NEW CLINICAL RESEARCH OPTIONS IN PANCREATIC CANCER

IMMUNOTHERAPY

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CANCER IMMUNOTHERAPY

- ‘Breakthrough of the Year’ in Science magazine 2013.

- After years of pre-clinical research, is becoming part of standard clinical practise.

- Works in melanoma, but now also evidence in eg lung, bladder.

- Entirely different to standard chemotherapy, radiotherapy.

- Potential and challenges in pancreatic cancer.
Activation of T cell responses against ‘Tumour Associated Antigens’

Vaccines are classically antigens administered exogenously in some form

But can also vaccinate in situ (endogenously), by instigating ‘Immunogenic (dangerous) tumour cell death’
IT’S REALLY QUITE COMPLICATED…

Priming and activation
- CD28/B7.1
- CD137/CD137L
- OX40/OX40L
- CD27/CD70
- HVEM
- GITR
- IL-2
- IL-12
- CTLA4/B7.1
- PD-L1/PD-1
- PD-L1/B7.1
- Prostaglandins

Cancer antigen presentation
- TNF-α
- IL-1
- IFN-α
- CD40L/CD40
- CDN
- ATP
- HMGB1
- TLR
- IL-10
- IL-4
- IL-13

Release of cancer cell antigens
- Immunogenic cell death
- Tolerogenic cell death

Trafficking of T cells to tumors
- CX3CL1
- CXCL9
- CXCL10
- CCL5

Infiltration of T cells into tumors
- LFA1/ICAM1
- Selectins
- VEGF
- Endothelin B receptor

Recognition of cancer cells by T cells
- Reduced pMHC on cancer cells

Killing of cancer cells
- IFN-γ
- T cell granule content
- PD-L1/PD-1
- PD-L1/B7.1
- Arginase
- IDO
- MICA/MICB
- TGF-β
- B7-H4
- BTLA
- TIM-3/phospholipids
- VISTA

Stimulatory factors
Inhibitors
THE CLINICAL CHALLENGE IN SHOWING THE BENEFIT OF IMMUNOTHERAPY FOR PANCREATIC CANCER
SHOWING THE BENEFIT OF NEW TREATMENTS FOR CANCER – THE CLASSICAL APPROACH

- Phase 1 trials – toxicity.
- Phase 2 trials – looking for a signal.
- Phase 3 trials – comparison with current treatment.
- How appropriate is this for immunotherapy?
SHOWING THE BENEFIT OF NEW TREATMENTS FOR CANCER – PHASE 1

• Dose escalation, often in groups of 3.

• Few patients only.

• Looking for ‘dose-limiting toxicity’. May not be seen in immunotherapy.

• Relies on concept that more is better - ? true for immunotherapy.

• All about setting a dose to take forward to Phase 2.

• Tends to be in patients with advanced cancer, whose immune system is already compromised – is this the best group to treat?
SHOWING THE BENEFIT OF NEW TREATMENTS FOR CANCER – PHASE 2

• Taking forward the dose from Phase 1.

• Everybody gets the treatment – tens of patients.

• Looking for a signal eg tumour shrinkage on scans – RECIST (response evaluation criteria in solid tumours).

• Complete response, partial response, stable disease, progressive disease.

• But this may not apply to immunotherapy.

• So need to adjust trials accordingly, including use of immune-related response criteria (irRC).
SHOWING THE BENEFIT OF NEW TREATMENTS FOR CANCER – irRC

- New lesions do not constitute disease progression if net tumor burden (including new lesions) is stable or decreases.

- Permits disease progression prior to response.

- Introduces the concept of confirmation of progression at a subsequent timepoint after first detection - accounts for the period required for activated T-cells to infiltrate the tumor, which may cause initial tumor volume increase but can subsequently translate into tumor shrinkage.

- Biopsy of residual masses may show no active tumour.

- Also classifies durable stable disease as clinical activity.
SHOWING THE BENEFIT OF NEW TREATMENTS FOR CANCER – ADJUSTMENTS FOR IMMUNOTHERAPY

- Trial design as well as readouts has to be different.
- Carry on treating after initial tumour ‘growth’ on scans.
- We do see patients feeling better while their scans are getting worse.
- Avoid expecting too much in patients with very advanced cancer.
- Be careful about combination treatments and sequencing eg chemotherapy can cause immunosuppression, avoid patients having steroids with immunotherapy.
SHOWING THE BENEFIT OF NEW TREATMENTS FOR CANCER – PHASE 3

- Comparison of new treatment with current standard of care.
- Patients are randomised between different treatments.
- May include placebo, ‘double-blind’.
- Hundreds of patients.
- Variety of readouts eg progression-free survival, but gold standard is overall survival.
- Phase 3 trials are what lead to changes in practise – the same standard needs to apply for immunotherapy.
CURRENT CLINICAL IMMUNOTHERAPY IN PRACTISE
MELANOMA AS AN EXAMPLE

CHECKPOINT INHIBTORS AS MOST PROMISING
AGENTS
Mechanism of anti-CTLA-4 on T-Cell Responses

Costimulation via CD28 ligation transduces T-cell activating signals

CTLA-4 ligation on activated T cells downregulates T-cell responses

Blocking CTLA-4 ligation enhances T-cell responses
FIRST-LINE
IPILIMUMAB

Phase 3 trial of DTIC + ipilimumab/placebo: 502 patients randomised
A: Overall survival
B: Progression-free survival
C: Duration of objective response
(NB number of patients)

Survival rates in the ipilimumab-DTIC group vs. DTIC-placebo:
At 1 year: 47.3% vs. 36.3%;
At 2 years: 28.5% vs. 17.9%;
At 3 years: 20.8% vs. 12.2%
(hazard ratio for death, 0.72; p<0.001)

Robert et al, NEJM 2011
ANTI-PD1

• PD-1 is inhibitory receptor on T cells

• PD-L1 widely expressed – expression on tumour cells correlates with poor prognosis in lung, kidney, pancreas and ovary tumours
  – PD-L1 limits anti-tumour immune responses

• Anti-PD1 and anti-PD-L1 antibodies show considerable promise in early trials

• Being tested in cancers other than melanoma.
ANTI-CTLA4
PLUS ANTI-PD1
SO WHAT ABOUT PANCREATIC CANCER?

• Lots of mice have been cured of pancreatic cancer with immunotherapy, but models are poor.

• Challenges of patient population, monitoring response etc. Particularly:
  • Rapidly progressive disease with poor prognosis.
  • Immunotherapy may be best tested in neoadjuvant/adjuvant setting.
  • Combination with radiotherapy/chemoradiation early in treatment?
  • Much of the tumour is stroma (including immune cells). So eg access of T cells to tumour cells may be problematic.
IMMUNOTHERAPY FOR PANCREATIC CANCER
EARLY STUDIES

• Checkpoint inhibitors – alone or in combination.

• Therapeutic vaccines:
  • Randomised Phase 2 of GVAX with Cyclophosphamide and CRS 207 Compared to Chemotherapy or to CRS-207.
  • GVAX is an allogeneic pancreatic cancer cell line expressing GMCSF.
  • CRS-207 is a listeria-based immune adjuvant.
  • 2nd or 3rd line treatment.
  • Paucity of immunocompetent animal models of pancreatic cancer, and how relevant are they anyway?
GVAX/CRS 207

- 90 patients.

- 51% had received ≥2 chemotherapy regimens.

- Randomized 2:1 to receive either CY/GVAX followed by CRS-207 (Arm A), or CY/GVAX (Arm B).

- Median OS 6.1 vs 3.9 mos (A vs B, p=0.011).

- CA19-9 stabilization was seen in 32% vs 13% of patients (A vs B; p=0.06).

- Toxicities included local reactions after GVAX and transient fevers, rigors and lymphopenia after CRS-207.
IMMUNOTHERAPY FOR PANCREATIC CANCER
ONGOING EARLY CLINICAL STUDIES

- Adoptive T cell therapy, for example:

- T cells genetically modified to express chimeric antigen receptors (CAR). Antigen is mesothelin. Artificial TCR of antigen-targeted antibody linked to T cell signalling domain.

- Tumour infiltrating lymphocytes.

- Bispecific antibodies which bring together tumour cell expressing target antigen (EGFR), with killer T cells.
IMMUNOTHERAPY FOR PANCREATIC CANCER
ANTIBODIES OTHER THAN CHECKPOINT INHIBITORS

- Targeting EGFR.
- Notch receptors.
- MUC.
- Not clear how such antibodies really work – engaging their target to directly kill cells, on eg stimulating antibody-directed cellular cytotoxicity?
IMMUNOTHERAPY FOR PANCREATIC CANCER

IMMUNE ADJUVANTS

- IL-10.
- TLR5 agonist.
CONCLUSIONS

• The immune response to cancer, including pancreatic cancer, is central to tumour growth and now, potentially, therapy.

• Immunotherapy is now established for some cancers and has potential in all.

• Pancreatic cancer represents a particular challenge in terms of its biology, and the development of pre-clinical models and early clinical trials.

• Immunotherapy as an entirely different therapeutic approach is worth exploring in pancreatic cancer. Proof of principle is established in mice, but not yet in humans.