Neuromuscular complications following target therapy in cancer patients

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In the last years, many new drugs have been developed targeting different oncology pathways, overall improving both quality of life and survival in several malignancies.
Nivolumab and Ipilimumab are monoclonal antibodies targeting the immune checkpoint molecules programmed cell death-1 (PD1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) respectively. Their role is to restore antitumor immunity.
Introduction

Vemurafenib and Cobimetinib are respectively BRAF and MEK inhibitors

Imatinib Mechanism of Action
Imatinib is a tyrosine kinase inhibitor
Introduction

• The increasingly widespread use of these therapies is associated to novel toxicities, mainly immune-related adverse events (irAEs), never observed before.

**AEs of BRAF/MEK Therapy (cont)**

- **Dabrafenib/Trametinib**
  - Pyrexia – most common
  - Fatigue
  - Rash
  - GI (diarrhea, nausea, vomiting)
  - Increased AST, ALT
  - Hand-foot syndrome

- **Vemurafenib/Cobimetinib**
  - Diarrhea – most common
  - Nausea/vomiting
  - Rash
  - Increased AST, ALT
  - Fatigue
  - Photosensitivity

**Pyrexia is the most common AE; less skin toxicity than vemurafenib/cobimetinib. Photosensitivity is a major concern; less pyrexia than dabrafenib/trametinib.**

IMATINIB

**Tossicità**: RASH CUTANEO, EDEMA, ESOFAGITE, NAUSEA, CRAMPI MUSCOLARI, DIARREA, TOSSICITA’ EPATICA, CARDIOTOSCICITA’
First case report 73 years-old woman

Past medical history: hypertension - partial thyroidectomy in Graves’ disease - pulmonary thromboembolism

Present medical history: lung adenocarcinoma diagnosed in 2016 - IV stage

Therapy: Carboplatin + gemcitabine → disease progression → Nivolumab + Ipilimumab in July 2017

Ipilimumab was discontinued after 2 cycles due to subclinical myocarditis → Nivolumab was continued alone for 4 cycles

One month after Ipilimumab withdrawal: the patient sub-acutely developed fatigable diplopia with right eye exotropia, hypertropia and ptosis, mild dysphagia, modest proximal upper limbs weakness → stop Nivolumab

Contrast-enhanced brain MRI - Orbit CT - Thyroid hormonal dosages: negative

Repetitive stimulation test: negative

Acetylcholine receptor antibodies (AChR-Abs): high-titre positivity → Myasthenia Gravis

Treatment: pyridostigmine (stopped due to gastro-enteric side effects) and prednisone (25 mg daily): mild improvement

→ IVIg (2g/kg) + prednisone 50 mg daily → almost complete resolution of the symptoms

The patient started a third line therapy with vinorelbine
Past history: worked as welder

Present medical history: pleural mesothelioma diagnosed in December 2017

Therapy: first line Nivolumab + Ipilimumab in February 2018

Two weeks after the first infusion he developed myocarditis (TnI 7 µg/l) and myositis (CPK 9000 UI)

Nivolumab and Ipilimumab were discontinued and steroid therapy was administered (methylprednisolone 120 mg/daily)

Two weeks later: he developed dysphagia, dysphonia, progressive respiratory failure that required NIV and dysautonomia

Brain and Chest CT scan: excluded CNS involvement and tumor progression

CSF analysis: protein 0,23 g/L - 0,3 cells/mmc

AChR-Abs - anti-MUSK-Abs - anti-VGCC-Abs – onconeural-Ab - myositis-Ab: negative

Repetitive stimulation test: incremental response to high frequency stimulation → Lambert-Eaton Myasthenic Syndrome

Treatment: methylprednisolone (120 mg/daily) - Plasma Exchange - IVIg (2g/kg - 3 cycles) - Rituximab (2 infusions, 1000 mg each, 15 days apart) - 3,4-diaminopyridine (10 mg tid): only mild benefit (weaning of NIV during daytime)
Third case 51 years-old woman

**Past medical history:** paroxysmal tachycardia

**Present medical history:** left leg cutaneous melanoma + inguinal lymph nodes micro-metastases diagnosed in 2014

**Therapy:** melanoma excision and lymphadenectomy + Vemurafenib in 2014 - Cobimetinib was added in February 2017

Adverse reactions: urticarial in face and chest and headache

One year after the beginning of the combined treatment: she sub-acute developed forehead corrugator weakness, difficulty in protrude her lips and puffing cheeks, diplopia, drooling

**Contrast-enhanced Brain MRI and Total body PET:** negative

**CSF analysis:** protein 1,280 g/L - 10 cells/mmc (lymphocytes)

**AChR-Abs - anti-MUSK-Abs - anti-VGCC-Abs - onconeural-Abs - anti-gangliosides-Ab:** negative

**NCS:** axonal motor neuropathy with predominant cranial nerve involvement ➔ **Sub-Acute Motor Axonal Neuropathy**

**Treatment:** methylprednisolone (1000 mg x 5 days) with remission
Fourth case 65 years-old man

Past medical history: arterial hypertension

Present medical history: emicolectomy and partial ileal resection for GIST (gastrointestinal stromal tumor) in January 2018

Therapy: KIT exon 11 mutation → adjuvant therapy with Imatinib began in April 2018

Few days after the first administration he developed neck muscles and masticatory weakness: Imatinib was discontinued for 2 days with benefit

Therapy was restarted and 2 days later: right eye ptosis, head drop, dysphagia and respiratory failure that required intubation and ventilation

Brain CT: excluded CNS involvement

AChR-Abs: high-titre positivity → Myasthenia Gravis

Total body CT: no thymoma - no tumor progression

Treatment: pyridostigmine - Plasma Exchange - methylprednisolone (120 mg, tapered): mild benefit

→ IVIg cycle (2g/kg): allowed extubation
Discussion and conclusions

• The exact mechanism of neuromuscular complications is still unclear, but it is strongly thought to be due to autoreactive T-lymphocyte activation

• With regard to immune checkpoint inhibitors:
  • PD-1 is expressed on the surface of autoreactive T lymphocytes
  • PD-1 prevents autoimmunity and maintains immune cell tolerance
  • CTLA-4 is an essential negative regulator of peripheral T cell function
  • CTLA-4 has a crucial role in mediating peripheral T cell tolerance

• The blockade of both PD-1 and CTLA-4 activates autoreactive T cells

• Concerning BRAF and MEK inhibitors:
  • the response to corticosteroids in our patient suggests an immune-mediated effect
  • BRAF inhibitors seem to increase recognition of melanoma cells by a hyperactivated T-cell response
  • Melanocytes and Schwann cells are both derived from neural crest cells and share surface molecules

• Molecular mimicry of surface molecules may result in autoimmune neuropathies
To conclude, we strengthen the relevance of neuromuscular complications in patients treated with new target therapies, because they can become life-threatening if not promptly managed.