Introduction to Immunotherapy in Bladder Cancer

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Cancer Immunotherapy

- Association between febrile illness and cancer regression known for centuries

- 19th century – William Coley demonstrated regression of soft tissue sarcomas in subset of patients who received intratumoral injections of heat-killed S. pyogens and S. marcescens

- Modern immunotherapy currently divided into three broad categories:

  - **Active immunization** (peptides, whole tumor cells, recombinant viruses encoding tumor associated antigens, dendritic cells loaded with tumor antigen)

  - **Nonspecific/semi-specific Immune Stimulation** (IL-2, GM-CSF, ipilimumab, nivolumab, pembrolizumab, atezolizumab)

  - **Adoptive Cell Transfer**

Where is cancer immunotherapy currently focused?

REVIEWS SCIENCE 348:62-8, 2015

Adoptive cell transfer as personalized immunotherapy for human cancer

Steven A. Rosenberg* and Nicholas P. Restifo*

Review CellPress

Checkpoint blockade for cancer therapy: revitalizing a suppressed immune system

Yago Pico de Coaña[1], Aniruddha Choudhury[2], and Rolf Kiessling[1] Trends Mol Med 2015

Recent results in immunotherapy (2015)

The NEW ENGLAND JOURNAL of MEDICINE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

- PFS 11.5 months (both) vs 2.9 months (ipi) vs 6.9 (nivolumab)
- There was, however, significant increase in treatment related adverse events in combination group

Anti-programmed Cell Death Protein 1 (PD-1) Antibody Nivolumab Leads to a Dramatic and Rapid Response in Papillary Renal Cell Carcinoma with Sarcomatoid and Rhabdoid Features

- After 3 doses of nivolumab, patient showed significant radiographic improvement of pulmonary, subcutaneous, and bony lesions

Larkin et al. N Engl J Med 2015
Geynisman Eur Urol 2015

Immunotherapy in bladder cancer began with BCG

- Febrile response following intravesicular instillation of BCG has been shown to be good prognostic factor and correlates with longer recurrence free survival

- Effective BCG response is dependent on CD4 and CD8 T-cell mediated inflammatory monocyte recruitment

- PPD positivity prior to intravesicular instillation of BCG correlated with improved recurrence free survival and that pre-existing BCG-specific T-cells improved intravesicular therapy

Biot et al. Sci Transl Med 2012

Current immunotherapeutic approaches in bladder cancer

- Equivocal results with IFN-α-2b
  - No advantage when used with BCG for BCG naïve patients (Neppel et al. J Urol 2010)
  - May have some benefit in BCG failure patients (O'Donnell et al. J Urol 2004)

- Carthon et al. *Clin Cancer Res 2010* in a dose escalation trial for ipilimumab in localized bladder cancer showed limited toxicity and increased frequency of $CD4^{+}$ $ICOS^{high}$ (activated T-cells) in systemic circulation

- Powles et al. *Nature* 2014 demonstrated efficacy for PD-L1 blockade in advanced urothelial tumors

- 2015 ASCO – Petrylak et al. A phase Ia study of MPDL3280A. Updated response and survival data in urothelial bladder cancer

  -Atezolizumab (formerly known as MPDL3280A) was well tolerated and had durable activity in UBC pts. Response, PFS and OS data are promising for IHC 2/3 and IHC 0/1 UBC pts vs historic controls. Response also correlated with in-tumor and blood-based biomarkers

A sampling of trials using checkpoint inhibitors in bladder cancer

- Phase III NCT02302807 currently recruiting for anti-PD-L1 in locally advanced and metastatic bladder cancer compared to chemotherapy

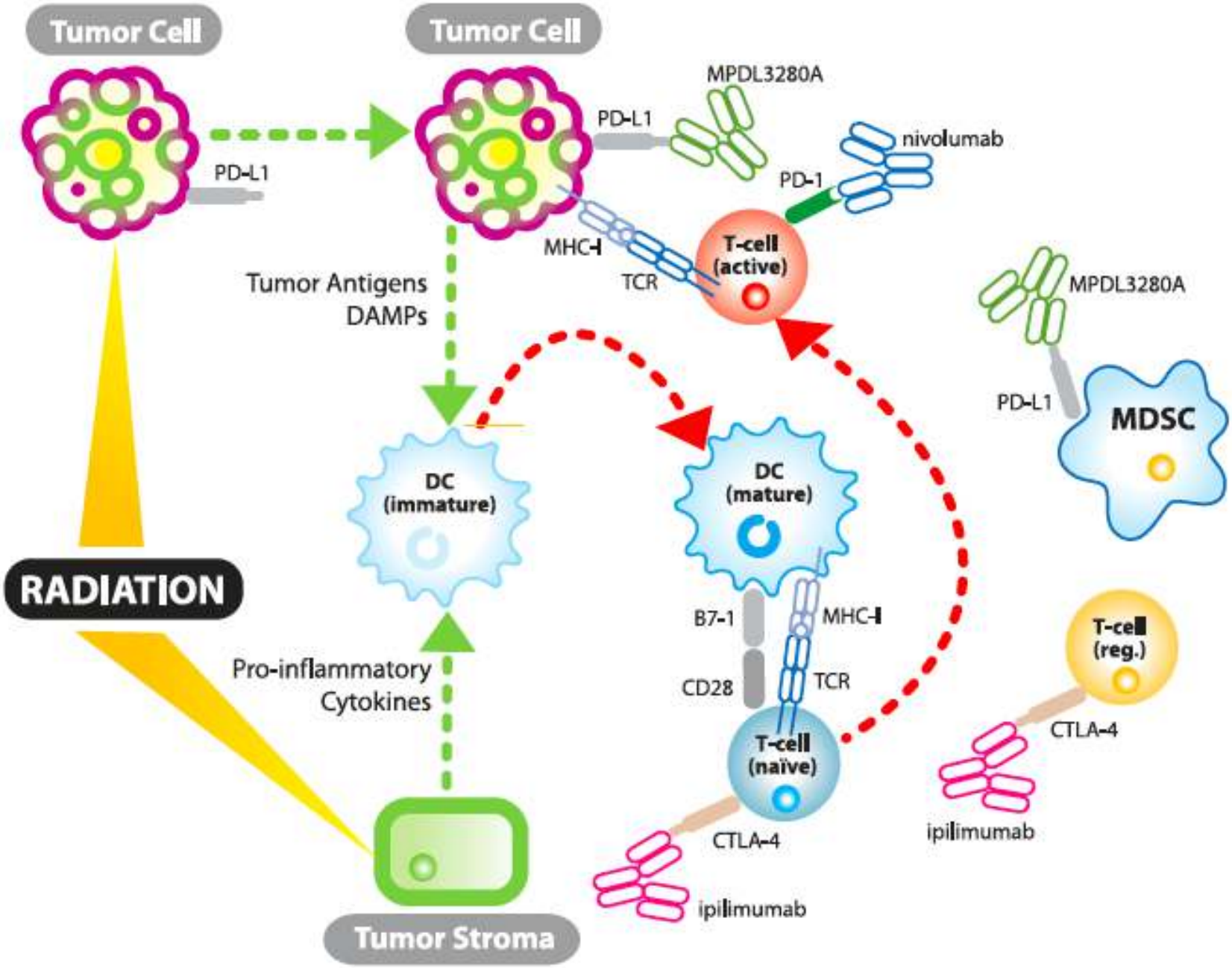
- Phase II NCT02108652 active, not recruiting for anti-PD-L1 in locally advanced and metastatic bladder cancer. Contains two cohorts: 1) treatment naïve and ineligible for platinum based chemo and 2) patients that progressed on platinum based chemo. Both get anti-PD-L1

- Phase I NCT02324582 currently recruiting for anti-PD-1 in high risk superficial bladder cancer. Anti-PD-1 will be used in combination with intravesicular BCG.

Limited data from combination of RT and immunotherapy in bladder cancer

- O'Toole et al. *Cancer Res 1979* showed that patients with T1-T4 urothelial carcinoma who were clinically tumor free 5 years after RT had a more rapid increase in post-radiotherapy lymphocyte numbers

- Mizutani et al. *Immunol Lett 1989* showed irradiation of bladder carcinoma cell lines may enhance their susceptibility to NK cell mediated killing



Bladder Cancer 2015

Recent data for RT + immunotherapy

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti

Lancet Oncol 2015

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Eugene D Kwon, Charles G Drake, Howard I Scher, Karim Fizazi, Alberto Bossi, Alfons J M van den Eertwegh, Michael Krainer, Nadine Houede, Ricardo Santos, Hakim Mahammedi, Siobhan Ng, Michele Maio, Fabio A Franke, Santhanam Sundar, Neeraj Agarwal, Andries M Bergman, Tudor E Ciuleanu, Ernesto Korbenfeld, Lisa Sengeløv, Steinbjorn Hansen, Christopher Logothetis, Tomasz M Beer, M Brent McHenry, Paul Gagnier, David Liu, Winald R Gerritsen, and **for the CA184-043 Investigators***

Lancet Oncol 2014

Combining Radiation and Immunotherapy

- Some potential relevant therapeutics:
  - atezolizumab (anti-PD-L1)
  - ipilimumab (anti-CTLA-4)
  - nivolumab (anti-PD-1)
  - pembrolizumab (anti-PD-1)
  - Interferon-α2b
  - GM-CSF
- Timing and Dose of Radiation
  - Current data from pre-clinical model supports concurrent administration of RT + immunotherapy
  - Data also demonstrates fractionated regimen is generally superior to single dose (8 Gy x 3 > 6 Gy x 5 > 20 Gy x 1) for the induction of an abscopal effect. However, absocopal effect also observed with 8 Gy x 1

A sampling of clinical trials combining RT and Immunotherapy

Clinical trials.gov identifier	Sponsor	Immunotherapy	Radiotherapy	Treatment timing	Phase	Condition
NCT01436968	Advantagene, Inc	ProstAtak (AdV-tk) injected into prostate	Standard of care	Radiation 0–3 days after second AdV-tk injection	3	Prostate Cancer
NCT00751270	Advantagene, Inc	AdV-tk injected into tumor/ tumor bed	Standard of care	Radiation 3–7 days following AdV-tk injection	1b	Malignant Glioma
NCT00589875	Advantagene, Inc	AdV-tk injected into tumor bed	Standard of care	Radiation 3–7 days following AdV-tk injection	2a	Malignant Glioma
NCT00634231	Advantagene, Inc	AdV-tk injected into tumor/ tumor bed	Standard of care	Radiation 3–7 days following AdV-tk injection	1	Pediatric Brain Tumors
NCT00589875	Advantagene. Inc	AdV-tk injected into tumor bed	Standard of care	Radiation 3–7 days following AdV-tk injection	2	Malignant Glioma
NCT01836432	NewLink Genetics Corporation	Algenpantucel-L (HAPa1, HAPa2)	50.4 Gy in 28 fractions	Radiation and immunotherapy on day 1.	3	Pancreatic Cancer
NCT01896271	University of Texas Southwestern Medical Center	High dose IL-2	Stereotactic ablative radiation therapy (SART) 8–20 Gy in 1–3 fractions	IL-2 administered immediately following radiation	2	Metastatic Renal Cancer
NCT01497808	Abramson Cancer Center of the University of Pennsylvania	Ipilimumab	Dose escalation for Stereotactic body radiation therapy (SBRT)	Not described	1/2	Metastatic Melanoma
NCT02303990	Abramson Cancer Center of the University of Pennsylvania	Pembrolizumab (anti-PD-1)	Hypofractionated radiation	Not described	1	Metastatic Cancers
NCT02086721	Maastricht Radiation Oncology	L19-IL-2	Patients receive a schedule of 1 × 30 Gy, 3 × 15–20 Gy; 5 × 12 Gy; 8 × 7.5 Gy	L19-IL-2 given one week after completion of radiation	1	Oligometastatic Solid Tumors
NCT01935921	National Cancer Institute	Ipilimumab	Standard of care	Ipilimumab started at beginning of week 4 of cetuximab course, given 3 courses total	1	Stage III-IVB Head and Neck Cancer
NCT02298946	National Cancer Institute	AMP-224 (PD-1 inhibitor)	Stereotactic body radiation therapy	Radiation day 0, AMP-224 on day 1 then q14 days	1	Metastatic Colorectal Cancer