Commentary

Pancreatic ductal adenocarcinoma—a new hope?

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Pancreatic ductal adenocarcinoma (PDAC) is typically an advanced and aggressive disease and improving outcomes for patients with this cancer remains a significant challenge. Few patients present with resectable disease, and recurrence rates after surgery remain high (70–80%). Modern chemotherapy (CMT) and radiotherapy (RT) regimens have made small improvements to survival and many of these treatments confer little benefit whilst delivering unpleasant side-effects. Alternative treatment modalities, such as electroporation, are under development and pancreatic cancer still awaits a "game-changer".

Immunotherapy uses the principle that a host immune system may recognise tumour-associated antigens and consequently target tumour cells for host-mediated lysis. This mechanism of action could conceivably act synergistically in combination with existing treatments. Immunotherapy has been deployed clinically to treat malignant melanoma, renal cell carcinoma and selected neuroendocrine tumours, and interest has been growing for PDAC.

Efficacy data from pre-clinical studies treating pancreatic cancer with type 1 interferon (IFN) (1,2) are compelling and support the rationale for clinical evaluation. Recently, the long term results from 37 patients receiving IFN + chemo-radiotherapy (CRT) after resection of PDAC were published (3). In this retrospective series by Rocha *et al*., patients (the majority with T3N1 cancer) received a 1 week course of IFN + CRT, followed by two 5-week courses of CMT. The 5- and 10-year overall survival (OS) rates were 41% and 24% respectively. Unfortunately grade 3 and 4 toxicities affected 79% of patients, and 42% required hospital admission. Equally high rates of severe adverse events have been observed by other early phase trials treating PDAC with IFN-based regimens (4-6). Therefore, the selection of those patients who are most likely to receive treatment benefit is critical.

The recent paper by Karakhanova *et al*. (7) is a biomarker study complementary to the CapRI trial (8) and prior to this reliable biomarkers to optimise personalised therapy in PDAC were lacking. The CapRI trial was a phase 3 multi-centre randomised trial of IFN-alpha2b (IFN-α2b) combined with adjuvant chemoradiation (CRT; 5-fluorouracil + cisplatin +28 fractions 50.4 Gy external beam radiation) versus CMT alone (5-fluorouracil and folinic acid) for patients with resected PDAC. Following on from preclinical (1,2) and then phase 1 (6) and phase 2 (4,5) clinical studies, the CapRI trial continued the natural progression of clinical research in to adjuvant IFN-α2b for treating PDAC. The biomarker component of this study aimed to identify predictive and prognostic immunological markers with interest in clinical response to CMT/CRT and IFN-α2b. Historically an antiviral drug, IFN-α2b is a powerful immuno-regulatory cytokine with several anti-cancer properties, including the induction of cell-cycle arrest and apoptosis. IFN-α2b transcribes for several genes and modulates T-helper cells, which in turn facilitate B-cell activity and antibody production.

Biomarker research sometimes lacks clear hypotheses and frequently very complex methodology arrives at unwieldy candidate lists, which fail to provide useful clinical endpoints. In this study, a succinct set of immunological biomarkers was chosen for blood and tissue samples. As

these can be assayed easily using tests employed routinely in the clinical setting (e.g., CD3+, CD8+, NK cells and neutrophils in blood samples), they are attractive candidates. The authors have identified several correlations between the biomarker panel and response or survival. The supplementary data tables allow full appreciation of the key findings. Briefly, elevated circulating T-cell populations may be predictive of a good response to 5-FU, but not combination therapy. More specifically, increases in circulating CD3+ and effCD8+ cells correlated well with OS and disease-free survival (DFS), although significance was only reached with an improved DFS in the presence of raised effCD8+ (log rank OS P=0.0131). CD8+ lymphocytes are important in the immune response to cancer and IFN promotes their development. CD8+ lymphocytes may be critical in guarding against systemic micro-metastases. It, therefore, seems sensible to administer IFN-based therapy early in the postoperative period to enhance CD8+ response. The timing of IFN-based therapy in relation to surgery and adjuvant CMT/CRT is probably important. CRT could possibly be more effective after immunomodulation.

The cytotoxic activity of CD8+ cells may be predictive of survival following resection and independent of any therapeutic regimen. Raised serum IL-10 concentrations correlated significantly with improved survival in patients receiving CMT alone, but the meaning of this is unclear. IL-10 is immunosuppressive and one might expect an inverse correlation. Neutrophil polymorphs are known to be an indicator of poor prognosis and here they were associated with poor OS after treatment. These cells frequently appear in biomarker studies but probably confound analysis as they form part of the innate response to acute inflammation, which has numerous triggers. Neutrophils may not be indicative primarily of the host immune cancer-response, but reflect potentially aggressive tumour biology manifest from defective cell signalling pathways over-expressing mediators such as COX-2 and NF-κB enhancing the inflammatory response.

Finding biomarkers in tissue can be problematic due to the technical aspects of sampling, handling, processing, and tissue heterogeneity. Despite these challenges, this study may have yielded some useful information from surgical specimens. An increase in tissue concentration of T-cell populations correlates with survival advantage. Kaplan-Meier survival estimates demonstrate that high tumour CD8+ count (>95 cells/mm^2) was related to increased OS and DFS (P=0.0054 and P=0.00145 respectively). Interestingly, median OS and DFS doubled in the presence of high numbers of CD8+ T-cells compared with tumours of low CD8+ counts. Perhaps, a subgroup of CD8+ cell-rich tumours exists. The identification of sub-groups of more immuno-sensitive tumour phenotypes for which IFN therapy could be reserved would generate personalised treatment plans.

Biomarker data processing can be difficult, but this has been aided in this study by a sensible shortlist of candidates. Statistical analysis with Kaplan-Meier estimates provide clear visual representation of clinical outcome, but analysis could go further to challenge the validity of the proposed biomarkers. It may be advantageous to adopt a strategy of multi-variate analysis, (such as Principal Component Analysis), which can be performed simultaneously with data modelling, thus deriving the sensitivity and specificity of a candidate marker. Furthermore, advanced techniques of statistical analysis allow for panels of biomarkers to be tested together, rather than on an individual basis, working on the principle that several markers combined may carry greater weight than one alone.

Median survival following resection of PDAC and adjuvant chemotherapy has been consistently reported to be 20–24 months (9,10). The CapRI trial has reported some of the most impressive survival rates of any published series (26.5 months with adjuvant CMT *vs.* 28.5 months CMT/RT/IFN) but the addition of IFN has not enhanced the effect of CMT significantly and ultimately, in keeping with the literature, 75% of patients had disease recurrence. In addition to high recurrence rates, major pancreatic resection comes with significant morbidity. Standard CMT confers serious adverse events to 14% of patients (9) and comparable toxicity is experienced by patients receiving CRT (10). The CapRI trial observed grade 3 and 4 toxicities in 85% of patients in the arm receiving IFN, compared with 16% for patients receiving chemotherapy alone. The vast majority of patients did proceed to 2nd and 3rd cycles of IFN, where the incidence of grade 3 and 4 events fell (12% and 4% respectively). Quality of life scoring dramatically reduced during the first cycle with IFN, but then recovered during the 2nd and 3rd cycles. There have been no adverse events resulting in death but such high morbidity to IFN, and in the aftermath of major surgery, is a serious consideration.

IFN-α2b is relatively inexpensive. If one proposes that an IFN containing regimen would be acceptable to patients, then it is imperative to identify which patients are most likely to benefit. Presently the role of IFN in treating

PDAC is unproven. Biomarker discovery is paramount in the evolution of managing PDAC and could hold the key to identifying who could be offered IFN-based or other forms of treatment.

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