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HIGHLIGHT ARTICLE

Clinical and Laboratory Biomarkers in the Management of Pancreatic Adenocarcinoma

Highlights from the "2012 ASCO Annual Meeting". Chicago, IL, USA; May 31 - June 5, 2012

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Summary

Despite improvements in the health service and the available treatment means, the outcome of the majority of patients with advanced pancreatic adenocarcinoma, even in the Western world, is disappointing. This fact necessitates invention and development of clinical and laboratory biomarkers that help us detect early enough those patients who have the worst prognosis, and who may benefit or not from our treatments and individualize thus our management accordingly. In the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, four interesting scientific works on biomarkers in pancreatic cancer were presented. Two of them presented new clinical data such as the correlation of hand and foot skin reaction with the prognosis of patients treated with capecitabine based treatment (Abstract #4023), and the independent association of early presentation of venous thromboembolic events with poor survival (Abstract #4037). The other two significant abstracts focused on new potential predictive laboratory biomarkers, such as the association of the baseline levels of serum albumin to benefit from bevacizumab enriched treatment (Abstract #4039) and the likely correlation of high insulin growth factor 1 (IGF-1) tissue expression to better prognosis in patients treated with the IGF-1 receptor monoclonal antibody (mAb) MK-0646 (Abstract #4054).

What Did We Know Before the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting?

Even seven years after the approval of a targeted agent (i.e erlotinib) in the treatment of advanced pancreatic cancer, there is still lack of a reliable predictive biomarker apart from the degree of skin rash, according to data presented by Moore *et al*. [1]. Though, many potential biomarkers of efficacy, toxicity or prognosis have been proposed in the recent years, mainly for patients treated with gemcitabine, none of them has been prospectively confirmed and approved [2]. Therefore, the prognosis and the treatment strategy are based on clinical parameters such as the stage of disease, performance status, concomitant diseases, etc. Understandably, there has been a continuous effort to develop reliable prognostic and predictive tools in order to maximize efficacy, minimize toxicity of drugs, avoid unnecessary treatments and guide appropriately our patients.

Keywords Biological Markers; Carcinoma, Pancreatic Ductal; Prognosis; Treatment Outcome

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What Have We Learnt from the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting?

In the current paper, we have captured and present the most noteworthy scientific data on pancreatic cancer biomarkers related to prognosis and prediction of treatment efficacy.

Hand and Foot Skin Reaction as a Predictive Biomarker of Capecitabine

Capecitabine is an oral fluoropyrimidine approved initially for treatment of colorectal cancer. There have been studies, including a recent phase III randomized study in advanced pancreatic cancer, suggesting a beneficial role of this oral agent in combination with gemcitabine chemotherapy [3]. The AIO-PK0104 phase III randomized controlled study tested the safety and efficacy of the combination of capecitabine and erlotinib, followed by gemcitabine on progression (Group 1) *versus* gemcitabine plus erlotinib, followed by capecitabine on progression (Group 2) in advanced pancreatic cancer patients [4]. The authors of this study underwent a subgroup analysis evaluating the association of hand and foot skin toxicity with clinical outcome (Abstract #4023) [5]. In this study, 279 patients were treated with the above combinations, of whom 141 received subsequently the 2nd line single

agent (gemcitabine or capecitabine) on progression. The primary endpoints were time to treatment failure after the 1st and 2nd line regimen and the overall survival. Data on skin toxicity were recorded in 255 out of 279 patients. A total of 73 patients (29%) developed hand and foot skin toxicity of any degree according to National Cancer Institute Common Toxicity Criteria version 2.0 (NCI CTCv2.0). The authors found that development of hand and foot skin toxicity was associated with significantly better time to treatment failure after the 2nd line regimen and overall survival compared to those who did not develop this toxicity (7.4 *versus* 4 months, P<0.001 for time to treatment failure after the 2nd line regimen and 9.7 *versus* 5.5 months, P=0.002 for overall survival). As far as analysis of the 123 patients on Group 1 is concerned, similar findings were reported on the 47 individuals (38%) who developed hand and foot skin toxicity (time to treatment failure after the 2nd line regimen 7.6 *versus* 3.2 months and overall survival of 10.2 *versus* 4.4 months). In conclusion, this particular skin toxicity might be a good predictive biomarker in pancreatic cancer patients treated with capecitabine.

Incidence of Venous Thromboembolism and Effect of Its Timing to Survival

Venous thromboembolic events are common findings in patients with malignancy of the upper gastrointestinal tract, especially in those with pancreatic cancer. So far, no data regarding the association of the timing of this occurrence with survival has been published. In abstract #4037, researchers from M.D. Anderson Cancer Center, Huston, TX, USA, reviewed 260 newly diagnosed patients with pancreatic cancer in 2006 and followed them up for two years recording the incidence of confirmed venous thromboembolic events [6]. Survival analysis was subsequently undertaken. The authors found 47 patients (18%) with venous thromboembolic events with a median age of 61 years and equal sex distribution. The majority of patients were diagnosed with pulmonary embolism (n=27), while 19 had developed deep venous thrombosis and one with both pulmonary embolism and deep venous thrombosis. The median overall survival of these patients was 192 days (range, 1-1,652 days). Survival analysis by Kaplan-Meier, showed that patients who developed early venous thromboembolic events, within 30 or 90 days from diagnosis, had worse prognosis than those who developed venous thromboembolic events later than 90 days. In particular, the median overall survival for patients with venous thromboembolic events within 30 days was 116 days (*versus* 295 in patients with late venous thromboembolic events, P=0.0003) and the overall survival of patients with venous thromboembolic events within 90 days was also short at 152 days (days not reached for late venous thromboembolic events, P=0.0006). Similarly, hazard ratio (HR) for death at 1 year was 3.52 (95% confidence interval: 1.71-7.23; P=0.0006) in patients with early venous thromboembolic events within 30 days, and 5.33 (95% confidence interval: 1.85-15.35; P=0.0019) for patients with early venous thromboembolic events within 90 days from diagnosis.

The Predictive Role of Baseline Albumin as a Biomarker for Efficacy of Bevacizumab

Addition of bevacizumab to standard chemotherapy in advanced pancreatic cancer has failed in terms of survival benefit. No obvious reasons have been identified for this failure, despite efforts of finding biomarkers of efficacy. Martin *et al*, from the University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA, investigated the impact of baseline albumin levels on the outcome of advanced pancreatic cancer patients treated with gemcitabine with or without bevacizumab (Abstract #4039) [7]. The working hypothesis is that low baseline albumin levels contribute to higher clearance of bevacizumab (by about 15-20%) and thus less exposure to the drug, affecting its efficacy. The researchers collected and analyzed data from 100 patients who received gemcitabine plus/minus bevacizumab in the context of 3 prospective phase II studies. Patients were stratified according to whether they had received bevacizumab (Group 1, n=42) or not (Group 2, n=58), and by the baseline albumin level above or below the lower limit of normal (less than 3.4 g/dL *versus* more than 3.4 g/dL). The median age in this analysis was 63 years with the majority of patients diagnosed with metastatic disease (94%) and with both treatment groups having comparable baseline albumin levels. The authors of this abstract, reported the interesting finding that normal baseline albumin levels were associated with statistically significant improvement in overall survival (10.7 *versus* 3.1 months, P=0.00175) and time to progression (7.7 *versus* 2.7 months, P=0.009) in patients of Group 1 as compared with those with low baseline albumin (less than 3.4 g/dL) levels. There was no impact of baseline albumin levels in survival or time to progression of patients of Group 2. This positive relation of baseline albumin levels to outcome was most notable in patients who maintained their normal albumin levels during their whole treatment period with bevacizumab (overall survival of 20.1 *versus* 8.6 months, P=0.003).

The Predictive Role of Insulin Growth Factor 1 (IGF-1) Expression in Pancreatic Cancer Patients Treated with IGF-1R mAb

There are many pathogenetic mechanisms for the development and progression of pancreatic adenocarcinoma [8]. Among the molecular pathways involved is the one mediated by insulin growth factor 1 which exerts its biological effects through activation of PI3K and mTOR molecules (Figure 1) [9]. Javle *et al*. from M.D. Anderson Cancer Center, Huston, TX, USA performed a translational study (Abstract #4054) within a phase II clinical study on advanced pancreatic cancer patients randomized to receive one of the three

treatment options: Group A: gemcitabine plus MK-0646 (an IGF-1R monoclonal antibody); Group B: gemcitabine plus MK-0646 plus erlotinib; and Group C: gemcitabine plus erlotinib (control arm) [10]. The primary endpoint of the clinical study was the progression free survival, and of the exploratory analysis the interaction of IGF-1 expression levels with treatment outcome and progression free survival. Within this study, the investigators measured the pre-treatment blood levels of IGF-1 by enzyme-linked immunosorbent assay (ELISA) and the IGF-1 mRNA expression on tissue from the diagnostic core biopsies.
A total of 50 patients were enrolled in the study with three identified finally as ineligible. The rest 47 patients were evenly randomized between the 3 treatment arms. The progression free survival in each arm was 5.5, 3.0 and 2.0 months, respectively (P=0.17) and the median overall survival 11.3, 8.9 and 5.7 months for Groups A, B and C (P=0.44). Of the above 47 eligible patients, adequate tissue for IGF-1 mRNA expression analysis was available only in 21 patients. By using a multivariate Cox proportional hazards model for progression free survival, the authors reported a large (76%) but non significant (P=0.16) reduction of disease progression and death between Group A and the control Group C in those patients with high IGF-1 expression compared to patients with lower expression (when IGF-1 was dichotomized at the median). This reduction was even larger when IGF-1 levels were taken as a continuous variable (96%, P=0.08). The investigators found no association between the blood and the tissue levels of IGF-1.

Discussion

The development of direct and indirect methods of predicting patients' outcome and treatments efficacy is reasonable and very much sought. These methods include both our clinical observational tools as well as laboratory tests, simple or fine as the molecular and genomic analysis. Following the data from the phase III study that led to the approval of erlotinib in the treatment of advanced pancreatic cancer, we have been using in our clinical routine skin pustulo-papular rash as a simple and early biomarker of erlotinib efficacy. In the same context, for those adding the oral fluoropyrimidine capecitabine in the 1st or 2nd line setting of pancreatic cancer, development of hand and foot skin toxicity might early and reliably suggest a better outcome and thus guide somehow the treatment strategy. Confirmation of this observation in the other large phase III study of capecitabine plus gemcitabine led by Cunningham *et al*. [3], will secure the role of hand and foot skin toxicity as a predictive biomarker of capecitabine.

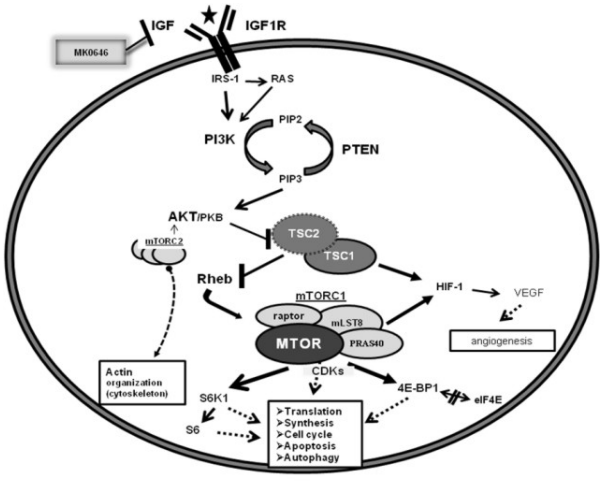

Figure 1. The IGF-1 downstream molecular pathway.

The recognition of a venous thromboembolic event in a cancer patient is always a very important clinical information, as its appropriate and timely management save indeed many lives. The observation presented above regarding the role of the timing of venous thromboembolic events development and prognosis might be helpful in the clinical scenario where we, clinicians and patients, have doubts regarding pursuing or not treatment or when questions on prognosis are raised. Although the differences in survival between the early and late venous thromboembolic events presentation are considerable, more data in larger cohorts and ideally prospective studies is needed to draw safe and reliable conclusion on this issue.
The most important probably information presented above, in the field of predictive biomarkers, was the identification of baseline albumin levels as an independent factor of efficacy of bevacizumab. There are many comments we can make on this exciting finding. First, it allows us to rethink the position of a very useful drug, such as the anti-angiogenetic agent bevacizumab, in our treatment battery against the highly aggressive pancreatic cancer. Second, providing the results are reproduced in the other phase III pancreatic cancer studies where bevacizumab was tested, it open new horizons on the planning of future studies in pancreatic cancer. Third, this information might prove extremely helpful in other solid tumors where bevacizumab has been licensed, or not, such as non-small lung cancer and gastric cancer where serum albumin levels are often below the normal limit. Of course, more research is required on this issue in order to confirm the exact mechanism that hypoalbuminemia attenuates the efficacy of bevacizumab. Further research also needs to answer the next possible clinical question whether exogenous administration of albumin might be helpful or not. In any case, this is very intriguing information that needs confirmation and further exploration.
Finally, the data on the predictive role of IGF-1 expression in the treatment with an IGF-1R inhibitor is very limited, as based on a small patient size, which leads to a low statistical power and, therefore, more information are required.
Nevertheless, it highlights once more the importance of pharmacogenomics in the outcome of targeted agents and the need nowadays to develop accurate biomarkers.

The above data raise also the issue of how future studies have to be designed in order to maximize and reach the so-called individualized management.
There is no doubt that now more than ever before, only novel agents which prove to be cost-effective and highly efficacious will be eventually approved in this very competitive and challenging environment of modern oncology.

Conflict of interest The authors have no potential conflicts of interest

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