*. 12.6 months, P=0.005; overall survival: 19.8 *vs*. 26.6 months, P=0.033). Cytoplasmic SPARC expression in the cancer cells was also associated with worse patient outcome (disease free survival: 7.4 *vs*. 12.1 months, P=0.041; overall survival: 14.1 *vs*. 25.6 months, P=0.011) [15]. However, the prognostic impact was restricted to patients who received adjuvant treatment with gemcitabine and not in the control group.

The prognosis associated with SPARC seems to be a puzzling phenomenon. Initial functional studies showed that SPARC has growth inhibitory function; SPARC knockout mice grew cancer faster than SPARC expressing mice; therefore, it should be a good prognostic factor in cancer patients [16, 17]. However, two above studies have clearly demonstrated that expression of SPARC in stroma has adverse prognostic factor independent of other pathologic variables in resected pancreatic cancer. In metastatic setting, SPARC level was studied in chemotherapy using gemcitabine and nab-paclitaxel. A significant improvement in overall survival was noted in high-SPARC group compared to the low-SPARC group (median overall survival: 17.8 *vs*. 8.1 months, respectively; P=0.0431) [18]. Furthermore, SPARC level remained a significant predictor for the overall survival in a multivariate Cox regression model after adjusting for clinical covariates, including sex, race, age, treatment, and baseline CA 19-9 level (P=0.04). The pilot study had only 36 patient samples but the recent MPACT study will be able to further elucidate the role of SPARC in advanced pancreatic cancer.

JASPAC was an adjuvant study in pancreatic cancer randomizing patients to gemcitabine *vs*. S-1 conducted in Japan. S-1 is an oral fluoropyrimidine combining tegafur; a prodrug of 5-FU, 5 chloro-2,4-dihydroxypyridine (CDHP); a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate. In metastatic setting S-1 has shown non inferiority to gemcitabine in terms of overall survival with good tolerability in Asia [19]. The primary endpoint of this study was to assess non-inferiority of S-1 to gemcitabine in overall survival. Surprisingly, the results actually showed that S-1 was superior to gemcitabine in terms of overall survival and relapse free survival. Overall survival at 2 years were 53% for gemcitabine and 70% for S-1. Recurrence free survival at 2 years were 29% for gemcitabine and 48% for S-1. However, S-1 seems to be more effective and better tolerated in Asian population compared to Western population. Therefore the trial needs to be replicated in Western hemisphere. DPD is an enzyme responsible for up to 90% of 5-FU catabolism and expressed much higher in Asian population with gastric cancer [20]. Given that S-1 contains CDHP, a reversible inhibitor of DPD, it is postulated that S-1 may be more active than 5-FU in Asian population. Another potential reason for differences in drug tolerability is thought to be reflective of differences in CYP2A6 gene polymorphisms existing between Asians and Caucasians, affecting S-1 to 5-FU conversion. It is postulated that this enzyme is more efficacious in whites than in Asians, converting S-1 to 5-FU at a greater rate and achieving a higher AUC of 5-FU at much lower doses of S-1 [21].

Understanding the molecular biology of pancreatic carcinogenesis has provided avenue for clinician to use different molecular biomarkers in prognosticating cancer patients. In 2013 ASCO Annual Meeting, we had insights on hENT1, SPARC and DPD. None of these markers are currently validated for use in routine clinical practice. However, it is an interesting time that we can now conduct biomarker based clinical trials in pancreatic cancer. Such prospective studies will be able to elucidate personalized cancer care even for pancreatic cancer.

Conflicts of interest The authors have no potential conflicts of interest to disclose

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