AOS in WALES - Our overall objective is that cancer patients in Wales should have access to safe, knowledgeable and appropriate care whichever team or point of care they are admitted to. In line with the best in the UK.
Key developments in Cancer Drugs

- 1953’s Chemotherapy –
  - 1960 Cured solid tumours – Germ cell and lymphoma
  - Useful adjuvant & palliative role in Breast, Bowel

- 1998’s – Personalised Medicine
  - 1998 - Trastuzumab in Breast Cancer
  - 2001 - Imatanib in GIST

- 2011 – Immunotherapy
  - 2011 - Ipilimumab
  - 2014 – Pembrolizumab
New treatments- New toxicity

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

BACKGROUND
An improvement in overall survival among patients with metastatic melanoma has been an elusive goal. In this phase III study, ipilimumab—which blocks cytotoxic T-lymphocyte-associated antigen 4 to potentiate an antitumor T cell response—administered with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously treated metastatic melanoma.

METHODS
A total of 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (117), or gp100 alone (130). Ipilimumab, at a dose of 10 mg per kilogram of body weight, was administered with or without

RELATED ARTICLES

EDITORIAL
Treating Cancer by Targeting the Immune System
August 19, 2010 by P. N. Hwu

DIABETES FROM IPILIMUAB IN MELANOMA
December 2, 2010

CORRECTION
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma
September 23, 2010

MORE IN

Treatments in Oncology + Skin Cancer
Research - August 19, 2010 -
Mode of action of Ipilimumab

- **Ipilimumab** is an antibody that works to activate the immune system by targeting **CTLA-4**, a protein receptor that downregulates the immune system.

- **Pembrolizumab** is an antibody that binds & blocks activity of **PD-1**, programmed cell death protein on lymphocytes.

- **Cytotoxic T lymphocytes** (CTLs) can recognize and destroy cancer cells. However, an inhibitory mechanism interrupts this destruction. **Ipilimumab/PD-1 inhibitors** turns off this inhibitory mechanism and allows CTLs to function.

- Toxicity is secondary to dysregulation of immune system.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>EMA/FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Metastatic melanoma, Adjuvant therapy stage III melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Metastatic melanoma, 2nd line metastatic NSCLC</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Classical Hodgkin’s disease*</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Recurrent or metastatic SCCHN*</td>
<td>EMA + FDA</td>
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<tr>
<td></td>
<td>Locally advanced or metastatic UCC</td>
<td>EMA + FDA</td>
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<tr>
<td></td>
<td>Metastatic melanoma, 2nd line metastatic NSCLC (PD-L1 ≥ 18%)</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>1st line metastatic NSCLC (PD-L1 ≥ 50%)</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Classical Hodgkin’s disease</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Locally advanced or metastatic UCC</td>
<td>FDA</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Locally advanced or metastatic UCC</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Metastatic Merkel cell carcinoma</td>
<td>FDA</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Locally advanced or metastatic UCC</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Metastatic melanoma</td>
<td>FDA</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Locally advanced or metastatic UCC</td>
<td>FDA</td>
</tr>
</tbody>
</table>

*Auto-HSCT, autologous hematopoietic stem cell transplantation; chL, classic Hodgkin's lymphoma; CRC, colorectal cancer; dMMR, deficient MMR; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MMR, DNA mismatch repair; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; UCC, urethral carcinoma.
New challenges

Monthly Attendances For Newly Approved Immunotherapy Treatments (Feb 16 - Jan 20)
What are the common toxicities of Ipiilmumab?

1. Diarrohea, skin rash and impaired cardiac function?
2. Diarrohea, nephritis and hepatitis?
3. Diarrohea, skin rash and sepsis?
4. Diarrohea, hypophysitis and hypothyroid?
5. Diarrohea, hypophysitis, and sepsis?
What are the common toxicities of Ipilimumab?

- Diarrhoea, hypophysitis and hypothyroid?
- Most common toxicities are skin rash, diarrhoea, endocrine (hypophysitis, hypo/hyper thyroid, DKA) and hepatitis.

Incidence of toxicity in phase 3 clinical trial
Grade 1-2 (mild) toxicities occur in 60-85% of patients
Grade 3-4 (moderate to severe) toxicities occur in 10-30% & 2% mortality in first phase 3 trial

Outside clinical trial (576pts) - 85% experienced toxicities
Early recognition key to minimise complications

Unless an alternate etiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and Ipilimumab related.

Systemic high-dose corticosteroid (+/- immunosuppressive therapy)

Rarely onset may be months after the last administered Ipilimumab dose.

Diagnosis: 67 man

1) Stage 4 melanoma with lung metastasis (Jan 2015).

2) Treatment: Ipilimumab completed May 2015.

3) Subtotal colectomy for perforated sigmoid colon 4.7.15.

4) Bilateral pulmonary emboli in branches of left and right pulmonary arteries.

Figure 1. Timing of occurrence of immune-related adverse events following ipilimumab treatment. Reprinted from [86] with permission. © 2012 American Society of Clinical Oncology. All rights reserved.
How to manage toxicity

- **Consider** the diagnosis e.g. may be non specific – fatigue – check early am cortisol
- Remember toxicity may occur months later (adjuvant)
What is the cost of an ‘average course’ of combination immunotherapy for melanoma for 6 months?

1. < £25,000
2. < £50,000
3. < £100,000
4. < £200,000
5. > £200,000
What is the cost of an ‘average course’ of combination immunotherapy for melanoma for 6 months

110kg man currently on treatment at VCC, on treatment for ~ 9 months, receiving ongoing treatment

Drug costs - £164 000

Drug cost of a cycle of chemotherapy ~ £20-30
Cancer Survival - Living longer with metastatic disease

Cohorts of patients living for ‘lots’ years
- Breast Cancer (15-22% survive > 5 years)
- Ovarian Cancer – 39% survive >5 years
- Melanoma – 20-30% survive > 5 years

Cohorts patients living for ~ 2 years
- Colorectal Cancer ~ median survival around 2 years.
- Lung Cancer ~ variable

Limited progress ~ survival less than a year.
- Pancreatic
- Oesophageal gastric
- Cancer Unknown primary
- Cholangiocarcinoma
HOW AND WHEN CANCER PATIENTS ARE DIAGNOSED

% OF PATIENTS DIAGNOSED

STAGE WHEN DIAGNOSED

Via national screening programmes: 6%
By urgent GP two week wait referral for suspected cancer symptoms: 34%
By routine GP referral: 25%
In an emergency, via emergency GP transferral to hospital, as a hospital patient, or via A&E: 21%
Hospital in or outpatient: 11%
Unknown data: 3%

Source: National Cancer Intelligence Network, data for England 2012-2013

LET’S BEAT CANCER SOONER

cruk.org

Velindre Cancer Centre
Canolfan Ganser Feliandre
HOW AND WHEN BOWEL CANCER PATIENTS ARE DIAGNOSED

% OF PATIENTS DIAGNOSED

<table>
<thead>
<tr>
<th>Method</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Via national screening programme</td>
<td>10%</td>
</tr>
<tr>
<td>By urgent GP two week wait referral for suspected cancer symptoms</td>
<td>30%</td>
</tr>
<tr>
<td>By routine GP referral</td>
<td>24%</td>
</tr>
<tr>
<td>In an emergency, via emergency GP transferral to hospital, as a hospital patient, or via A&amp;E</td>
<td>24%</td>
</tr>
<tr>
<td>Hospital in or outpatient</td>
<td>10%</td>
</tr>
<tr>
<td>Unknown data</td>
<td>2%</td>
</tr>
</tbody>
</table>

STAGE WHEN DIAGNOSED

<table>
<thead>
<tr>
<th>Early (Stage I)</th>
<th>Late (Stage IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37%</td>
<td>8%</td>
</tr>
<tr>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>6%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Source: National Cancer Intelligence Network, data for England 2012-2013

LET'S BEAT CANCER SOONER cru.k.org
Evidence 1: countries where GPs are more willing to test have better cancer outcomes
International comparisons - crude colonoscopy rates per 1,000 in 2010/11
How Multidisciplinary Diagnostic Centres could improve early cancer diagnosis.

You are unsure of the correct dose of steroids for managing a patient with likely metastatic spinal cord compression. Do You?

1. Try to find the yellow ‘post it note’ you stuck on your office wall
2. Ask you favourite ‘Whats app’ group?
3. Quickly find the protocol on your hospital website?
4. Its time to go to the pub anyway and your friend might know.
5. You use the Acute oncology Support App?
The support tool for Cancer Emergencies

Download for free now on iOS and Android
Add animation please
Promote best evidenced based practice

Agreement across Wales – minimise variation

Promote early involvement AOS teams
Things to consider

Do not transfer unnecessarily patients with MSCC who are too frail or unfit for specialist treatment.

If possible, discuss patients with suspected MSCC, a poor performance status and widespread metastatic disease with their primary tumour site clinician and/or senior clinician and/or palliative care before any urgent imaging or hospital transfer.

If possible urgently discuss patients with suspected MSCC who have been completely paraplegic or tetraplegic for more than 24 hours with their primary tumour site clinician and/or senior clinician and/or palliative care before transfer.

Things to consider

If patient is on immunotherapy, toxicity can rapidly become life threatening - seek expert advice early.

Follow the Immunotherapy Guideline below

IMMUNOTHERAPY GUIDELINE
GUIDELINE
Advice for Chemotherapy Patients

GUIDELINE
Complications of Indwelling Lines

GUIDELINE
Diarrhoea following Cancer Treatment

GUIDELINE
Hypercalcaemia of Malignancy
Teaching ....

- Case 1 – patient on Ipilimumab via trial. ALT is 140 and Bilirubin is 40, alkphos is 350, Albumin 27 – please advise


- Case 3 – 37 lady in MAU recent fit and hx of breast cancer 4 years ago. CT head 1 lesion - please advise
Evaluation:- Is this a useful way to engage professional groups?

- Uniform access – no password, no cost to user, no user name, no WIFI, same for all professional groups
- Uniform clear protocols across Wales
  - Could this/ should this extend to rest of UK?
- Uniform & simple – Amazon, ASOS? – Does this increase clinicians use of evidence
- Understanding target user’s – ‘Gamefication’
How to develop an App in NHS?

- Define the remit and who will use app.
- Ensure all content/pathway’s are agreed upfront
- MHRA and drug doses = ? avoid
- Funding – the flexibility required is challenging
- Procurement & contract – commercial.
- It’s all in the design – visual and clear
- Keep decision making team small.
- Social Media expertise