1512 POSTER

Standards, options and recommendations: Clinical practice guidelines for diagnosis, treatment and follow-up in cutaneous melanoma (cm)

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Context: The "Standards, Options and Recommendations" (SOR) project is a collaboration between the Federation of the French Cancer Centers and specialists from French public Universities, general hospitals and private clinics. The main objective is the development of clinical practice guidelines to improve the quality of care and outcome for cancer patients. The methodology is based on literature survey and clinical appraisal by a multidisciplinary group of experts, with feedback from specialists in cancer care delivery.

Objectives: To develop clinical practice guidelines according to the definitions of SOR for the management of cuteneous melanoma.

Methods: Data have been identified by literature search using Medline and Current Contents (Dec. 1998) and the expert personal reference lists. Once the guidelines were defined, the document was submitted for review to national and international independant reviewers and to the medical committees of the 20 Cancer Centers.

Results and Conclusions: The main recommendations for CM management are:

Diagnosis of CM requires a surgical removal of the lesion and its histological examination.

The pathology report must state the presence of melanocytic cells, malignant features, the maximal thickness and the consistency of the surgical margins. If required, a new surgical excision must be performed. No additional treatment, including elective regional node dissection or medical adjuvant treatment, is integral to the standard care at this stage. In case of metastatic regional lymph nodes, a complete lymphadenectomy is required in the absence of other metastases. Adjuvant treatment with high-dose alfa interferon is optional in this case. In advanced disease, palliative teatments only are available and chemotherapy using DTIC represents the reference treatment. The role of sentinel node detection and prophylactic local lymphadenectomy as well as the potentiel benefit of interferon in adjuvant treatment are important issues for the future management of CM. We recommend to actively pursue clinical trials in this setting. Follow-up is based on physical exam and self-detection must be encouraged during the patient life. Medical follow-up for early diagnosis is also recommended in high-risk groups.

1513 PUBLICATION

Cost-effectiveness of interferon for high-risk (stage III) melanoma patients

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Objective: To determine the cost-effectiveness (C/E) relationship of adjuvant high-dose interferon alfa-2b (IFN) treatment vs. observation in patients with surgically resected stage III melanoma (AJCC).

Methods: Disease progression was studied using a Markov model (B.E. Hillner, J Clin Oncol 1997; 15: 2351–2358), according to the results of ECOG1684 (J.M. Kirkwood, J Clin Oncol 1996; 14: 7–17). The cost of each clinical state from the Health Authorities perspective was determined by an expert panel, according to routine clinical practice in Spain.

Results: For a patient with a mean age of 50 years, lifetime incremental cost (IC) with a 6% discount rate, life years saved (LYS) and incremental C/E relationship (6% discount cost per LYS) are shown below:

Cost (in euros) IC LYS IC/LYS

IFN vs. Control 17666 1.9 9015

According to the projection generated by the model, IFN treatment produces an increased survival of 1.9 years with an incremental cost per LYS of 9015 euros. This result was compared with essential procedures for survival which are accepted by our National Health System (NHS), such as hemodialysis for patients with renal failure (20194 euros/year).

Conclusion: IFN administration in high-risk (stage III) melanoma, a disease in which clinical efficacy has been demonstrated, is within the cost range acceptable by the NHS for routine medical interventions.

1514 PUBLICATION

Cutaneous malignant melanoma: Guidelines and practice

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Background: The Dutch Melanoma Working Party published guidelines for the management of malignant melanoma of the skin (last revision 1997 since 1984). According to these guidelines a diagnostic excisional biopsy must be followed by a therapeutic excision. In the histopathological report invasiveness of the tumour (thickness according to Breslow or depth of invasion according to Clark) and completeness of removal should be mentioned. We determined whether daily practice in 16 general hospitals served by 6 pathological laboratories was in line with these recommendations.

Methods: The Comprehensive Cancer Centre South (±1,000,000 inhabitants) selected 578 patients (37% men and 63% women; mean age 51 years) who were reported to have a malignant melanoma of the skin by the six pathology-laboratories of the region in the years 1988, 1993 and 1997.

Results: In 85% of all patients diagnostic tissue was obtained by excisional biopsy. Completeness of removal was determined in 88%. Therapeutic excision was performed in 65% of patients. In 20% of these excisions a residue of the melanoma was found. Both diagnostic excisional biopsies as well as therapeutic excisions were performed in 53% of cases. In only 50% of all patients the complete procedure was according to the guidelines.

Conclusion: In daily practice guidelines for cutaneous melanoma were followed in about 50% of the patients in this registry. The precise background of the discrepancies is still under study.

1515 PUBLICATION

Simultaneous analysis of thyrosinase mRNA, L/DOPA and L/Tyrosine in the blood of patients with metastatic malignant melanoma

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The prognosis of malignant melonoma (MM) is based on the histological features of the tumor and clinical presentation. At the present time, there is no laboratory test to provide additional information on prognosis and metastatic spread of melanoma cells. Several MM tumor makers in peripheral blood have been proposed including S100 protein, neuron-specific enolase, lipid-associated sialic acid, melanoma-inhibiting activity protein (MIA) and tyrosinase, an enzyme specific to melanocytes and Schwann cells and also an excellent molecular marker of melanoma cells because of it's primarily expression limited to melanocytes.

Determination of blood tyrosinase mRNA by RT-PCR and markers of tyrosinase activity (L-DOPA/L-Tyrosine ratio) by HPLC have been proposed as biological tools for the detection of metastases in melanoma patients. We prospectively evaluated their significance and clinical value in a group of 29 stage III (n = 6) and IV (n = 19) melanoma patients and one with melanosis of Dubreuilh. L-DOPA/L-Tyrosine ratio was elevated in 30% of stage III, 41% of stage IV patients (range: 7.5 to 261.10^5) and in melanosis of Dubreuilh (184.8) (reference values: $6–16.10^5$). Four patients (stage IV, evolutive disease) were positive for tyrosinase mRNA. Tyrosinase mRNA positivity, but not L-DOPA/L-Tyrosine ratio, was associated with disease progression ($p < 0.009$). The presence of tyrosinase mRNA in blood is more related to clinical status and poor prognosis than levels of melanin precursors, which reflect tumor burden.

1516 PUBLICATION

Primary vulvar melanoma: A clinicopathological study of 27 cases

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Purpose: A retrospective analysis of a series of all patients with Primary Vulvar Melanoma (PVM) was conducted to evaluate effects of initial therapeutic procedures on disease-free-survival and overall-survival.

Results: Twenty seven patients were referred from 1975 to 1998. Median age was 60 years (22 to 86). Median diameter of PVM was 2.0 cm (0.8 to 5.0). Mean Breslow thickness was 3.34 mm (0.22 to 10). Ulceration was present in 54.5%. Using AJCC's classification, 25 patients were stage I or II, 2 patients were stage III, and none was stage IV. Treatment consisted of wide excision in 6 patients and complete macroscopic resection in 20 patients. Among the latter, 11 excisions were pathologically complete, 4 incomplete, and 5 unspecified. Four patients underwent elective node dissection or adenectomy, with negative results. One therapeutic node dissection was performed with 2 positive nodes. One patient (stage III) was followed without treatment. Twenty one patients had relapsed. First relapses were mainly local (10 cases) and/or regional (10 cases), and occurred after a median delay of 9 months (2 to 189). At time of analysis, 15 patients had died of disease, 5 patients were lost for follow up, either in metastatic condition (4 cases), or disease free (1 case), and 7 patients were alive. Overall 5 and 10 years survivals were respectively 43% and 36%.

Conclusions: Wide local excision or partial vulvectomy are first line treatments for PVM. Pathological assessment of complete resection is mandatory. ELND is not recommended. However, high locoregional relapse rates are observed, which may be related to late diagnosis or high Breslow thickness.

1517 PUBLICATION

Risk for malignant melanoma in a cohort of young patients with multiple atypical melanocytic naevi

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Purpose: Atypical (dysplastic) melanocytic naevi (AMN) are well-known precursor of cutaneous malignant melanoma (CMM). The aim of this study was to estimate the risk for development of CMM in a cohort of young patients (age 10 to 35 at the time of diagnosis) with at least three clinically AMN (defined as flat or slightly elevated naevi with a diameter over 5 mm, asymmetrical shape, ill-defined border and irregular color) in a long-term prospective follow-up.

Methods: For a period of 6 years (1991–1996) 62 consecutively diagnosed patients were enrolled in the study. There were 41 females (age 11–35, mean 20 years) and 21 males (age 17–33, mean 25 years). All patients were carefully examined, all melanocytic lesions were counted using a detailed standard protocol, photos were taken, and some lesions were surgically removed (55 specimens were obtained).

Results: The number of AMN varied from 3 to 67 but most patients were with more than 5 AMN. The follow-up ranged from 13 to 74 months (median 32.5 months). Except for two patients with three clinically atypical melanocytic lesions removed at the time of entering the study and diagnosed as having CMM, only one patient (35 year-old female) developed a CMM during the follow-up.

Conclusion: Although the number of patients is small and the duration of follow-up is not long enough, it seems that in young persons with multiple AMN the risk for developing CMM is relatively higher than in the general population. The study is on-going and with gathering more patients and with a longer follow-up it probably be possible to estimate the risk accurately.

1518 PUBLICATION

Expression of estrogen and progesterone receptors in breast metastases from malignant melanoma

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Purpose: Although several findings suggest that hormonal factors can influence biology of malignant melanoma, the effective presence of estrogen (ER) and/or progesterone (PgR) receptors in melanoma cells is unclear. We evaluated the expression of ER and/or PgR in breast metastases (BM) from malignant melanoma.

Methods: From 1950 to 1998, 77 cases of BM from extra-mammary tumors were identify. Between all cases, 13 patients (pts) were affected by malignant melanoma. An immunohistochemical method was utilized to determine the presence of ER and/or PgR.

Results: Eleven pts were female and only 2 pts were male. Median age was 34 years (range 4–61), at the time of diagnosis of primary tumor and 38 years (range 20–61) at the time of BM diagnosis. All but one female pts developed BM in premenopausal age (<50 years). Primary tumor was localized in inferior limbs (6 cases), superior limbs (2 cases), trunk, face and choroid (1 case, respectively), while in 2 pts primary tumor was not identified. The median time from primary tumor diagnosis to the evidence of BM was 13 months (range 0–194). At the time of this analysis the first 4 pts were evaluated, and in all cases both ER and PgR resulted negative.

Conclusions: Our preliminary results suggest that BM from malignant melanoma occur in premenopausal pts. Determination of ER and PgR is ongoing and definitive data will be presented.

1519 PUBLICATION

Taxane-containing chemotherapy in patients (pts) with disseminated malignant melanoma (DMM) (Preliminary results)

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Purpose: The antitumour activity of monotherapy with Paclitaxel (P) or Do-cetaxel (D) in DMM ranges from 12% to 18%. Both in vitro and in vivo data support the concept that Tamoxifen (T) is synergistic with Cisplatin (C) in mela-noma. We use the combination of these three drugs in expectation to improve the results of treatment of patients with DMM.

Methods: From January 1997 to February 1999 21 pts (11 males, 10 females, median age – 46 yrs, range 16–64) were enrolled to receive P 175–200 mg/m^2 i.v. for 3 hours (17 pts) or D 100 mg/m^2 i.v. for 1 hours (4 pts) d1, C 120 mg/m^2 i.v. d3 and T 100 mg/m^2 d7–16 every 3–4 weeks. 6 pts had been previously treated with DTIC and/or a-interferons. The response evaluation was made every two cycles. 18 pts are evaluable for response and 20 for toxicity.

Results: 1CR (skin, lymph nodes and lung mts) and 6PR (primary tumour, skin, lymph nodes, lung, liver and other visceral mts) were observed for an overal re-sponse rate 39%. The duration of CR is 14+, and the median duration of PRs is 9 months. Also we have registered 1 minor response for 7, and 3SD for 7, 10 and 12+ months. The most common side effects were nausea and vomiting (80%), alopecia (60%), leukopenia gr. I–III (45%), neutropenia gr. I–IV (40%), periferal neuropathy gr. I–II (35%), thrombocytopenia gr. I–II (20%), nephrotoxicity gr. I (20%). The treatment was interrupted in three pts because of toxicity. The dose reduction was necessary in four pts.

Conclusion: Taxanes in combination demonstrated a better activity than in monotherapy in pts with DMM. The toxicity of the above regimen is acceptable.

1520 PUBLICATION

Cisplatin (CDDP), dacarbazine (DTIC), interferon (IFN) and amifostine (AMI) in advanced melanoma. A phase I study

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Purpose: AMI, an organic thiophosphate, can protect against CDDP toxicities and offers the possibility of improving the quality of life of patients (pts) receiving chemotherapy. The aims of this study were to define the maximum tolerated dose (MTD) and the dose limiting toxicity (DLT) of CDDP in combination with fixed doses of DTIC and AMI.

Patients and Methods: Pts affected by advanced malignant melanoma, received DTIC 300 mg/m^2 i.v. days 1-2-3, and escalated doses of CDDP i.v. days 2–3, every 3 weeks. The starting dose of CDDP was 50 mg/m^2 for day, escalating to 65–75 mg/m^2 to DLT. When DLT will be reached, AMI 375 mg/m^2 will be administered before CDDP. IFNα2b was administered at 3MUI i.m. 3 times a week. Response was evaluated after 3 courses of chemotherapy.

Results: Available clinical data are summarized below.

Step	CDDP/DTIC	Pts	DLT	Type	Response
1	50/300	6	0	3 PR	
2	65/300	7	1	Anemia 4	1 CR, 1 PR
3	75/300	3	3	Neutropenia 4	too early
Total		16	4		5/13 (3 too early)

Conclusion: Accrual is ongoing at 4th level with CDDP at 75 mg/m^2 and AMI. These preliminar results suggest a good clinical activities of this combination.