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Let's Stop Worrying About Pigmented Skin Lesions in Children

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THE OPINION that cutaneous melanoma (CM) arises only after puberty is widespread among non-specialists. In fact, although the disease is well documented in prepubescent children [1, 2], its incidence is so low that it should not be a major concern for the pediatrician or general practitioner, nor indeed a source of stress to parents who are now much more aware of the increasing incidence of the disease. To identify guidelines for managing pigmented skin lesions in paediatric patients, we retrospectively reviewed cases excised and histologically examined at the National Cancer Institute, Milan, over 16½ years.

A total of 632 children (285 males, 347 females; age range 1–14 years, mean 10.6, median 11 years) had their melanocytic naevi removed surgically from January 1975 to June 1992. Of the 656 lesions removed, 577 were excised under local anaesthesia at the day hospital, and 79 under general anaesthesia. Only 2 (0.30%) were subsequently diagnosed histologically as CM.

Excluding the 45 cases of lesions > 2 cm in maximum diameter—and excised for aesthetic reasons or because considered at risk for development of malignancy—611 cases remain in which the decision to remove the lesion for histological examination was based on clinical perplexity, or the erroneous belief, widespread in the 1970s, that pigmented skin lesions with the clinical characteristics of junctional naevi could develop into CM. In only 31 cases was the preoperative clinical diagnosis suspect CM [including the 2 (6%) confirmed histologically].

When approaching pigmented lesions in children, it is important to bear in mind that although it may present atypically, CM is rare: our 2 cases of primary paediatric CM constituted only 0.09% of all the CMs (2150) observed and treated over the period considered.

At our outpatient clinic, the ratio between histologically diagnosed CM and pigmented skin lesions removed is currently 1:4.8; our much less impressive long-term ratio for paediatric lesions is 1:306, and due more to past "overdiagnosis" arising from false beliefs and emotional factors than to real problems with the differential diagnosis of naevi and melanoma. When CM presents with its typical clinical features [3, 4] it does not pose diagnostic difficulties, while atypical forms of CM (pedunculated or nodular, partially or totally amelanocytic lesions) are admittedly more problematic; these are rarer, however, and have been amply described in children [5, 6]. Alternatively, darkly pigmented benign naevi may often resemble CM, as testified by the fact that of the 29 suspect lesions that were not malignant 20 were dark (33% Spitz and 13% congenital).

We conclude that diagnostic excision of a pigmented skin lesion in children is only warranted if there is a well-founded clinical suspicion of malignancy or if the lesion evolves quickly or has atypical morphology; in cases where perplexity remains, we suggest continued observation (annually until puberty). Where excision is justified, the width should be limited (2–3 mm from lesion margins) for functional and aesthetic reasons: histologically confirmed CM can be radicalised later. By following these guidelines, we have drastically reduced the number of such operations in children at our institute, sparing many children and parents unnecessary stress, avoiding complications and conserving medical resources.

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Phase I Clinical Trial of Gemcitabine Given as an Intravenous Bolus on 5 Consecutive Days

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GEMCITABINE (DIFLUORODEOXYCYTIDINE, LY188011) is a deoxycytidine analogue of cytosine arabinoside. In model systems it has an altered metabolism and better activity in solid tumours [1, 2]. Because of the promising preclinical antitumour activity, phase I studies of gemcitabine were undertaken.

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Table 1. Toxicity in patients treated with gemcitabine (no. of patients with any grade toxicity/no. patients at dose level)

Dose level (mg/m^2)	No. of patients	No. of cycles	Fever	Flu-like symptoms	Nausea and vomiting	Headache	Hypotension	Anaemia	Leucopenia
1	3	4	0/3	0/3	0/3	0/3	0/3	1/3	0/3
2	3	6	2/3	0/3	0/3	1/3	0/3	0/3	0/3
3	3*	20	3/3	2/3	1/3	1/3	1/3	0/3	0/3
5	7*	18	6/7	4/7	4/7	4/7	1/7	4/7	0/7
7	7	24	7/7	7/7	4/7	1/7	2/7	3/7	0/7
9	6	14	6/6	2/6	3/6	1/6	3/6	2/6	0/6
12	6	31	6/6	5/6	6/6	5/6	4/6	3/6	3/6

* One patient received treatment at both of the two dose levels indicated.

Patients were considered for this study if they had histologically confirmed advanced solid tumours refractory to standard therapy. Other criteria for study entry included age $\geq$ 18 years, performance status (Eastern Cooperative Oncology Group criteria) of 2 or better, life expectancy of at least 12 weeks, recovery from any toxic effects of prior treatment, no concomitant anticancer treatment and adequate organ function. Informed consent was obtained in accordance with federal and institutional policies.

Gemcitabine at the indicated dose was diluted in 100 ml of normal saline and given daily over 30 min intravenously for 5 consecutive days with each cycle repeated every 21 days. At least 3 patients were treated at each dose level. Dose levels were 1, 3, 5, 7, 9 and 12 mg/m^2/day. After fever was consistently observed as a toxicity, patients above the 3 mg/m^2/day dose level were given oral acetaminophen 650 mg every 4 h for the 5-day treatment period. Gemcitabine was supplied by Lilly Research Laboratories (Indianapolis, Indiana, U.S.A.) as a lyophilised powder in vials of 20 or 100 mg of active drug.

34 evaluable patients received 117 cycles of treatment. There were 23 males and 11 females with a median age of 58 years. Tumour types included colon (11 patients), lung (7 patients), kidney (4 patients), unknown primary (4 patients), and pancreas (3 patients). No antitumour activity was seen.

Toxicities observed are listed in Table 1. The dominant toxicity was fever of grade $\geq$ 2 (temperature 38°C), which was documented in 23 of 34 patients. The fever was often associated with chills and sweats, tended to occur late in the 5-day treatment course, and subsided within 24 h of the last dose. In one patient at the 7 mg/m^2 dose level, fever was accompanied by nausea and vomiting, obtundation, hypotension and renal failure. The renal failure seemed to follow the nausea, vomiting and hypotension and was not felt to be directly related to the drug. Dose-related hypotension was an additional significant toxicity. Three episodes of grade 3 hypotension (symptomatic, requiring intravenous fluids) occurred at the three highest dose levels. A direct correlation was not evident between hypotension and fever. Less severe and readily manageable toxicities included nausea, vomiting and headache. All of these toxicities were reversible.

Haematological toxicity was limited to grade 1–2 anaemia (haemoglobin 7.0–9.9 g/dl) in 13/34 patients and leucopenia in 3 patients. One patient who had received eight treatment courses experienced grade 3 neutropenia with leukopenia consistently during the second week of each cycle.

The sporadic but potentially life-threatening hypotension that occurred at the higher dose levels was felt to preclude further dose escalation. Phase I studies utilising gemcitabine on twice weekly and every 2 weeks schedules have achieved greater dose intensities with dose-limiting toxicities of myelosuppression and, in some cases, dermatitis [3–6]. Although significant toxicities were observed in patients receiving gemcitabine during this study, a maximum tolerated dose on this daily × 5 schedule was not determined.

The mechanism of fever and flu-like symptoms is unclear but seems to be schedule-dependent since these toxicities have been seen on the daily × 5 and twice weekly phase I trials but not on the weekly or every 2 weeks trials. Fever has also been documented in a small number of rheumatoid arthritis patients receiving 6-azauridine triacetate, a related antimetabolite [7]. In contrast, myelosuppression has been minimal on the daily × 5 schedule but dose-limiting on the less frequent schedules.

Because sporadic life-threatening toxicities were seen at doses far below those attained on other schedules, the daily × 5 schedule is not recommended for further development.

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