New developments in the systemic treatment of melanoma

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Some Melanoma facts

• Incidence worldwide is increasing
  • 160,000 new cases each year
    – More frequent in males and Caucasians
    – Highest incidence rates Australia and New Zealand

• Most new cases cured by surgery

• Metastatic disease
  – Poor prognosis
  – Median survival 6-9 months
  – 48,000 deaths

• Approved treatments last decades
  – Dacarbazine (DTIC)
  – Interleukin-2 (IL-2), high dose, high toxicity

• No effective second line treatment established until…..
Melanoma gives cancer a bad name!

High urgent need for new systemic therapies
Two new treatments

**Immunotherapy**
Monoclonal Antibody targeting CTLA-4
Ipilimumab (Yervoy®)

**Targeted therapy**
B-RAF inhibition
Vemurafenib
Ipilimumab

- Fully humanized monoclonal antibody
- Monoclonal antibodies are big molecules (protein) which all have affinities for the same antigen (IgG1)
- High affinity for CTLA-4 on activated T-lymphocytes
- Is activating the immune system
Ipilimumab

Mechanism of action
A small reminder..........
And now: Ipilimumab……..

Appearance of CTLA4 Following Receptors T-Cell Activation

Dendritic cell

MHC Antigen TCR

CD28

B7

T cell

CTLA-4
CTLA4 Negatively Modulates T-Cell Activation

CTLA4 binds B7 with greater affinity than does CD28 and sends an inhibitory signal to the T cell.
Rationale for CTLA4 Blockade
Releasing a Brake for T-Cell Activation

Antibody to CTLA4 prevents interaction with B7.
Rationale for CTLA4 Blockade
Releasing a Brake for T-Cell Activation

Antibody to CTLA4 prevents interaction with B7 and blocks the inhibitory signal.
Ipilimumab

- Administration: intravenous (with filter)
- dose: 3mg/kg  body weight: in 90 ml NaCl 0,9%
- Infusion rate: 90 minutes
- Scheme:
  - Induction: 4 cycles of 3 weeks
  - Maintenance: every 12 weeks
- CT evaluation after Induction period
- CT maintenance period once in 12 weeks

In case of serious toxicity skip ipilimumab: no dose reductions are allowed!
Safety

Ipiplimumab

Does not

• penetrate the skin
• change the genetic material
• belong to the cytotoxic regimes

For nurse and patient no specific safety procedure is required
Side effects can be caused by an auto-immune reaction

2-8%
Immune related side effects

- Enterocolitis (grade 3/4 up to 16%)
  - Colon perforation / colectomie: 2.5%

- Oesophagitis, gastritis

- Dermatitis (rash) up to 50%

- Thyreoiditis (5%)

- Hypophysitis (5%)

- Pancreatitis (1-2%)

- Hepatitis (<5%)

- Uvietis (1-2%,

Treatment associated mortality: 1%
Gastrointestinal side effects

Symptoms
• Increased bowel movements / onset of diarrhea
• Black, bloody stools
• Abdominal pain, cramping, or bloating
• Inability intake due to nausea or vomiting
• **Colitis**: serious side effect: CTCAE grade 3 of 4
  Danger: perforation!

Interventions
• Loperamide
• Endoscopy
• Grade 3-4 toxicity: stop ipilimumab and start oral corticosteroids
  No restart!
Management Algorithm

- Diarrhea
- Endocrinopathy
- Hepatotoxicity
- Neuropathy
- Suspected immune-related adverse events
Skin related adverse events

Symptoms

• Rash
• Itching

• TEN (toxic epidermal necrolysis) blisters, serious peeling: serious side effect: CTC grade 3 of 4.

Interventions

• Cooling cream
• Aerius tbl 5 mg 1-2 dd / zn clemastine 1 mg before the night
• dermatologist: if necessary dermatocorticosteroids
Hepatotoxicity / Hepatitis

Symptoms
- Increased liver function tests
  CTC grade 4:  - ASAT (> 8x ULN)
               - ALAT (> 8x ULN)
               - Bilirubine (> 5x ULN)
- Icterus /dark urine
- Nausea / vomiting

Interventions
- CTC grade 3-4: Stop ipilimumab
  Start oral corticosteroids

Liver function tests should always be evaluated prior to administration of the ipilimumab!!
Endocrinopathy
inflammation of the pituitary gland

Symptoms

Pituitary - / adrenal - / thyroid gland insufficiency

- Increasing or abnormal headache (> 2 days)
  – or symptoms like sinusitis –
- Malaise
- Lethargy
- Chilly
- Weight change
- Changing of moods
- Forgetfulness
- Dizziness
- Loss of libido

Interventions

Laboratory results: LD, TSH, FT4, ACTH, Cortisol, glucose
If laboratory tests are abnormal: MRI brain
CTCAE grade 3-4: stop Ipilimumab, start oral glucocorticosteroid
Resolve Grade 1: restart is possible
Eye toxicity

Symptoms
• Vision change
  – Blurred vision
  – Double sight
• Eye pain / Pressure behind the eye
• Eye redness
• Uvietis

Interventions
• Ophthalmologist
• Corticosteroids local in the eye
• Oral corticosteroids when fast progression of vision change
Neurologic toxicity

Symptoms

- Less power arm / leg / face
- Rigid, tingling hands/ feet
- Paralysis

Interventions

- Consultation neurologist
Drug related Infusion reaction

CTCAE grade 1
Transient flushing or rash, drug fever < 38°C
decrease infusion rate by 50%

CTCAE grade 2
Rash, urticaria, dyspnoea, drug fever > 38°C
Interrupt infusion. Administer bronchodilators, oxygen if medically indicated.
Reaction resolved or decreased grade 1: restart on 50% infusion rate. Monitor closely!

CTCAE grade 3 and 4
Symptomatic bronchospasm, with or without urticaria, oedema /angioedema, hypotension
Anaphylaxis
Stop infusion immediately! Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, oxygen etc as medically indicated
Respons to Ipilimumab

• Late immunological effect:
  – Evaluation after 4 courses
    • Response sometimes even later
• Response chance 30%
• Response can be sustained

• 1 patient (NKI-AVL) received 2,5 years ipilimumab (10 mg/kg)
Ipilimumab Pattern of Response

- Responses after appearance and subsequent disappearance of new lesions

Pretreatment

July 2006

Wk 20: Regression

Wk 12: Progression

Wk 36: Still Regressing

3 mg/kg ipilimumab q3w x 4

New lesions

Nursing interventions / skills

The nurse plays an important role in recognising side effects in an early stage and manage them!

- **Good and extensive patient education is crucial!**

Knowledge for nurse and patient!
Nursing skills

Side effects management is crucial in ipilimumab treatment

- Record symptoms before, during and after treatment
- Vital signs before, during and after treatments
- Knowledge of drug related infusion reaction
- Knowledge of auto-immune reactions
  - Know when to warn the physician
  - CTCAE grade
- Laboratory evaluation before every treatment
Targeted therapy of melanoma

vemurafenib
B-RAF mutation

- BRAF mutation identified in 50-60% of malignant melanomas
- Correlate with poor prognoses

BRAF: important target!
Vemurafenib (Zelboraf®)
BRAF inhibitor

Small molecule

- Selective inhibitor of the activated oncogenic BRAF proteine
  - Stop signal function of the BRAF pathway
  - Stop cell proliferation

- Response rate 50%

- PFS 6.2 months
“sideway information”
.....target in or out.....

Monoclonal antibodies
• Big molecules
• Target on- or outside the cell surface
• Intravenous therapy

Small molecules
• Target inside the cell
• Oral therapy
Vemurafenib

Oral therapy (continuous)
- Intake 2 dd 960 mg (= 2 dd 4 tbl)
- Every 12 hours, same time each day
- 1 hour prior or 2 hours after a meal
- In case of vomiting: no re-dosing
- 1 Cycle = 28 days
- No period of interruption
- Evaluation after 2 cycles

Do not break, swallow whole
Side effects

- **Dermatologic**
  - next slides

- **Musculoskeletal**
  - arthralgia
  - Myalgia
  - Musculoskeletal pain
  - Arthritis

- **Gastrointestinal**
  - Nausea / vomiting
  - Diarrhea
  - Loss of appetite

- **Laboratory abnormalities**
  - Elevated liver transaminases
  - Elevated bilirubin

- **Fatigue**
Dermatologic side effects 1

- Rash
- Itching
- Warts
- Photosensitivity
- Squamous cell carcinoma
- Keratoacanthoma
- Hyperkeratosis (HFS)
- Dry skin / “sandpaper skin”
- Alopecia

*ASCO 2011 preview, Anna Azvolinski, 16 mei 2011*
Dermatologic side effects 2

Rash
- acneiform rash
- maculopapular rash
- Papulovesculair dermatosis (Grover’s disease)

Itching

Intervention
- Dermatocorticosteroid: Cutivate / Elocon
- Peeling of the skin: Calmurid (hydrocortison/ureum)
- Itching: Aerius 5 mg tbl 1-2 dd or Clemastine 1 mg before sleeping

CTCAE grade 3
Stop vemurafenib until recovery grade 1
Restart with dose reduction

Dermatologist!
Dermatologic side effects 3

**Warts / Filiform warts**
- Some or numerous
- Inconvenient
- Intervention
- Cryotherapy / liquid nitrogen

**Keratoacanthoma**
- Intervention
- Excision
- Histological confirmation needed

**Squamous cell carcinoma**
- Intervention
- Excision
- Histological confirmation needed
Dermatologic side effects 4

Photosensitivity

**Intervention**
Prophylactic sun protection: factor 50 every two hours or every half an hour in case of perspiration or swimming

Intervention sunburn: Flamacine
Dermatologic side effects 5

Hyperkeratosis (HFS)

Intervention
Sports shoes
Topical cream / urea cream
CTCAE grade 3: stop vemurafenib until recovery grade 1
Restart with dose reduction
Every side effect CTCAE grade 3 or 4: Stop vemurafenib until resolve grade 1, then restart with a dose reduction

Start dose
- 960 mg 2 x dd

Levels of dose reduction
- 720 mg 2 x dd
- 480 mg 2 x dd
- 240 mg 2 x dd
Nursing interventions

- Record symptoms and side effects before (!), during and after treatment
- Know when to consult physician or dermatologist

Patient education most important!

Knowledge is safety
Future developments

BRAF V600 mutation positive
• Phase I/II MEK inhibitor
• Phase III BRAF/MEK inhibitors
• Phase I ERK inhibitor
• Phase I P13K/AKT/mTOR inhibitors

BRAF wild type (=normal), NRAS mutation positive
• Phase I MEK inhibitors
• Phase I P13K/AKT/mTOR inhibitors

BRAF wild type, NRAS wild type
• Phase I P13K/AKT/mTOR inhibitors

C-KIT mutation positive
• Phase II nilotinib

Uveal melanoma
• Phase I Oral PKC inhibitor
• Phase II ipilimumab+radiofrequency ablation (RFA)

WINO, Working group Immunotherapy Netherlands for Oncology
Hopeful developments!

Hopeful future
Thank you for the attention

Questions

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Literature

- **Targeting Mutant BRAF in Melanoma: Current Status and Future Development of Combination Therapy Strategies**

- **Current advances and perspectives in the treatment of advanced melanoma**

- **Systemic therapy for metastatic melanoma in 2012: dawn of a new era**

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- **CTLA-4 Blocking Immunotherapy With Ipilimumab for Advanced Melanoma**

- **Ipilimumab: A Promising Immunotherapy for Melanoma**

- **Improving the Therapeutic Benefits of Ipilimumab**

- **Improved Survival with Ipilimumab in Patients with Metastatic Melanoma**