Role for immunotherapy in GTN

Michael J Seckl
Charing Cross Hospital GTD Centre, Imperial College London, UK

Conflicts of interest: none to declare
GTN needing salvage?

• High Risk or PSTT/ETT failing:
  
  EMA/CO and EP/EMA and/or TE/TP
  and/or FAEV

• PSTT/ETT interval ≥ 4 yrs or stage IV
Salvage approaches

More chemo?

Escalated EP, BEP, ICE, TIP, Gem-TIP, FAEV

Pemetrexed/plat, capecitabine

Hi dose

Seckl et al Annals Oncol 2013 and ISSTD meeting Amsterdam 2017
High Dose UK experience

32 patients (Carbop-EC-T > CEM)
  22 single high dose
  10 tandem high dose

Median 3 previous lines of treatment

- 13 alive in remission
  - 6/14 (43%) chorios
  - 7/18 (39%) PSTT/ETT

~ 40% may benefit

El-Helw et al Brit J Cancer 2005
Frijstein et al ISSTD Amsterdam meeting 2017
Surgical salvage is important

Allifrangis et al J Reprod Med 2012
Salvage with new agents?

- TKIs: Erlotinib/gefitinib
- Anti-hCG antibodies/vaccine
- Anti-vascular: Bevasuzimab
  TRC105 (Anti-endoglin)
- Immune checkpoint inhibitors

Seckl et al Annals Oncol 2013, ISSTD meeting Bali 2015 Amsterdam 2017
Worley et al Gynae Oncol 2018
How anti-PD-1/L1 therapy works: Taking the brakes off the immune system
How ipilimumab works:
Taking the brakes off the immune system

Tumour cell/ APC

Anti-PD-L1
Atezolizumab
Durvalumab

Anti-PD-1 therapies
Nivolumab
Pembrolizumab

T Cell

L-Tryptophan
Epacadostat

IDO ↑

B7-1 or B7-2

PDL-1 or PDL-2

CTLA-4

Ipilimumab

Tryptophan ↓
Immune-checkpoints are important in normal pregnancy

- Well expressed in placental tissue
- Anti-PD-L/L1, Anti-CTLA-4/B7 cause preg loss
- IDO null or drug inhibitors (L-Tryp): preg loss
- Are these good GTN targets?

PD-L1 is expressed in all placental, CHM and GTN tissues

Pembrolizumab is active in choriocarcinoma

Ghorani et al Lancet 2017
Do immunotherapies work in PSTT?
What about ETT? A case study

Mar ‘15  40 yr old lady

  6 months lethargy, poor appetite, ireg PV bleeding
  2 girls 5 and 7yrs plus miscarriage 3 yrs ago
  hCG ~ 400 IU/L
  Pelvic US vascular uterine mass

Body imaging: CT chest/abdo, MRI brain -ve
US and MRI pelvis
Mar '15
ETT case study

Biopsy: PSTT/ETT

What would you do next?

TAH with ovarian preservation

Histology: ETT>>PSTT with serosal involvement

What would you do next?
ETT case study

EP/EMA for 12-16 wks

What would you do next?

Genetics: derived from 8 yr old child

What would you do next?

Tandem high dose with stem cell transplant x 2
ETT case study

Repeat imaging negative, hCG normal

What would you do next?

Surveillance hCG + CXR, MRI abdo/pelvis 6 mnthly

12 months: sarcoid in mediastinal nodes
18 months: well
24 months: symptoms of lethargy

What would you do next?
Re-imaging of case

Post high dose  Sep ‘17

Multiple bilateral small lung lesions

What would you do next?
ETT case study

Left thoractomy and excision bx

Histology: recurrent ETT

What would you do next?

Pembrolizumab 2mg/kg 3 weekly

6 weeks: lethargy gone

12 weeks: CT no change in lesions
ETT case study

Jan ’17 (3 mnths Pembro)  April ’17 (6 mnths Pembro)

What would you do next?
ETT case study

Right thoracotomy: 12 mets excised

Histology: fibrosis, immune cells, no cancer

Surveillance hCG + CT chest, MRI abdo/pelvis

Cured?
Will checkpoint / other immuno-therapies help everyone?

- 7/10 CR pembrolizumab
  1 PSTT + 2 chorio failed
- 1 ETT failed ipilimumab
- 1 Chorio failed L-Tryptophan

No

Ghorani et al Lancet 2017 + unpublished observations,
Sebire et al J Reprod Med 2008
Can we predict for response?

• All strongly PD-L1/PD1 +ve
• All lack MHC class I/II
• 3 responders had TILs + strong HLA-G
• 1 non-responder no TILs + weak HLA-G
• Fast growing disease may not do well

Not yet

Ghorani et al Lancet 2017 + unpublished observations
Which GTN for immunotherapy?

TROPHIMMUN trial: cohorts A and B

- **Low-risk**
  - Single agent regimen (MTX, ACT-D)
  - hCG normalization
  - Resistance
  - Cohort A

- **High-risk**
  - Polychemotherapy EMA-CO; EMA-EP
  - hCG normalization
  - Resistance
  - Cohort B

Benoit You et al in Lyon, France trial using anti-PD-L1 antibody atezolizumab

Cohort A: 11 patients Cohort B: 4 patients
What about combinations?

Balancing toxicity vs efficacy vs cost
Summary: Immunotherapies for GTN

• Pembrolizumab is active ~70% cases so far
• Toxicity < combination chemo << high dose
• Questions remain:
  - when to use? Pre-high dose vs earlier, PSTT/ETT
  - effect on future fertility
  - selection of responders vs non-responders
  - duration of therapy
  - role of combinations and mechanisms

Elimination of last GTN deaths??
Acknowledgements

Dr Naveed Sarwar
Dr Philip Savage
Dr Baljeet Kaur
Prof Neil Sebire
Dr Rosemary Fisher
Dee Short
Sabrina Positano
Emma Humble
Dr Anna Tommasi
Dr Olivier Pardo
Dr Fieke Froeling
Marina Georgiou
Rajat Roy
Mr Richard Smith
Ms Cristina Fotopoulou
Dr Edward Kanfer
Mr John Anderson
Mr Long Jiao
Dr Costi Alifrangis
Tina Barker
Dr Adrian Lim
Daksha Patel
Dr Ehsan Ghorani
Dr Preetha Aravind
Dr Richard Harvey
Terry Tin
Sarah Strickland
Linda Dayal
Lauren Jordan
Xianne Aguiar
Sinead Cope
Eimear Tummon
Jeanette Aristobal

Ulrika Joneborg
Joseph Carlson
Ayse Akarca
Teresa Marafioti
Sergio Quezada
Ross Berkowitz
François Golfier
Leon Massuger
Christianne Lok
Benoit You

Prof Edward Newlands
Prof Ken Bagshawe

m.seckl@imperial.ac.uk
www.hmole-chorio.org.uk

wellcome
NCRN
Department of Health
National Cancer Research Network
Cancer Research UK
Imperial College London
MRC Medical Research Council

CTRI
Immunotherapy over the ages

- **Enthusiasm Phase (1978-1985)**
  - 1960s: Adjuvants (e.g., BCG) shown to eradicate some tumors
  - 1978: Tumor-specific mAbs

- **Skepticism Phase (1985-1997)**
  - 1986: IFN-α approved as HCL cancer immunotherapy
  - 1996: IFN-α approved as adjuvant therapy
  - 1998: IL-2 approved for RCC & melanoma

- **Renaissance Phase (1997-2011)**
  - 2004: Avastin & Cetuximab Approved
  - 2006: Panitumumab Approved
  - 2011: Peg IFN approved (adjuvant)
  - Ipilimumab/Anti-CTLA-4 approved for advanced melanoma

- 1953: Coley’s work first published
- 1976: Immune component to spontaneous regressions in melanoma
- 1985: Adoptive immunotherapy for patients with cancer & hybridoma methodology
- 1991: First tumor-associated antigen cloned (MAGE-1)
- 2010: First cellular immunotherapy approved for prostate cancer (Provenge)
**Immunotherapies for cancer**

- **Discovery of dendritic cell**
- **Tumor-specific monoclonal Abs**
- **Adoptive T-cell immunotherapy**
- **IFN-α as adjuvant therapy for melanoma**
- **BCG approved for bladder cancer**
- **Discovery of checkpoint inhibitors**
- **First immunotherapy approved for prostate cancer (sipuleucel-T)**
- **Pembrolizumab and nivolumab approved for advanced urothelial carcinoma**
- **Pembrolizumab and nivolumab approved for advanced melanoma**
- **Atezolizumab approved for advanced urothelial carcinoma**
- **Nivolumab approved for RCC**
- **Nivolumab approved for HL**

**Timeline**

- **1970s**: Immune component to spontaneous regressions in melanoma
- **1980s**: First tumor-associated antigen cloned (MAGE-1)
- **1990s**: IL-2 approved for RCC and melanoma (US)
- **2000s**: First checkpoint inhibitor (ipilimumab) approved for advanced melanoma
- **2011**: First immunotherapy approved for prostate cancer (sipuleucel-T)
- **2014**: Nivolumab approved for NSCLC
- **2015**: Pembrolizumab approved for PD-L1+ NSCLC
- **2016**: Atezolizumab granted Priority Review for PD-L1+ NSCLC