Cutaneous Melanoma in Children and Adolescents: The Italian Rare Tumors in Pediatric Age Project Experience

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Objective To describe a series of cutaneous melanoma in children collected by the Italian Rare Tumors in Pediatric Age project.

Study design From 2000 to 2012, 54 patients younger than 18 years of age were prospectively registered and treated at 12 Italian pediatric centers on the basis of the same diagnostic/therapeutic recommendations and with the same forms to record clinical data.

Results Considering the estimated annual incidence in Italy, the registered cases accounted for 30% of those expected in children and 10% of adolescents. Clinically, 47% of the tumors were amelanotic and 81% were raised, 39% of cases had tumor thickness >2 mm, and 36% had lymph node involvement. For the whole series, 5-year event-free survival and overall survival rates were 75.2% and 84.6%, respectively. Patient survival correlated with tumor stage and ulceration. No relapses were recorded for T1-2 (thickness <2 mm), N0, and stage 0-I-II cases.

Conclusion We suggest that the variables influencing survival in children with melanoma are the same as for adults, the clinical approach used in adults is feasible in children, and pediatric cases are more likely to have advanced disease at diagnosis but similar survival. New effective drugs are needed for advanced disease, and biological studies and international cooperative schemes are warranted. *(J Pediatr 2014;164:375-82)*.

The incidence of melanoma is increasing by 2%-4% a year, faster than any other malignancy.[1] With an incidence of approximately 20 per 100 000 population and an estimated 76 250 new cases in the US in 2012, melanoma is the fifth most common malignant tumor (after prostate, breast, lung, and colorectal cancer).[2] Cutaneous melanoma is considered rare in childhood: 2% of all cases occur in patients younger than 20 years of age, but only a small number of these develop in prepubertal children. Epidemiologic findings from North American and European registries indicate an incidence of 0.7-0.8 per million population a year in the first decade of life but more than 10 per million in the second.[3-5] According to the epidemiologic definition in the Italian national-scale cooperative initiative for rare pediatric tumors (the so-called TREP project, Tumori Rari in Età Pediatrica, ie, Rare Tumors in Pediatric Age,[6] that defines rare pediatric tumors those with an annual incidence of less than 2 cases per million population), melanoma should definitely be considered rare in children but not in adolescents.[7] Relatively few data are available on the biology of melanomas in children and on their clinical management. The rarity of the tumor makes it very difficult to conduct useful clinical trials on pediatric melanoma.

The TREP project was launched in Italy in 2000[6] under the auspices of the Associazione Italiana Ematologia Oncologia Pediatrica to improve the clinical management of and basic research on rare pediatric cancers by creating a network of pediatric oncologists and surgeons who cooperate with other experts, collect clinical data, develop diagnostic and therapeutic recommendations, and promote biological studies. We describe the clinical features, treatment, and outcome of a series of patients younger than 18 years of age prospectively registered in the TREP database with a diagnosis of cutaneous melanoma.

Methods

Patients younger than 18 diagnosed with rare pediatric tumors[6] were centrally registered as of January 1, 2000, by the TREP Data Center (at the Clinical Trials and Biostatistics Unit, Istituto Oncologico Veneto, Padova, Italy).

Ad hoc printed forms were used to collect data on clinical findings, histopathology, diagnostic work-up, therapy, and follow-up. All patients, or their guardians, gave their informed consent to participate in the TREP study. In all cases, the

AJCC	American Joint Committee on Cancer
EFS	Event-free survival
OS	Overall survival
SLNB	Sentinel lymph node biopsy
TREP	Tumori Rari in Età Pediatrica (Rare Tumors in Pediatric Age)

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histologic diagnosis was established directly by one of the pathologists on the TREP panel and/or centrally reviewed by the panel. The TREP diagnostic and therapeutic recommendations included obtaining chest radiograph, abdominal ultrasound, and regional lymph node ultrasound for patient staging. Total-body computed tomography scanning and positron emission tomography were recommended for thicker lesions (>0.75-1 mm) or at the physician's discretion. Sentinel lymph node biopsy (SLNB) for the staging of regional lymph nodes (to establish whether elective node dissection was warranted) was recommended in cases with a Breslow thickness >1 mm or an increased mitotic rate, evidence of histologic ulceration, or lymphovascular invasion. Patients were classified according to the adult American Joint Committee on Cancer (AJCC) staging system (modified in 2009).[8]

As for treatment, the TREP recommendations strongly suggested that each case should be discussed with the TREP coordinator and other expert physicians (dermatologists, adult surgeons, and medical oncologists) professionally dedicated to managing melanoma in adults and working at primary oncology centers. For this purpose, a network of cooperative links was established with different teams of melanoma specialists at various Italian centers. After the initial resection, primary re-excision was suggested to achieve at least 1 cm of clear surgical margins. If the outcome of SLNB was positive, complete lymph node dissection was recommended. In cases of advanced disease, it was advisable to discuss the indication for systemic therapy with experts on adult melanoma.

The number of pediatric melanoma patients enrolled in the TREP database was compared with the number of cases expected to be diagnosed in Italy. The latter was calculated from incidence data (for the years 2000-2006)[7] reported by the Italian network of population-based cancer registries, the Italian Association of Cancer Registries (which includes 22 general registries and 3 specialist registries and covers 33% of Italian children).[9]

Statistical Analyses

The χ^2 test was used to analyze associations between categorical variables. The survival distribution was estimated by use of the Kaplan-Meier method, and CIs for the 5-year survival estimates were calculated with the Greenwood formula.[10] The log-rank test was used to compare the survival curves for patient subgroups obtained by univariate analysis with a view to ascertaining the potential role of prognostic factors.[11] Overall survival (OS) was calculated from the date of diagnosis to the date of death, or latest follow-up for patients who were still alive. The event-free survival (EFS) was calculated from the date of diagnosis to the date of disease recurrence, death, or latest follow-up for patients still alive and in complete remission. All P values were 2-sided and those <.05 were considered statistically significant. The SAS package (v 9.2; SAS Institute, Cary, North Carolina) was used for data analysis. Because of the small number of events, multivariate analysis was not performed.

Results

From January 2000 to June 2012, 713 cases of rare pediatric tumors were registered in the TREP database; 100 were registered as melanoma or other cutaneous tumors. Among them, 59 cases had cutaneous melanoma, 35 had so-called melanocytic tumors of uncertain malignant potential (29 of them being atypical Spitz tumors), 2 melanomas of the meninges, 2 metastatic melanomas in newborn (transplacental melanomas), and 2 cutaneous carcinomas. Adequate clinical data were available for 54 of the 59 cases of cutaneous melanoma, which formed the object of the present analysis. These 54 cases were registered and treated at 12 different centers, but 78% of them came from only 2 (the Istituto Nazionale Tumori in Milano and the University Hospital in Padova).

Table I shows the characteristics of this series. All patients were white and equally distributed between the sexes. A family history of melanoma was reported in 1 case. Melanoma arose from congenital nevi in 9 cases (none of the giant type). The trunk was the most common site of origin (one case had an unknown primary tumor and was diagnosed from cervical lymph node metastasis). No correlation was found between sex and site.

The clinical appearance of the primary lesion was amelanotic/pink in 15 of 32 cases for which data were available, the tumor's shape was raised in 26 of 32 cases, 21 of 29 cases were reported as having well-defined borders, and 20 of 29 were asymmetric.

Histologically, superficial spreading melanoma was the most common subtype. Ten patients had tumor ulceration. The tumors ranged in Breslow depth from 0.1 to 7.6 mm (median, 1.4 mm); 3 patients had in situ melanoma, and 39% of cases had tumors >2 mm in size (T3-T4). Eighteen patients had regional lymph node involvement at the time of their diagnosis; 4 of them had clinically detectable enlarged nodes (including the case with an unknown primary skin lesion), and nodal spread was detected histologically after SLNB in 14 cases (10 micrometastases and 4 macrometastases). SLNB was performed in 33 cases (and findings were positive in 14); it was omitted in 13 cases of melanoma with a Breslow thickness <1 mm (and in the 4 cases with clinically detectable enlarged nodes). Lymph nodes were not staged (either radiologically or pathologically) in the 4 cases with an initial diagnosis of atypical Spitz tumor.

Tumor thickness was strongly associated with ulceration and node positivity (**Figure 1**; available at www.jpeds.com). In particular, ulceration occurred more in thicker tumors (χ^2 for linear trend test P = .0058), and node positivity increased with increasing tumor thickness (χ^2 for linear trend test P = .0004). Nodal status and ulceration were strongly associated (χ^2 test, P = .0005): nodes were more often positive in patients with ulcerated lesions (8/9 cases) than in those without signs of ulceration (10/38).

According to the AJCC system, 3 cases were classified as stage 0, 20 as stage I, 9 as stage II, and 17 as stage III. None of the patients had distant metastases at the time of diagnosis.

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