MELANOMA IN ADOLESCENTS AND YOUNG ADULTS

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Adolescents & young adults malignancies
Lugano, Switzerland 11 May 2018
Overview

✓ Epidemiology
✓ Risk factors
✓ Molecular characteristics
✓ Approach to hereditary melanoma
✓ Clinical features and diagnosis
✓ Treatment
✓ Prognosis and follow up
Incidence

✓ Melanoma is rare in AYA: 9 cases/million in those aged 15-19 years\textsuperscript{1}.

✓ Even rarer in children: 1-2-3/million in the age groups 1-4, 5-9, 10-14 respectively\textsuperscript{1}.

✓ A notable decrease in incidence among AYA aged 15-19 has been reported between 2003-2010 (SEER data)\textsuperscript{2}.
  - improved awareness
  - improved histopathologic classification.

Risk factors

✓ Same as adult melanoma.

✓ Genetic factors (family history, light skin, high nevus counts, congenital nevi, inherited DNA repair defects).

✓ Environmental factors (excessive exposure to sunlight, history of sunburns).

✓ Immunosuppression.

- Cohort of 70 pediatric patients: 40% had numerous nevi, 27% family history and 25% history of sunburn.

Pathogenesis I

✓ Biologically distinct from adult melanoma:

- greater thickness at presentation.
- higher frequency of amelanotic lesions.
- greater rate of SLN positivity.
- overall less aggressive course.

✓ WGS, WES and targeted sequencing (n=15):

- high burden of somatic variants.
- 80% consistent with UVA radiation damage.
- *BRAF* V600E mutation in 13/15 (87%) patients.
- *TERT* promoter mutation in 12/13 patients.
- *CDKN2A*: 15% mutations in 21% biallelic deletions.
- *PTEN*: 23% mutations in 14% biallelic deletions.
- No germline mutation.

Conventional melanoma in AYA is similar to **BRAF**-mutant adult melanoma

An approach to hereditary melanoma

Overview of Genetic Testing in Melanoma Dominant and Subordinate Cancer Syndromes

**Melanoma Dominant**

- **FAMMM**
  - Only Melanoma
  - +/- Pancreatic OR
  - +/- astrocytoma or other neurological tumor

- **BAP-1 Pattern**
  - Melanoma
  - + Uveal Melanoma OR
  - + Paraganglioma OR
  - + Mesothelioma OR
  - + Clear Cell Renal Carcinoma
  - + Atypical Spitz tumors

- **CDKN2A**
  - If negative
  - **CDK4**

- **BAP1**
  - If negative

- **PANEL TEST**

**Melanoma Subordinate**

- **Cancer Syndromes with Melanoma**
  - Melanoma
  - Breast/Ovarian
  - Pancreatic
  - Prostate
  - Colon

- If constellation of suspicious clinical findings, then consider
  - Li Fraumeni Syndrome
  - Cowden Syndrome
  - Lynch Syndrome
  - Xeroderma Pigmentosum

How common is hereditary melanoma?

✓ Cohort of Greek patients
  - 304 single melanomas (SM)
  - 9 familial cases (FM)
  - 7 multiple primaries (MM)

✓ *CDKN2A* germline mutation rate:
  - 10/304 SM (3.3%)
  - 2/9 FM (22%)
  - 4/7 MM (57%)

Pedigree of a family with CDK4 p.R24H mutation

Hereditary melanoma

Melanoma predisposition due to germline CDKN2A mutation

Brother's histology report: undifferentiated malignant melanoma, liver & spleen metastasis

Ethnicity: Albanian
Date: 12-6-2012

From Florentia Fostira with thanks
Prevention strategies for mutation carriers
Clinical features

A. Assymetry
B. Border irregularities
C. Color variegation
D. Diameter >6mm
E. Evolving lesion

40% of melanomas in adolescents lacked the ABCDE criteria

ABCD CUP more sensitive/less specific

- **A** melanotic
- **B** bleeding, bump
- **C** color uniformity
- **D** de novo, any diameter
- **E** evolving lesion

- **A** symmetry
- **B** border irregularities
- **C** color variegation
- **D** diameter >6mm
- **E** evolving lesion

Popup of new lesions

Biopsy is warranted when there is clinical suspicion.

- Entire lesion should be removed!
- Subcutaneous fat plus a small rim (2mm) of normal appearing skin should be pursued.
- Shave biopsies are not recommended!
Differential diagnosis

Common or dysplastic nevi

Spitz nevi and atypical Spitz tumors

Blue nevi
Management I

✓ **Surgery**: wide excision to the deep fascia, narrower margins may be considered.

✓ **SLN**: controversial in children.
  - 126 patients < 21 years: 62 SLNB, 29% were positive and positivity was correlated to thickness, 5-year survival rate 78% vs 98% for those with positive and negative SLN respectively.
  - if SLNB is positive surveillance and serial ultrasound may be appropriate (lymphedema risk ~20%).

Management II

✓ **Adjuvant:** data are scant.
   - node positive and high-risk primaries.
   - few reports on IFN or pegylated IFN.

✓ **Metastatic disease:** no data with PD1 or TKIs.
   • Phase II study of ipilimumab in 17 patients 12-18 years
   - 2 experienced an objective response.
   - No grade 2 toxicity with the dose of 3 mg/kg.

Patients ≥ 18 years eligible for TKIs and immunotherapy trials both in adjuvant and metastatic setting.

*Navid F, et al. Cancer 2005*
Prognosis and follow up

✓ International registry data: 10-year OS rate 70% for patients aged 10-15 and 80% for those aged 15-20 years.

✓ Tumor thickness, ulceration and stage at diagnosis important for prognosis.

✓ Total-body skin examination and lymph node surveillance are recommended.

✓ CTs are generally pursued less aggressively.
