Malignant melanoma clinical aspects

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Malignant melanoma

- **Definition:**
  - arise from melanocytes
  - the most serious oncological problem
  - incidence and mortality rise
  - affects relatively younger population
  - great tendency to early metastasis
  - the only treatment is the early recognition and the surgical excision
  - advanced tumor responds poorly

Epidemiology

- Incidence dramatically increases

- Australia: 50/ 100 000
- Europe: 15-20/ 100 000
- Mexico 40 /100 000 (above 2000 m)
- Hungary 2110 / year (2009)
Incidence of Malignant melanoma in Hungary 2008 (male)

Number of incidence and mortality of male MM patients / 100 000 males


Hungarian Cancer Inst. 2009.
Incidence of Malignant melanoma in Hungary 2008 (female)

Number of incidence and mortality of female MM patients / 100 000 females

Hungarian Cancer Inst. 2009.
Epidemiology

- F>M
- Age affected
  - ~40-60 years (increased 20-30 y)
- Among blacks is very rare, mainly localized subungual, on palm, soles and mucosa
Epidemiology

- Life time risk in USA
  - 1935  1:1500
  - 1980  1:250
  - 2000  1:70
  - 2010  1:50

- Life time risk in Australia
  - 2000  1:60
Etiology and pathogenesis

- The exact cause is unclear
- Genetical and environmental factors
- 10% show familial occurrence
- Iatrogenic or acquired immunosuppression
  - Melanoma risk increased 3x
Etiology, pathogenesis

- UV irradiation - UVA-pirimidin dimers
  - Single, high dose exposition
  - Sunburns, mainly in childhood
    - >3 sunburns, melanoma RR increased 3x

- Presence of nevi
  - 25-40% of melanoma arise from nevi
  - >50 nevi melanoma risk is 5X higher
  - Atypical or dysplastic nevi, dysplastic nevus syndrome
  - Giant congenital nevi
  - Mechanical irritation and repeated damages

Etiology, pathogenesis

- Chromosomal alterations:
  - 9p21- cell cycle regulation (CDK2A)
  - BRAF és RAS mutation
  - Raf-MAPK kinase-ERK (RAF-MEK-ERK)
  - PI3K/PTEN/AKT pathway (leads to apoptosis blockade)
  - Interaction between tumor cells and stroma

Etiology, pathogenesis

Familial incidence,

- Red hair and freckles in skin types I-II,
- both parents have melanoma the child risk for melanoma 100%
- 10% of melanoma are familial
Precursor lesions

- Congenital nevi
  - mainly giant and deeper type

- Dysplastic nevi

- *In situ* melanoma (lentigo maligna)

- Without precursor lesion, de novo

Clinical form of malignant melanoma

- Lentigo maligna melanoma 1%
- SSM 70%
- Nodular melanoma 21%
- Acrolentiginous melanoma 5%
- Non classifiable 3%
  (mucosal, amelanotyc, desmoplastic)

Lentigo maligna melanoma 1%

The most favorable prognosis

Grows very slowly

Mainly on the face of elderly patients,

Superficial spreading melanoma (70%)

Favorable prognosis
Long horizontal growth phase
In vertical phase bad prognosis

SSM with vertical growth
The prognosis is worse

Nodular melanoma 21%

The 2nd most frequent type
Early tendency to vertical growth
Gives early metastases

Acral lentiginous melanoma 5%

Palms, soles, subungual
Poor prognosis

Hutchinson sign

29 April 2010.
Amelanotic melanoma

R. P. 71 év


He (100x)
Suspicion of malignant changes

- Asymmetry
- Border (irregular)
- Color (multiple)
- Diameter (>6mm)
- Elevation

Malignant melanoma Dermoscopy

Irregular pigment dots

Multiple colors

Malignant melanoma dermoscopy

Irregular pigment streaks

Bluish black color, with milky glass shadows

The new diagnostic possibility

- Digital dermoscopy - dermoscopy
- 22 MHz ultrasound investigation
- MRI

By lymphatic way

By hematological way

Pulmonal
Cerebral
Liver
Skin

Differential diagnosis

- Nevi
- Dysplastic nevi
- Pigmented basal cell carcinoma
- Verruca seborrhea
- Pyogen granuloma
- Hemangioma
Clinical prognostic factors of melanoma

- Clinical type (LMM, SSM, ALM, NM)
- Tumor location (extremities, BANS region)
  - BANS: back, arm, neck, scalp
  - Multi-directional lymph drainage
- Age of patients (prognosis worsens with age)
- Sex (male is unfavorable)
- *Worse prognosis*
- Ulceration
- Regression
- Bleeding
Histological prognostic factors

- Tumor thickness
- *(Invasion level-)* mitotic rate $<; > 1/mm^2$
- *(Number of mitoses HPF)*
- Micro-ulceration (important in stage I-II-III)
- Lymphocytes infiltration (lack of infiltration)
- Satellites, in transit metastases
- Vascular invasion

New findings and definitions in the new version of staging

Stage I and II

- In patients with localized melanoma most dominant factors
  - Tumor thickness
  - Mitotic rate (mitosis/mm²)
  - Ulceration
Survival rate comparing the different T categories and stage I and II

![Graph showing survival rate comparison]
New pronostic parameter
The mitotic rate

- Mitosis/mm² mitotic rate $<; > 1$/mm²

- Mitotic rate replaces level of invasion as a primary criterion for T1b melanoma


New findings and definitions in the new version of staging **Stage III.**

- Determinant by patients with regional metastases
  - Number of metastatic nodes
  - Tumor burden
  - Ulceration of the primary melanoma
- All patients with microscopic nodal met., regardless of tumor burden classified as **Stage III.**
- Micro metastases detected by immunohistochemistry are specifically included (HMB45, Melan-A/MART )

Balch CM. J Clin Oncol. 27:6199-6206 2009
Survival rate comparing the different N categories and stage III

29 April 2010.

Survival curves with metastatic melanoma at distant site and serum LDH level

Survival Rate (proportion)

Time Since Stage IV Diagnosis (years)

Survival Rate (proportion)

Time Since Stage IV Diagnosis (years)

Balch CM. J Clin Oncol. 27:6199-6206 2009
Disseminated metastases
Stage IV.

- The determinant is the location of metastases
- Level of se LDH
- se S100
- Circulating tumor cells
**NEW 7th TNM classification AJCC 2009.**

**pT**

<table>
<thead>
<tr>
<th>pT</th>
<th>Tumor thickness</th>
<th>Ulceration</th>
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| T1  | ≤ 1,0 mm       | a: without ulc. *(Clark II/III)*  
|     |                | mitosis<1/mm² |  
|     |                | b: with ulc. or *(Clark IV/V)*  
|     |                | mitosis<1/mm² |  
| T2  | 1,01 – 2,0 mm  | a: without ulc.  
|     |                | b: with ulc. |  
| T3  | 2,01 – 4,0 mm  | a: without ulc.  
|     |                | b: with ulc. |  
| T4  | > 4,0 mm       | a: without ulc.  
|     |                | b: with ulc. |  

TNM classification pN

Number of metastatic lymph node

N1  1  lymph node

N2  2-3 lymph node

N3  ≥ 4 lymph node
    lymph node conglomerate
    or in transit/satellite metast.
    with lymph node metast.

TNM classification pM

Sites

Mo  No distant metastasis

M1a  Distant skin, subcutaneous
     nodal metastasis

M1b  Lung metastases

M1c  All other visceral metastases
     Any distant metastases

Tumor mass lymph nodes

a: micromet
b: macromet.
a: micromet.
b: macromet
  c: in transit/satellite
  met. without lymph nod

LDH

normal

normal

elevated
## Anatomic stage Groupings for cutaneous Melanoma

<table>
<thead>
<tr>
<th>Clinical staging</th>
<th>Pathologic staging</th>
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<td>IV.</td>
<td>Any T</td>
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The role of histology in the diagnosis of malignant melanoma

- Melanocytic vs. non melanocytic lesion
- Benign vs. malignant pigmented lesion
- In situ vs. invasive tumor
- Characteristics of primary tumor
  - Histological type of melanoma
  - Tumor thickness
  - Mitotic rate
  - Ulceration
  - Lymphocytic infiltrations
  - Vascular or lymphatic invasion
- Specification of the lymph node status

Treatment of malignant melanoma

Primary tumor pT

- Plastic surgical excision
  - Electric knife
  - To fascia of muscle
  - Safety margin depends on the tumor thickness
    - In situ melanoma (pT\textsubscript{is})   0,5 cm
    - 1-2 mm (pT1-2)   1,0 cm
    - >2 mm (>pT3)  2,0 cm

INCISIONS BIOPSY PROHIBITED

Loco-regional management

- Sentinel lymph node biopsy
  - Indispensable
  - Together with primer tumor surgery
  - or within 2-3 weeks later
  - general anesthesia
- Indications:
  - tumor < 1mm, ulceration, >1 mitosis/mm² (lev. IV/V) regression (pT1b)
  - tumor >1 mm (pT2)
- Regional lymph node dissection Stage III.
  - by histological positive sentinel lymph node
  - palpable or detectable lymph node

Uncertain diagnosis of MM

- Excision with 5 mm safety margin
- Histological examination
- Further surgical treatment
  - Depends on the tumor thickness

INCISIONS BIOPSY PROHIBITED

Adjuvant interferon α treatment

Interferon alpha 2a, 2b

- Effects
  - Antiproliferative
  - Immunomodulatory
  - Inhibition of angiogenesis
  - Increase MHC1 antigen expression
  - CD4+ T cells infiltration into melanoma

- Response rate 15% (5% CR)
- Median response duration 6-9 month

(Agarwala SS. 1996)

Adjuvant treatment of melanoma

- **Indication**
  - II. A, B, C, (pT2b, pT3, pT4)
  - III. A, B, C after tumor resection

- **Mode the administration**
  - **Low dose**: 3 x 3 MU/week sc. for 18 months prolong the PFS (Grob. Phehamberger)
  - **Intermediate dose** 3x9-10MU/week sc. 12 months
  - **High dose**
    - 20MU/m² iv. 5x/week 1 Month (induction)
    - 10 MU/m² sc. 3x/week 11 Months (maintain)
  
  Significantly prolong the OS (Kirkwood)

Chemotherapy

- Indication: stage IV
  5 years survival 6%
  main survival 7,5 months

- Monochemotherapy
- Polychemotherapy

Monochemotherapy

- Distant metastases
- *Dacarbasin (DTIC)*
- Remission rate 10-25% (CR 5%)
- Median response duration 5-6 month
  - < 2% survive 2 years (Comis R. 1976)
New drug: Temozolomid

- imidazotetrazine
- *equivalent* with DTIC for survival, response rate and toxicity,
- *superior* for progression free survival and quality of life
- Efficacy in CNS metastases
  - Better blood-brain barrier penetration than DTIC

(Middleton MR. 2000)

New drug: Fotemustin

- The most active nitrosourea in metastatic melanoma
- Cross the blood-brain barrier
- Response rate 20-25%
- CR 5-8%
- The first significant efficacy in brain metastases
  
(Khayat D 1994)

- Not universally available
Polychemotherapy

Many side effects, no better clinical efficacy as DTIC

( Huncharek M. 2001 meta-analysis)

Bio-chemotherapy

don’t prolong OS

Falkson CI. 1998.
Immunotherapy IL2

- High dose treatment in stage IV melanoma
- Response rate 15-20%
- CR 4-6%
- 1998. FDA approved in unrespectable cases
- Severe toxicity
- Usage effective in selected patient groups
- Low - dose treatment is ineffective

(Atkins MB, 1997, 1999,

29.April 2010.)
Radiations treatment  Stage III, IV

- Palliative treatment
  - Vascular invasion
  - Multiple lymph node metastasis with capsule involves
  - Cerebral metastases
  - Symptomatic treatment

- Treatment modalities
  - Whole brain irradiation
  - Stereo-taxis irradiation
  - After loading treatment
  - Electron radiation

Special treatment modalities

- hyperthermic Isolated limb perfusion,
  - In case of isolated limb metastases
- Chemo-embolisation of liver
New treatment modalities and future
● Melanoma intrinsic drug resistant tumor
● Melanocytes acquire further mutation
● Multiple signal transduction pathways are aberrant (PIEK, MAP, nFkB)
● Enhanced cell survival
● The targeted treatment, use small molecule inhibitors reducing the treatment resistance
New treatment modalities and future

- Anti CTLA-4 antibodies
- BRAF inhibitors
- Pro-apoptotic agents
- Anti-angiogenic treatment
- mTOR inhibitors
- Proteosoma inhibitor
- MEK inhibitors
Cytotoxic T- Lymphocyte Associated protein – 4 (CTLA-4)

- CTLA 4 ag critical immuno-modulatory molecule
- Expressed on activated and other regulatory T- cells
- Dow-regulation of T cell activation

Anti CTLA-4
- Enhance T cell dependent immunity

Anti CTLA-4

Monoclonal antibodies anti-CTLA-4

- ipilimumab
- tremelimumab

- Phase II/III trials
  
  - the median overall survival increased to 1 year of 25-35% for patients stage 3-4 (O’Day SJ. 2008)
  
  - The treatment related toxicity is significant with 43% grade III/IV, autoimmune –mediated manifestations, which appeared dose dependent (Phan GQ. 2003)
BRAF inhibitors
Sorafenib

- Small molecule
- Multi tyrosin kinase inhibitor
- Inhibit cell proliferation by targeting MAPK pathway at level of RAF kinase
- Phase I/II trial well tolerated as single agent

(Eisen T. 2006, Strumber D. 2007)

- Combination with DTIC or temozolomid encouraging in PFS

(Eisen 2007, McDermott DF. 2008)

Anti-sens BCl2 Oblimerzen

- Anti Bcl-2 antisense
- Phase III trial combination with DTIC
  - Response rate increasing
  - Improve PFS
  - Improve median OS - but not significant
  - Efficacy is higher in patients with normal level of LDH (Bedician AY. 2006)
Anti-angiogenic treatment

- **Semaxanib**
  - selective inhibitor of VEGFR-2
  - and Kit receptor kinase
  - In phase II trial is well tolerated *(Peterson AC. 2003)*

- **Bevacizumab**
  - Monoclonal antibody against VEGF-A
  - Block its binding to receptor
  - Phase II trial minimal toxicity and prolonged disease stabilization *(Vaker KA: 2007)*
mTOR inhibitors

- Inhibition of signal transduction pathways (PI3K/PTEN/AKT)
- CCL-779 hasn’t sufficient antitumor activity as a single agent
- Phase I trial in combination with low dose INFα well tolerated, an potentially active
  - Direct antitumor
  - Antiangiogenic effect (Dutcher JP. 2003)

Proteosoma inhibitor
Bortezomib

- Dipeptidyl boronic acid analog
- Potent and reversible proteosoma inhibitor
- Phase II trial shows infectivity and toxicity as single agent (Markovicz SN. 2005)

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MEK inhibitors

- PD0325901 (Phase I.)
- AZD6244 (Phase II.)
- BRAF mutant melanomas may be sensitive to this agent
- Side effects retinal vein thrombosis (Dummer R. 2008)
Thalidomide (lenalidomide)

- Immuno-modulatory
- Anti-angiogenic
- Anti-proliferative
- Pro-apoptotic properties
- Phase II trials shows
  - Low efficacy of TMZ, thalidomid and WBRT in treatment of CNS metastatic melanoma
  - DTIC+ thalidomid activity is insufficient
Take home message

- The only effective treatment the early detection and the appropriate surgical therapy
- The adjuvant treatment more effective in cases of micrometastases
- The high dose interferon α regime prolong the OS
- The mono-chemotherapy indicated only in stage IV
- The new treatment modalities, the targeted therapy can ameliorate the prognosis of metastatic cases

29 April 2010.
"Malignant melanoma writes its message in the skin with its own ink and it is there for all of us to see. Some see but do not comprehend."

Dr Neville Davis, Queensland surgeon

29 April 2010.