1. Recent Advancements in the Role of Immunotherapy for the Treatment of Cancer: Hype vs. Reality

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Immunotherapy

- Targets and harnesses the body's own immune system to attack cancer cells
- Encompasses a range of targets and types of treatments:
  - Vaccines
  - Oral agents
  - Monoclonal antibodies

Milestones in Immunotherapy Development

- 1893: William Coley uses live bacteria as immune stimulant to treat cancer
- 1949: Sir Mac Burnet publishes theory of acquired immunological tolerance
- 1957: discovery of tumour specific antigens in mice by George Klein
- 1967: Burnet proposes theory of immunosurveillance
- 1973: dendritic cells discovered by Ralph Steinman
- 1991: discovery of molecularly defined tumour antigens recognized by human T cells
- 1992: IL-2 approved as anti-cancer therapy
- 1997: first approval of monoclonal antibody as anti-cancer therapy
- 1998: first report of complete/partial regressions with therapeutic cancer vaccine
- 2010: first approval of therapeutic cancer vaccine

Immunotherapy in Melanoma (CTLA-4 Inhibition)

(Original study results published in 'The New England Journal of Medicine', Vol. 363, No. 8)

Ipilimumab in Melanoma

- Fully human monoclonal antibody (IgH1) that blocks CTLA-4
- 676 pts, pre-treated melanoma
- Median OS was 10 vs. 6.4 months ($p<0.001$)
- Best overall response rate in ipilimumab arm 10.9%
- 60% of responders maintained an objective response for >2 years
- Approved by FDA in 2011
- Listed on PBS for treatment of metastatic melanoma in 2013
- Ongoing clinical trials evaluating activity of ipilimumab and other CTLA4 inhibitors (e.g. tremelimumab)

Ipilimumab Toxicity

- Activation of T-cell immune response can be a powerful tool against tumour cells
  - Immune response is not tissue specific
- Increased immune activity in normal tissues can lead to a diverse range of toxicities
  - Important to recognize and treat potentially serious toxicity

Toxicities

- Dermatological
  - Pruritis
  - Rash (early, in 30-50%)
  - Vitiligo (late)
  - Stevens-Johnson syndrome/TEN (rare)
- Gastrointestinal
  - Diarrhoea/colitis (after ~6 weeks)
- Hepatotoxicity
  - Raised ALT/AST (~10%, with high grade hepatotoxicity in ~2% often slow to resolve)
- Endocrinopathy
  - Hypophysitis (up to 10%), hypothyroidism (~10%)
  - Adrenal crisis rare but potentially life-threatening

Less-Frequent Toxicities

- Respiratory
  - Pneumonia
  - Sarcoidosis
  - Pneumonitis
- Ocular toxicity
  - Episcleritis
  - Conjunctivitis
  - Uveitis
- Renal toxicity
  - Interstitial nephritis
  - Membranous nephropathy
- Pancreatitis
- Neurological syndromes
  - Posterior reversible encephalopathy
  - Aseptic meningitis
  - Guillain-Barre syndrome
- Haematological syndromes
  - Red cell aplasia
  - Neutropaenia
  - Coagulopathies (all rare)

Immune-Mediated Adverse Reactions

- Gastrointestinal
  - Diarrhoea
  - Abdominal pain
  - Blood or mucus in stool
  - Bowel perforation

  - Peritoneal signs
  - Ileus
- Liver
  - Abdominal liver function tests (e.g. AST, ALT) or total bilirubin
- Skin
  - Pruritus
  - Rash
- Neurologic
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia
- Endocrine
  - Fatigue
  - Headache
  - Mental status changes
  - Abdominal pain
  - Unusual bowel habits
  - Hypotension
  - Abnormal thyroid function tests and/or serum chemistries
- Other adverse reactions (e.g. ocular manifestations)

Immunotherapy in Melanoma (PD1 Inhibition)

Nivolumab (PD1 Inhibitor)

Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

(Original Article Published in 'The New England Journal of Medicine', Vol. 366, No. 26)

- Objective responses induced by anti-PD-1 (nivolumab) are rapid and durable
  - Sixty-five of 306 patients had ORs (CR+PR, 21%):
    - 30 of 65 (46%) responses were evident at first tumour evaluation (8 weeks)
    - 42 of 65 (65%) patients had responses lasting >1 year
    - 35 of 65 (54%) responses were ongoing at time of data analysis (March 2013)
    - Responses persisted off-drug

Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab

(Original Report Published in the 'Journal of Clinical Oncology', Vol. 32, No. 10)

- Confirmed activity of nivolumab (monoclonal antibody targeting PD1)
- Phase II study
- n=107
- Heavily pre-treated (>1 and up to 5 lines)
- Received up to 96 weeks of nivolumab

- Median OS was 16.8 months
- 1 year survival 62%
- 2 year survival 43%

Nivolumab in Previously Untreated Melanoma without BRAF Mutation

(Original Article Published in 'The New England Journal of Medicine)

- Phase III study
- 418 patients
- Previously untreated melanoma
- No BRAF mutation
- Compared nivolumab (with dacarbazine matched placebo) with dacarbazine (with nivolumab matched placebo)

Pembrolizumab

Prembrolizumab versus Ipilimumab in Advanced Melanoma

(Original Article Published in 'The New England Journal of Medicine)

- Randomized controlled phase III study
- 834 patients with advanced melanoma
- Randomized 1:1:1 ratio to pembrolizumab (at a dose of 10mg per kilogram of body weight) every 2 weeks/every 3 weeks/4 doses of ipilimumab (at 3mg per kilogram) every 3 weeks
- Primary outcome 6 month progression-free-survival:
  - 47.3% for pembrolizumab every 2 weeks
  - 46.4% for pembrolizumab every 3 weeks
  - 26.5% for ipilimumab
  - Grade 3-5 toxicity lower in both pembrolizumab groups (13.3 and 10.1%) than in ipilimumab group (19.9%)

Drugs Blocking PD-1/PD-L1

- Active against multiple cancer types
- Drugs targeting a single molecular pathway have an unprecedented activity spectrum and provide a "common denominator" for cancer therapy
- Durable objective tumour regressions in patients with:
  - Melanoma (17-40% of patients responding)
  - Lung cancer (10-30%)
  - Kidney cancer (12-29%)
  - Bladder cancer (25%)
  - Ovarian cancer (6-23%)
  - Head and neck cancer (14-20%)
  - Hodgkins lymphoma (87%)
  - Gastric cancer
  - Breast cancer
  - Mesothelioma

PD1 Inhibition in Lung Cancer

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer

(Original Article Published in 'The New England Journal of Medicine')

- Nivolumab:
  - N=135
  - Median OS = 9.2 (7.3-13.3)
  - 1 year OS = 42% of patients (34-50)
  - No. of deaths = 86
  - Patients with ongoing response = 63% (17 of 27 patients with response)
- Docetaxel
  - N = 137
  - Median OS = 6.0 (5.1-7.3)
  - 1 year OS = 24% of patients (17-31)
  - No. of deaths = 113
  - Patients with ongoing response = 33% (4 of 12 patients with response)

PD1 Inhibition in Renal Cell Carcinoma

Nivolumab Versus Everolimus in Advanced Renal-Cell Carcinoma

(Original Article Published in 'The New England Journal of Medicine', Vol. 373, No. 19)

- Randomized phase III study of 821 patients with previously treated advanced clear cell RCC
- Randomized 1:1 to nivolumab or everolimus
- Nivolumab median OS = 25.0 months (95% confidence interval [CI], 21.8 not estimable)
- Everolimus median OS = 19.6 months (95% CI, 17.6 to 23.1)
- HR for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002)
- Less toxicity in nivolumab arm

Combination Therapy

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

(Original Article Published in 'The New England Journal of Medicine')

- Phase III study of 945 patients with untreatable unresectable stage III or IV melanoma
- Randomized 1:1:1 to combination therapy or ipilimumab/nivolumab as monotherapy
- At median follow up of ~12 months: PFS significantly better in combination arm:
  - 11.5 months (combo) = 95% CI 8.9-16.7
  - 6.9 months (nivolumab) = 95% CI 4.3-9.5
  - 2.9 months (ipilimumab) = 95% CI 2.8-3.4

Challenges in Clinical Practice

- Finding new ways to evaluate therapy
  - Immunotherapy works in a different way to standard chemotherapy
  - Clinical trials are needing to adapt to allow for differences (e.g. different endpoints, different radiological response criteria)
- Who to give immunotherapy to?
  - While a wide range of tumours show some response, there are disappointing results in others (e.g. colorectal cancer)
  - Not all patients suitable:
    - Any autoimmune condition can be unmasked/aggravated by immune checkpoint blockade
    - Pivotal clinical trials have excluded any patient with a history of autoimmune disease or steroid requirement
- Need for biomarkers/predictors of response
  - PDL1 expression on tumour cells has been demonstrated to be prognostic/predictive of response to anti-PD1 therapy in some studies, however have failed to show similar results in others
    - To date, no reliable predictor of response identified
  - "Mutational load" of tumours may correlate with response to immunotherapy
- Potential for combination therapy (other drugs/radiotherapy) to increase likelihood of tumour response (many studies ongoing)

Further Challenges

- Cost and access:
  - Nivolumab, pembrolizumab and ipilimumab approved by PBS listing for use in advanced melanoma
  - Many clinical trials still underway and many more planned
  - Cost of treatment course for individual patient may range up to tens or even hundreds of thousands of dollars

Conclusion

- Immunotherapy has been the most exciting development in cancer treatment in the past decade, and has increased treatment options for many patients
- As more patients gain access to these drugs, all clinicians should be aware of immunotherapy and its potential toxicity and early management
- A number of patients from early immunotherapy studies remain disease free >5 years post treatment = much hope for a "cure' in a small percentage of patients, but a long way to go in others

2. The Role of Radiotherapy Used in Conjunction with Immunotherapy for the Treatment of Cancer

Dr David Blakey MBBS, FRANZCR (Radiation Oncologist)

Clinical Trials of RT and Immunotherapy

- Currently 91 active clinical trials in the US combining radiation and immunotherapy

Stereotactic Radiotherapy

- Planning using all imaging modalities
- Motion management (immobilisation devices, 4D CT)
- On-treatment image guidance
- Tight margins