Immunotherapy – changing the way we manage cancer

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Evolving role of the Melanoma CNC

2007
- Generally involved for a short period time
- Supportive – often little hope for patients with advanced disease
- Education – melanoma, treatment options to patients (limited)

2016
- Prolonged involvement
- Supportive – mixed focus
- Education – melanoma and treatment education to patients, nurses, other health professionals melanoma support group
Different patient needs compared with chemotherapy

- irARs can be life threatening - patients must know when to report symptoms
- Possibility of life-long impact of irARs e.g. need for hormone replacement or effects from bowel resection for colitis
- The delayed action of immunotherapy means the tumour may appear to increase in size when imaged before shrinking
- Effect of immunotherapy on pre-existing chronic illnesses
- Side effects can develop after cessation of Rx
Eligibility & Dosing

- Unresectable stage III or stage IV melanoma
- Treatment duration is ongoing if responding & tolerating (anti PD 1)
- Studies ongoing when to stop anti PD1 Rx
- Anti CTLA4 – total of 4 cycles
- Unlike chemotherapy infusion reactions are rare
Patient resources

- Patient Information booklet
- KEYCARE patient app
- Patient Wallet card
Patient & HCP resources

www.eviq.org.au
Consult the Oncologist or Oncology Nurse

**Lung**
- Shortness of breath
- Chest pain
- Coughing

**Hormone gland** (e.g., thyroid, pituitary, and adrenal glands)
- Rapid heart beat
- Weight loss/gain
- Increased sweating
- Hair loss
- Feeling cold
- Constipation
- Your voice gets deeper
- Muscle aches
- Dizziness or fainting
- Headaches that will not go away or unusual headache

**Intestine**
- Diarrhoea or more bowel movements than usual
- Stools that are black, tarry, sticky, or have blood or mucus
- Severe stomach pain or tenderness

**Liver**
- Nausea or vomiting
- Feeling less hungry
- Pain on the right side of your stomach
- Your skin looks yellow
- The whites of your eyes look yellow
- Dark urine
- You bleed or bruise more easily than normal

**Other**
- Feeling tired
- Rash or itching
- Needing to urinate more often
- Feeling more hungry or thirsty
- Changes in eyesight
- Fever
Effective Surveillance, Recognition, and Intervention Minimizes the Potential Impact of ARs$^{1,2}$

Management of ARs

- Proactive monitoring
- Early recognition and reporting
- Appropriate management
- Vigilant follow-up

A team approach – Communication is KEY!
Jody

Social History

- 44 YO single mother of 2 young adults
- Lives in metro area with her partner

Medical History

- PMHx - Carcinoma in-situ cervix 2009, vertigo, depression 2001
- 0.66mm melanoma exc back 2001
- Dec 2012 –subcut nodules back - metastatic melanoma
  BRAF – no codon 600 mutation
- CT - right lung, pelvic adnexal mass and adrenal gland mets
Treatment

- 3/5/12 - Rx with DTIC → no response

- Rare BRAF mutation (pK601E) – application for Mekinist®

- RT to supraclavicular fossa node and anterior neck deposit

- Rv 9/10/12 - RT = no response: Rx with Mekinist®
Treatment cont’d

- 5/12/12 CT - POD – 2\textsuperscript{nd} line chemo Fotemustine – (x 1 episode febrile neutropaenia)

- 13/2/13 - POD – accessing superannuation and fund raising to purchase Yervoy®

- Completed Yervoy®  05/13

- Rv 19/06/13 - CT - good response; no major irARs
Immune related Adverse Reactions (irARs)
- Yervoy

- Occur in 60% of patients
- Grade 3-4 10-15%
  - Colitis
  - Skin
- May be predictive of response??

Weber et.al  JCO 2012
Treatment cont’d

- Jan 2014: ovarian & 2 small bowel mets – BSO and small bowel resection

- 13/02/14: reinducted Yervoy®

- 28/5/14: CT ↑ in disease in one lung met; all others stable → SRS right lung met
Treatment with Keytruda

- 28/7/14 - commenced Keytruda® (MK-3475 on access programme) Baseline TFTs, LFTs and U&Es, FBC, Cortisol, BSL – NAD ECOG = 0

- rv 15/8/14 (cycle 2) – Jo c/o feeling a little “shaky”, sweaty & low grade fatigue
  - TFTs - T3 - 9.4 (3.0-5.5), T4 – 25 (9-19) ,TSH - 0.01 (0.4-4.0) (consist with hyperthyroidism) *

- 22/9/14 CT – mild progression of lung mets

* NB 2.9% incidence of hyperthyroidism reported in trials
Treatment with Keytruda

- rv 23/9/14 (c 4) Jo c/o increased fatigue and intolerance to cold - T4 <5, TSH - 35 → hypothyroid*

- Commenced on Thyroxine 50mcg

- rv 15/10/14 (c 5) – still experiencing fatigue, intolerance to cold and some weight gain. Also mild sinus congestion and manageable “flu like” aches – TSH - 38, T4 – 8

- Thyroxine ↑ 75mcg

- rv 26/11/14 (c 7) – c/o myalgia - prescribed magnesium and nurofen

*NB 7.8% incidence of hypothyroidism reported in trials
KEYTRUDA Safety Information: Time to Onset

![Graph showing the time after initiation of therapy to onset of various immune-mediated adverse events (n = 411) with incidences of hypophysitis (0.5%), hyperthyroidism (1.0%), colitis (1.0%), pneumonitis (2.9%), and hypothyroidism (8.3%) with median time to onset represented.](image)

Adapted from Tepley 2014.6

* Pooled safety data from 411 patients studied across three doses (2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks) during KEYNOTE-001.
Management Algorithm

**Adverse event**

- Any Grade 1 (mild)
- Grade 2 (moderate):
  - Pneumonitis
  - Hypophysitis
  - Nephritis
- Grade 2 or 3 (moderate or severe) colitis
- Grade 3 (severe) hyperthyroidism
- Symptomatic hypophysitis

**Management**

- Supportive care
- Withhold treatment and administer corticosteroids
  (see specific details in KEYTRUDA HCP Guide)
  - Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month

**Follow-up**

- Continue treatment with KEYTRUDA and monitor
- Resume treatment with KEYTRUDA when
  - Adverse event recovers to Grade 0-1 within 12 weeks after last dose
  - Corticosteroid dose is reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
- Permanently discontinue KEYTRUDA when
  - Adverse event does not resolve to Grade 0-1 within 12 weeks after last dose
  - Corticosteroid dosing cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
  - Any severe (Grade 3) treatment-related adverse event recurs

**Hepatitis associated with**

- AST/ALT >3 to 5 x ULN
- Total bilirubin >1.5 to 3 x ULN

**Hepatitis associated with**

- AST/ALT >5x ULN
- AST/ALT increases >50% relative to baseline and lasts >1 week in patients with liver metastasis who begin treatment with moderate (Grade 2) elevation of AST/ALT
- Total bilirubin >3 x ULN

**Grade 2 (moderate) recurrent pneumonitis**

- Grade 3 or 4 (severe or life-threatening):
  - Nephritis
  - Infusion-related reaction
  - Hypophysitis
  - Any Grade 4 (life-threatening) adverse event

**Isolated hypothyroidism**

(Manage other thyroid disorders as described above by grade)

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*Grades are defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

† Pituitary gland inflammation
Treatment with Keytruda

rv 17/12/14 (C 8) – ongoing mod fatigue*

- CT – PR in right lung met & resolution of hilar lymphadenopathy
- TFTs – within normal range - Cont Thyroxine 75mcg daily
- Serum cortisol test (exclude adrenal insufficiency)

rv 7/01/15 (c 9) – fatigue impact significant on QOL– referred to physiotherapy for fatigue management plan. Cortisol & TFTs – within normal limits

*NB: 30.2% incidence of fatigue reported in trials
Treatment with Keytruda

- rv 1/4/15 (C 12) Jo feeling quite well; CT – ongoing response, planning a trip to the UK.

- rv 8/7/15 (c 17) returned from holiday, feeling quite well, considering returning to work.
  - 5kg weight gain – TFTs within normal range ?? to holiday.
  - Itchy rash* on arms, upper chest and back – interfered with sleep and skin broken from scratching - advised re emollients, no soap, anti-histamine and topical steroids

- 10/8/16 –(C34) - CT - stable disease – stopping Rx

*NB: 19.8% incidence of rash & 22.8% pruritis reported in trials
The paradigm shift…..

- Expectation of response is high
- **No** data on length of Rx currently
  - Would you want to stop when side effects are minimal and if it is working?
  - Consequences of 2/3-weekly indefinite treatment

- **Learning to live with advanced cancer**
  - Psychologically – realistic optimism
    - Uncertainty around maintaining tumour responses
    - Potential for ongoing treatment duration
  - Impact on ability to work / finances
  - Living a new “normal” life
    - Side effects may need ongoing intervention/ have long term impact
Take home messages

- Life-changing responses for immunotherapy in metastatic melanoma means it is now “standard of care”
- These immune therapies are a major breakthrough in our approach to cancer treatment
- They require a unique approach to educating patients, monitoring & managing toxicity