Neue Substanzen bei Kombinationstherapien

New substances in combinational therapies

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New substances in oncology and their combinations

Topics of our talk

- mode of action of new drugs and their combinations
- efficacy
- adverse effects
- Patient counseling

New substances in the cancer treatment

- Immunotherapy (checkpoint inhibitors)
- Targeted agents (tyrosine kinase inhibitors)
Immunotherapy: checkpoint inhibitors

Immune cells (T-cell responses) are regulated through a balance of inhibitory and activating signals.

Tumors cells can inhibit immune cells -> tumor growth

Mechanism of action of Immune therapy (Checkpoint inhibitors): «releasing the brake» -> immune cells recognize tumor.
Checkpoint inhibitors: mechanism of action

Monoclonal antibodies binding on cell surface proteins (receptors or their ligands)

Anti CTLA 4 (on immune cells): Ipilimumab

Anti PD 1 (on immune cell): Nivolumab, Pembrolizumab

Anti PD L1 (on tumor cells) Avelumab, Durvalumab, Atezolizumab

(LAG3, TIM-3-GAL9)
Approval for Checkpoint inhibitors in Switzerland

**Melanoma** (Nivo: monotherapy or combination with Ipi; adjuvant; pembro; 1st line)

**Lung cancer 1st line** (nivo: 1st line; pembro: 1st line if PDL1>50%)

**Lung cancer 2nd line** (pembro)

**Head&neck cancer 2nd line** (nivo)

**Kidney cancer** (nivo: 1st line in combination with Ipi; 2nd line monotherapy)

**Urothelial cancer** (nivo 2nd line; pembro after platinum)

**Hodgkin disease** (nivo after HD/ASCT und brenduximab; pembro after 3 line)

**CRC MSI high**

**Merkel cell carcinoma** (avelumab)
Combinations of Checkpoint inhibitors

Goal: to achieve better response and prolong survival

Costs: higher rates of adverse effects

two different checkpoint inhibitors (Melanoma, lung, renal cell, trials…)

Immunotherapy and chemotherapy (lung, different trials)

Immunotherapy and radiotherapy (trials, some completed)

Immunotherapy and vaccines (melanoma, trials)

Immunotherapy, chemotherapy and anti-VGEF antibody (published)
Combination of pembrolizumab and chemotherapy in patient with head and neck cancer

51 year old female patient, heavy smoker; high alcohol consumption

10/2017:
Squamous cell ca of the floor of the mouth
cervical lymphadenopathy
distant metastases (liver, bones)

12/17:
Pembrolizumab, carboplatin and 5FU (clinical trial)
followed by pembrolizumab for 2 years

8/18: still in remission
Combination of two checkpoint inhibitors (clinical trial)

68 yo male patient, heavy smoker

1/2016:
Laryngeal cancer pT3 pN0 M0
Radiotherapy with 70 Gy and cisplatin

12/16: Pulmonary metastases

Therapy:
*ipilimumab and nivolumab* (clinical trial)

After 2 cycles: Partial response
Combination of pembrolizumab and radiotherapy in patient with recurrent nasopharyngeal carcinoma

2010: chemotherapy (Cis/5FU) followed by RCT (70 Gy); bilateral neck dissection (2011)

2013: diplopia; metastasis of the right occipital condyle and clivus (confirmed)

Chemotherapy (carboplatin, fluorouracil and docetaxel): partial response

2014: progression; infiltration of the cavernous sinus and abducens nerve: stereotactic re-irradiation with docetaxel and gemcitabine

CyberKnife, SD

10/15: progression (skull base, cavernous sinus, Meckel's cave and the internal carotid artery on the right side as well the middle cranial fossa

docetaxel and gemcitabine; SD

1/16 pembrolizumab; SD

6/2016 stereotactic re-re-irradiation (45 Gy)

9/16 Pembrolizumab

progression Doxetaxel and pembrolizuab; SD
Combination of immunotherapy and oncolytic virus (clinical trial Talimogene laherparepvec)

51 year old female patient, no risk factors

6/15
Carcinoma of base of the tongue, pT2pN1 (1/15)
Transoral resection; adjuvant radiotherapy (30x2 Gy)

11/15 Relapse (cervical lympha nodes)

12/15 Chemotherapie (doxetaxel, cisplatin, 5FU)
minor response

1-3/16 Accelerated RT 25x2.5 Gy=50 Gy
Progression

Clinical trial with checkpoint-inhibitor and vaccine, exitus
Adverse effects of checkpoint inhibitors

**Monotherapy vs combination:**
More active in some trials; no benefit in other trials -> higher rates of AE

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N=311)</th>
<th>Nivolumab plus Ipilimumab (N=311)</th>
<th>Ipilimumab (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Grade 3 or 4</td>
<td>Any</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>311 (99.4)</td>
<td>136 (43.5)</td>
<td>312 (99.7)</td>
</tr>
<tr>
<td>Treatment-related adverse event†</td>
<td>257 (82.1)</td>
<td>51 (16.3)</td>
<td>299 (95.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (19.2)</td>
<td>7 (2.2)</td>
<td>138 (44.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107 (34.2)</td>
<td>4 (1.3)</td>
<td>110 (35.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>59 (18.8)</td>
<td>0</td>
<td>104 (33.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>81 (25.9)</td>
<td>2 (0.6)</td>
<td>126 (40.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (13.1)</td>
<td>0</td>
<td>81 (25.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (5.8)</td>
<td>0</td>
<td>58 (18.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>34 (10.9)</td>
<td>0</td>
<td>56 (17.9)</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>12 (3.8)</td>
<td>4 (1.3)</td>
<td>55 (17.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (6.4)</td>
<td>1 (0.3)</td>
<td>48 (15.3)</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>12 (3.8)</td>
<td>3 (1.0)</td>
<td>48 (15.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>27 (8.6)</td>
<td>0</td>
<td>47 (15.0)</td>
</tr>
<tr>
<td>Colitis</td>
<td>4 (1.3)</td>
<td>2 (0.6)</td>
<td>37 (11.8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24 (7.7)</td>
<td>0</td>
<td>33 (10.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (7.3)</td>
<td>0</td>
<td>32 (10.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14 (4.5)</td>
<td>1 (0.3)</td>
<td>32 (10.2)</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>24 (7.7)</td>
<td>16 (5.1)</td>
<td>114 (36.4)</td>
</tr>
</tbody>
</table>

Most common AE:
Rash, Pneumonitis, Diarrhoea, Endocrine

University Hospital Zurich

Combined Ipilimumab and Nivolumab or Monotherapy in untreated Melanoma; Larkin et al, NEJM 2015
Adverse effects of immunotherapy: Skin

Patient with local relapse of head&neck cancer

1st cycle ipilimumab and nivolumab: rash and pemphigoid skin reaction

-> good response to steroids

Discontinuation of Immune therapy (patient’s decision)

-> salvalge surgery

Skin reaction (3 months after last therapy):
response to steroids
Secondary infection
Adverse effects of immune therapy: collitis and pneumonitis

Patient with local relapse of mesopharynx ca

2 cycles with nivolumab monotherapy

Diarrhoea (6-7x day)

- good response to steroids

Patient with local relapse of Ca of floor of the mouth

Combination of nivolumab and anti-LAG3 (clinical trial)

Cough -> pneumonitis

- good response to steroids
Management of AE of immunotherapy
Protein Kinase Inhibitors

**Tyrosin kinase Inhibitors (TKI):**

Inhibition of kinase domains (intracellular part of receptor) -> blocks cell signalling

Different receptors: EGFR, HER2..

TKIs: gefinitib, erlotinib, osimertinib, lapatinib

lung ca, renal ca, mama ca, CML..

**Serine/threonine kinase inhibitors:**
(BRAFi, MEKi)

Melanoma, Thyroid ca
Braf inhibitors (monotherapy)

vemurafenib, dabrafenib

Active in melanoma with brafV600 mutations

BUT

short remissions

Skin AE
Combination of Braf/mek inhibitors

Results:

- Combination of braf/mek inhibitors compared to monotherapy braf i
  - improves response and survival
  - Less AE!
Concept of nurse consultation at the comprehensive cancer center Zurich (CCCZ)

- Start of new treatment or change of treatment: management of possible side effects, schedule, self-care

- Venous access: peripheral access vs central line (peripheral arm assessment)

- Psychological support: distress thermometer, referral to specialists if required

- Basic dietary advice to prevent weight loss

- Referral to the institute of complementary medicine if required and requested
Possible patient pathway

Red flags for patients receiving immunotherapy

Patients need to know when to contact the medical team, as early assessment is crucial:

- Diarrhoea or bowel movements more frequent than usual
- Abdominal pain
- Skin changes such as rash or pruritus
- Shortness of breath
- New or worsening symptoms of cough

->NO SELF-TREATMENT<-

Dermatological reactions during immunotherapy

Ipilimumab (Yervoy®), CTLA-4 antibody

Very common (≥ 10%):
- Exanthema
- Pruritus

Common (≥ 1% to < 10%):
- Xerodermia (skin dryness)
- Hypopigmentation (Melanoma patients)
- Generalised mucositis

Occasional (> 0.1% to < 1%):
- Conjunctivitis
- Intensified lacrimation/inflammation of the lacrimal gland
- Change of hair colour

Nivolumab (Opdivo®), PD-1 antibody

**Very common (≥ 10%):**
- Xerodermia (skin dryness)/Pruritus

**Common (≥ 1% to < 10%):**
- Exanthema
- Hypopigmentation

**Occasional (> 0.1% to < 1%):**
- Conjunctivitis

Pembrolizumab (Keytruda®), PD-1 antibody

Very common (≥ 10%):
- Pruritus
- Exanthema

Occasional (> 0.1% to < 1%):
- Hypopigmentation (Melanoma patients)
- Conjunctivitis
- Intensified lacrimation/inflammation of the lacrimal gland
- Change of hair colour/depigmentation of eye lashes and hair

Atezolizumab (Tecentriq®), PD-L1 antibody

**Very common (≥ 10%)**: 
- Exanthema
- Pruritus

Reference: www.compendium.ch
Avelumab (Bavencio®), PD-L1 antibody

**Common (≥ 1% to < 10%):**
- Exanthema
- Pruritus

Reference: www.compendium.ch
Durvalumab (Imfinzi®), PD-L1 antibody

Very common (≥ 10%):
- Exanthema
- Pruritus

Common (≥ 1% to < 10%):
- Oral Mucositis

Reference: www.compendium.ch
Basic care advice

Exanthema

- Early patient education
- Avoiding sun exposure and use of sun protection (SPF > 30)
- Skin cleaning with mild, soap free, pH-neutral wash lotions and wash syndets (e.g. Lubex®, Der-med®, Procutole® or with cleaning oils (e.g. Excipial® Balmandol)
- Face: once a day use of O/W systems (e.g. Excipial® U Hydrolotio)
- Whole body: consequente alcohol and perfume free, moisturising skin care with or without urea (e.g. Excipial® U Lipolotio)
- Careful tapping of the skin after washing
- Avoiding exposure to toxic-irritant substances on the hands
- Lowering the room temperature and increasing air moisture (humidity)
- Face: only dry shave and no use of aftershave
Skin

- During the dry phase to use urea-containing lipolotion in an adequate amount (100gr lotion to use within 10 days) after showering or bathing (e.g. Excipial® U Lipolotion, Eucerin® 10% Urea Lotion, Bepanthol® Körperlotion, Antidry® calm Lotion)
- Skin cleaning with mild, soap free, pH-neutral wash lotions and wash syndets or with cleaning oils (see products on previous slide)
- High room humidity
- To apply consequent sun protection

Scalp

- Lotions can as well be used for the scalp to treat itchyness (e.g. Excipial® U Hydrolotion)
- Hair care with mild shampoos (e.g. Johnsons® Baby Shampoo, Lubex hair®, Crimanex® Shampoo)
- To blow dry hair with cold or room temperature air
- To apply consequent sun protection
Changes of the skin pigmentation and photosensitivity

- Early patient education

- To avoid sun and sun beds to exposed skin areas (i.e. face, ears, neck, arms and hands), to wear thickly woven clothes, if required to use UV-impermeable foils on windows

- Sun protection products against UV-A and UV-B rays with high sun protection factor (> 30)

- To avoid dry skin, itchyness and scratch marks or pressure marks on the skin (e.g. from wearing rucksacks or bras)

- Good skin moisturising

Hair depigmentation

- No prevention possible

- Early patient education

- To use gentle hair tint from the hair dresser if the depigmentation is cosmetically disturbing
Intensified lacrimation/inflammation of the lacrimal gland

Basic care
- Initial eye assessment
- Eye hygiene
- To avoid mechanical and cosmetical eye irritation
- Sun glasses during sun exposure
- To treat conjunctivitis

Interventions
- Reassessment
- Continuation of the basic care
- Referral to ophthalmologist (in case of inflammation urgent referral required)
Conjunctivitis

Basic care
  - Initial eye assessment
  - To avoid exposure to other patients with conjunctivitis (avoid contamination)
  - To avoid allergens
  - To avoid eye drops with potential surface-toxic properties (preservatives, especially benzalkonium chloride)
  - To avoid using moisturising eye drops over the expiration date

Interventions
  - Reassessment
  - Continuation of the basic care
  - To use moisturising eye drops/gels in incomplex cases
  - Referal to ophthalmologist in purulent cases, sticky coated eyes, treatment refractory or prolonged cases
− Early patient education with regards to symptoms and management
− To clean teeth at least twice daily during 2 minutes with a soft tooth brush
− Electrical or ultrasound tooth brush is allowed if the patient is used to it
− The use of dental floss is allowed if the thrombocytes or neutrophil granulocytes are within range
− To rinse the mouth at least 4 times daily with water or salt water (1 tea spoon of salt in 1 litre of water)
− To moisturise the lips (e.g. Bepanthen® Nasensalbe)
− To drink at least 1.5 – 2 litres daily to avoid dry mucosa and lips
− To refrain from alcohol and tabacco as they both irritate the oral mucosa additionally
− To avoid sour, spicy and crusty foods which could potentially damage to mucosa
− To avoid mouth washes from the pharmacy or drug store, since they normally contain alcohol which can dry out the mouth additionally

Onkologiepflege Schweiz (OPS) have created a patient information leaflet called «changes to skin, mucosa, hair and nails during medical anticancer treatment» (Original: «Veränderungen an Haut, Schleimhäuten, Haaren und Nägeln während der Krebsbehandlung mit Medikamenten»).

This leaflet gives an overview about possible dermatological side effects and recommendations to prevent these.
Thank you for your attention
Any questions?