Toxicity of new Immunotherapies for Melanoma

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Disclosure slide

• Consultant for MSD, BMS, Amgen, Novartis, Amgen
• Mr I. 72
• 1.25 mm Melanoma on the back in December 2012
• Wide excision + SN in January 2013
  – One positive left cervical SN
• Lymphadenectomy February 2013
  – 34 negative LN: 1N+/35N
• June 2013: 3 Infracentimetric lung and skin metastases
• BRAF WT
• Wait until activation of a clinical trial with an anti-PD1 mAb
• Randomized in Keynote 006:
  – ipilimumab versus pembrolizumab (2 doses)
• Randomized in the ipi arm, and retracted
• Randomized in the BMS 069 trial October 31st 2013
  – ipilimumab versus ipilimumab + nivolumab
• After 4 weeks:
  – prurit grade 1
  – Disseminated grade 2 maculopapular erythematous rash
• After 4 weeks:
  – prurit grade 1
  – Disseminated grade 2 maculopapular erythematous rash

• Topical steroid and therapy continued
• After 8 weeks:
  
  – Vitiligo on the back and around the skin metastases
• After 8 weeks:
  – Vitiligo on the back and around the skin metastases

• Treatment continued
10 weeks

- Deep asthenia
- Headache
- Nausea
- Blood pressure: 100/60 mmHg
• Biology
  – Hyponatremia
  – Low blood and urinary cortisol
  – Low ACTH, testosterone
  – T3, T4, TSH : normal

• Normal hypophyse MRI
• Hormonal compensation
  – hydrocortisone 30 mg/day
  – testosterone 250 mg/3 weeks

• Treatment continued
12 weeks

- Evaluation: Partial response with 75% decrease of the target lesions

- Abdominal pain and diarrhea with 7-9 stools/day last two days

- Colonoscopy
  Gr 3 colitis
  Pathology: epithelial ulceration, cryptitis, lymphytic and neutrophilic rare plasmocytes
• Treatment interruption
• Steroids 1 mg/kg for 10 days
• Infliximab one infusion 5 mg/kg
• Steroids tapered in 8 weeks
• Normal colonoscopy after 10 weeks
Questions

• Can we give anti-PD1 mAb in patients who had severe irAE with ipilimumab?

• Should we give anti-TNF earlier in case of severe colitis?
Ipilimumab Kinetics of irAEs

Toxicity grade

Time (weeks)

- Rash, pruritis
- Liver toxicity
- Diarrhoea, colitis
- Hypophysitis

Weber et al. JCO 2012
Nivolumab Kinetics of irAEs

A. Most common select AEs (≥10%)

- Skin
- Gastrointestinal

B. Less common select AEs (<10%)

- Endocrine
- Hepatic
- Pulmonary
- Renal

Weber et al ASCO 2014
Frequent AE

Incidence per 1000 person-months of all grade and grade 3 to 5 adverse events under immunotherapy using the SAS System. The results include data from the following studies: CA-184-002, KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, CheckMate-037, CheckMate-066, CheckMate-067, and CheckMate-069.
AE « of special interest »

![Graph showing incidence of adverse events](graph.png)
### Vitiligo and clinical response to pembrolizumab

<table>
<thead>
<tr>
<th>Patient</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitiligo (N=17)</td>
<td>3 (18)</td>
<td>9 (53)</td>
<td>3 (18)</td>
<td>2 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non vitiligo (N=50)</td>
<td>4 (8)</td>
<td>10 (20)</td>
<td>1 (2)</td>
<td>35 (70)</td>
<td></td>
</tr>
<tr>
<td>Total (N=67)</td>
<td>7 (10)</td>
<td>19 (28)</td>
<td>4 (6)</td>
<td>36 (54)</td>
<td></td>
</tr>
</tbody>
</table>

*Complete/partial response versus stable/progressive disease/progression progression in patients with and without vitiligo, exact fisher test

**Graphs**

- [A] First 12 wk of treatment
- [B] First 20 wk of treatment

**References**

Hua et al. *JAMA Dermatol*. 2015
Diarhhea/colitis

- More frequent with ipi
- Neutrophilic, lymphocytic infiltrate or both
- Beware of infection (C difficile, CMV)
Endocrine AE

- Dysthyroidisms more frequent with anti-PD-1 than CTLA-4
- Hyper frequently precedes hypothyroidisms
- Hypophysitis induces pan or partial hypopituitaris, more frequent with anti-CTLA-4
- Long lasting AE requiring replacement therapy
Be aware of Rare and serious AE

- 56 year old man
- Anti-CTLA4 adjuvant for resected stage III disease
- One week after last ipi infusion progressive severe meningo-radiculo-nevritis with increased CD4+ Th1 and Th17 T cells in CSF
- HD steroids and iv-Ig
- Recovery after 2 years

Bompaire et al Invest New drugs 2012
General Management of Immune Checkpoints
* Except skin toxicity and endocrine toxicity

Grade (CTCAE v4) → Management → Follow-up

Grade 1
- Continue immunotherapy
- Symptomatic treatment

Grade 2
- Delay immunotherapy*
- Symptomatic treatment

Grade 3-4
- Discontinue immunotherapy*
- Initiate glucocorticosteroids 1-2 mg/kg/day
- Consider hospitalisation

Follow-up
- Frequent monitoring
- If worsening: treat as grade 2 or 3/4

Follow-up
- Resume immunotherapy when symptoms improve to grade 1
- Consider glucocorticosteroids 0.5-1 mg/kg/day if symptoms persist more than 5-7 days
- If worsening with steroids: treat as grade 3/4

Follow-up
- Continue glucocorticosteroids until grade 1
- Taper over at least one month
- If persistence or worsening: consider alternative immunosuppressive therapy