Biomarkers in Pancreatic Adenocarcinoma

Highlights from the “ASCO Annual Meeting”. Chicago, IL, USA. May 30-June 3, 2014

Nicholas Joza, Muhammad Wasif Saif
Tufts University School of Medicine. Boston, MA, USA

ABSTRACT
Pancreatic adenocarcinoma is a highly aggressive cancer, with a median patient survival of less than one year. Clinically useful biomarkers capable of accurately assessing prognosis, as well as response to therapy, are urgently needed. At the 2014 ASCO Annual Meeting, Maus et al. (Abstract #e15199) and Neuzillet et al. (Abstract #e15200) present data on use of c-MET as a prognostic biomarker, and Shultz et al. (Abstract #4133) use a multiplex antibody panel to identify predictive markers of response to gemcitabine and erlotinib.

What We Knew Prior to the 2014 ASCO Annual Meeting
Pancreatic ductal adenocarcinoma (PDAC) carries a grim prognosis; with 1- and 5-year survival rates about 27% and 6%, respectively [1]. A contributing factor to this high mortality rate is the lack of effective screening methods. Indeed, 80-85% of patients are diagnosed at a late stage, precluding curative surgical resection [2]. There has been an intense effort to discover pancreatic cancer-associated biomarkers to assist in early detection and diagnosis, as well as predicting response to treatment.

Currently, the serum carbohydrate antigen 19-9 (CA19-9) is the sole biomarker routinely used to make clinical decisions in pancreatic cancer. It is primarily limited to monitoring treatment efficacy and recurrence of resected tumors [3]. In addition, baseline (pre-treatment) CA19-9 levels have prognostic value. However, it has insufficient sensitivity and specificity to have clinical utility in diagnosis of pancreatic cancer [4]. Moreover, as a Lewis blood group antigen, it is not expressed in up to 10% of the population. Wide ranges of other biomarkers are currently under investigation [5].

What We Learned at the 2014 ASCO Meeting
IL-8, CEA and HIF-1 Alpha as Predictive Surrogate Markers for Overall Survival in Response to Gemcitabine With or Without Erlotinib
Shultz et al. [6] developed a multiplex antibody panel, based on the proximity ligation assay (PLA), to simultaneously quantitate 35 key serum proteins in patients with PDAC. They used baseline (pre-treatment) plasma samples from nearly 500 patients that had been randomized to gemcitabine with erlotinib versus gemcitabine alone (NCIC CTG PA.3 [7]). Samples were divided into training and validation sets. They found that elevated levels of interleukin-8 (IL-8), carcinoembryonic antigen (CEA) and hypoxia-inducible factor-1 alpha (HIF-1 alpha) predicted lower overall survival (OS) in the group receiving gemcitabine and erlotinib (hazard ratio (HR) 0.51, 0.60 and 0.59, respectively, in the validation set). Elevated IL-8 also predicted lower OS in patients in the gemcitabine only arm (HR 0.51). These results reveal a possible biomarker “signature”, predictive of therapeutic response. Interestingly, these molecules are linked to the c-MET signaling pathway, which is involved in pancreatic tumorigenesis (see below). In response to hypoxia, HIF-1 alpha induces expression of c-MET in pancreatic cancer cells, promoting invasive activity [8]. Furthermore, IL-8 is a pro-angiogenic chemokine produced in response to c-MET signaling [9].

C-MET Expression in PDAC is a Marker of Poor Overall Survival
The tyrosine kinase receptor c-MET plays important roles in tumor cell survival, local invasion and metastasis, and has emerged as a key target for cancer therapy [10]. Under physiological conditions, c-MET and its ligand Hepatocyte Growth Factor (HGF) are expressed at low levels in pancreatic acinar cells and stromal cells, respectively, and interact in a paracrine manner to promote cell survival and motility [11]. By contrast, MET is overexpressed in the majority of pancreatic tumors [11-13], and has been shown to correlate with advanced TNM stage, risk of relapse and poor overall survival [14]. Small molecule inhibitors to MET are currently being evaluated in clinical trials, and stratification of patients based on MET expression may be important.
Neuzillet et al. [15] assessed c-MET expression by immunohistochemistry in resected PDAC. They developed a scoring method for c-MET expression (high c-MET was defined as ≥ 20% of tumor cells with strong membrane staining), and retrospectively analyzed 37 pancreatic tumors from patients with resected PDAC who did not receive adjuvant chemotherapy. As shown in Table 1, high c-MET expression (7/37 patients) was associated with improvement in disease-free survival (6.3 vs 33 months) and overall survival (10.8 vs 39.0 months).

Maus et al. [16] investigated c-MET mRNA expression in tumor specimens from patients who had undergone resection and adjuvant gemcitabine treatment. Using microdissection and quantitative PCR, they showed that c-MET mRNA expression was significantly divergent between pancreatic stromal (median 1.0, range 0.37-5.05) and tumor (median 3.8, range 0.78-12.27) tissue (p<0.0001). Using a cut-off of 5.0, they found that elevated c-MET levels in tumor correlated with worse overall survival (p<0.003); c-MET levels in stroma showed no correlation.

**Discussion**

There is intense research focused on identifying clinically robust biomarkers to better stratify patients based on risk of aggressive disease and identify those who will respond to therapy. In Abstract #4133, Shultz et al use a multiplex biomarker panel to simultaneously measure multiple serum biomarkers, and found that low IL-8, CEA and HIF-1 alpha was predictive of improved survival in the gemcitabine/erlotinib treatment group. In Abstract #e15200, Neuzillet et al. developed a simplified method to score for c-MET expression immunohistochemically, and showed that high c-MET levels correlated with poor survival. Maus et al. (Abstract #e15199) showed a relationship between c-MET mRNA levels and poor survival. Further studies are needed to evaluate c-MET and response to therapy, particularly with the growing interest in MET inhibitors in the treatment of PDAC.

---

**Table 1.** c-MET expression in PDAC is a negative prognostic marker of disease-free survival (DFS) and overall survival (OS) (Abstract #e15200) [15].

<table>
<thead>
<tr>
<th>Low c-MET expression</th>
<th>DFS (N=37)</th>
<th>OS (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS 6.3 vs 33.0 months (HR 3.456, p=0.0036)</td>
<td>OS 10.8 vs 39.0 months (HR 4.257, p=0.0004)</td>
<td></td>
</tr>
</tbody>
</table>

---

**References**


---