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Docetaxel in combination with dacarbazine (DTIC) in patients with advanced melanoma: a phase II study of the hellenic cooperative oncology group

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Background: Chemotherapy for advanced melanoma remains disappointing. The number of agents that are active in patients with metastatic melanoma is limited. The aim of the study was to evaluate the efficacy and safety of a new combination regimen consisted of docetaxel and DTIC, as first line chemotherapy, in advanced melanoma.

Patients and methods: Patients with advanced melanoma, including cerebral metastases, were eligible. Docetaxel 80mg/m2, IV over 1h infusion, D1 and DTIC 400mg/m2, IV over 45', D1+2, were given every 21 days for 6 cycles.

Results: 41 pts entered the study; 39 were assessable for response. Objective responses were seen in 10 pts (24%). Three of them achieved a CR and 7 a PR, while 8 pts demonstrated stabilization of their disease. After a median follow-up of 20 months, the median TTP was 7 months (0.5-22) and the median survival 10 months (1-28). The main toxicity (G3-4) was neutropenia, which occurred in 8 pts. Additional patients had reversible G3-4 toxicities including alopecia, nausea/vomiting and fatigue; 3 presented mild hypersensitivity reactions to docetaxel. No toxic death was noted.

Conclusion: The above combination is well tolerated and has definite activity in pts with advanced melanoma.

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US scan and sentinel node biopsy (SNB) in the diagnosis of nodal metastases in patients with melanoma

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Introduction: In our experience US of nodal basins proved to be very accurate in detection of node metastases >2 mm. This technique, in theory, could avoid a subgroup of clinical stage I melanoma patients unnecessary SNB. This study is aimed to challenge this hypothesis.

Patients and Methods: Our series consisted of 130 consecutive clinical stage I cutaneous melanoma patients (62 M, 68 F; mean age 50.5 ys). The tumor was sited in limb in 81 patients, trunk in 42 and head-neck region in 7. Patients underwent preoperative US and FNAC (if nodal mets were suspected) and preoperative Tc99m-nanocolloid lymphoscintigraphy the day before surgery. Patent blue dye was intradermally injected at the tumor site 20 minutes before skin incision. Any SN(s), identified as blue stained and/or hot spot (hand-held gamma probe), were sent to the pathologist for E-E and immunohistochemistry (s-100 and HMB-45)sectioning. All the patients with positive findings at US and/or SNB underwent radical node dissection.

Results: SNB was performed in 143 basins, as 13 patients had dual-drainage at lymphoscintigraphy: 41.6% were in the axilla, 52.8% in the groin and 5.6% in the head-neck region. Patent blue dye with intraoperative lymphoscintigraphy allowed the identification of SN(s) in 98.6% of cases. Twenty-nine patients(22.3%)had lymph node metastases (31 basins). US findings were positive for 11 of the 31 metastatic basins (35.5%). Among the patients with positive US, nodal involvement was found partial in 8, massive in 2 and extranodal in 1, whereas, among the US negative cases, 11 had micrometastases, 8 partial and 1 extranodal metastases.

Conclusions: US +/- FNAC has an important impact on melanoma patient selection, allowing the identification of more than one-third basins with metastatic deposits (its main drawback being the resolution power of the probe), in which SNB is unnecessary.

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Detection of nodular and superficial spreading melanoma ≤ 2 mm – An interview study

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Purpose: To investigate differences in signs and symptoms between nodular melanoma (NM) and superficial spreading melanoma (SSM) with a tumour thickness ≤ 2.00 mm and factors for seeking medical attention.

Material and Methods: Semi-structured interviews with 22/25 patients with NM (all patients in the Stockholm-Gotland Regional Cancer Registry with NM ≤ 2.00 mm, diagnosed between 1994–1999 and still alive). A comparison group of 32/35 patients with SSM diagnosed during the same period, matched to the NM on age at diagnosis, gender and tumour thickness.

Results: NM were smaller in diameter than SSM according to patients' reports. NM were more often described as a new lesion than SSM. No other statistically significant differences between NM and SSM were found. The median time from detection to diagnosis were 4 months (range 1 day to 18 months) for NM and 6 months (1 week to 3 years) for SSM. In 61% the melanoma was detected by the patient herself/himself, but in 17% of the cases a family member or a friend was involved in the detection. The most important reason to seek medical attention (65%) was a change in the lesion or a symptom. 35% took the opportunity to show or ask about the lesion while at a doctors office for other reasons. 52% were encouraged by others to seek medical attention. In four cases, a physician detected the melanoma.

Conclusion: The results have implications for prevention of melanoma. Early detection of NM appears possible, provided that it is emphasised in public education that melanoma may have a diameter < 6 mm. Strategies for involving family members should be elaborated, since they play an important role in detection of melanoma and in motivating medical advice.

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Locally advanced uveal melanoma:primary and postoperative external radiotherapy

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Purpose: The effect of external radiotherapy on local control and survival in patients with locally advanced uveal melanoma was analysed retrospectively.

Material and Methods: Eleven patients (4 men, 7 women) with an median age of 69.8 years (range, 48.6-82.2) were treated at the Div. of Radiotherapy between 1987 and 1998. External radiotherapy either was given postoperatively (n=7) in advanced tumours with infiltration in adjacent structures or primarily in medical inoperable patients (n=2) and in patients with local recurrence following enucleation (n=2). A total dose of 40-56 Gy was used with single doses of 3-4 Gy.

Results: Mean follow-up was 38.2 months, (mean, 20.1; range, 5.4 to 94.7 months). The 5-year-disease-free, disease-specific and overall survival according to Kaplan-Meier were 33.7% (95% Confidence Interval, CI, 5-67), 43.8% (95% CI, 12-73) and 27,2% (95% CI, 5-54), respectively. Local control was achieved in all seven postoperatively irradiated patients. In three out of four primary irradiated cases, tumour regression could be obtained with complete remission in one of them. No severe radiation late effects were obtained.

Conclusion: Postoperative external radiotherapy is effective to achieve local tumour control also in patients with advanced local disease, however metastasis rate remains high. Radiation also has a potential as an primary treatment in selected inoperable patients or recurrent tumours by improving quality of life in those very cases.

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The role of serum S-100 protein and tyrosinase RT-PCR in staging patients with malignant melanoma

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Background: Staging of patients with malignant melanoma (MM) is crucial to determine prognosis and for planning adjuvant treatment. Unfortunately, there is no good clinical method to detect systemic micrometastases in patients with stage III disease.

The aim of this study was to evaluate the usefulness of serum S-100 protein and tyrosinase RT-PCR in detecting systemic micrometastases in patients with MM.

Patients and methods: From June 2000 to March 2001 measurement of S-100 protein and tyrosinase RT-PCR from peripheral venous blood was

performed in 42 patients (25 men and 17 female, aged 28 - 81 years) with stage III and IV MM. Results were correlated with other clinical tests.

Results: Tyrosinase RT-PCR was positive in 8/29 patients with stage III and in only 2/13 patients with stage IV MM. In 5/8 patients with positive tyrosinase systemic metastases already developed despite short follow-up (0-9 months). In a group of 21 patients with negative tyrosinase only 3 developed systemic metastases. S-100 protein was normal (<0.01 g/L) in 25 and elevated in 4 patients with stage III MM. Systemic metastases developed in 5/25 with normal and in 2/4 with elevated S-100 protein. There was a positive tyrosinase reaction in 3/5 patients with normal S-100 protein who developed systemic metastases. With a combination of tyrosinase RT-PCR and S-100 protein we were able to predict systemic metastases in 5/7 patients.

Conclusions: Positive tyrosinase in peripheral venous blood is a better predictor of systemic metastases than serum S-100 protein. However, since there are cases with negative tyrosinase and elevated S-100 protein, we recommend the combination of both tests. Moreover, with longer follow-up we can expect these results to became even better.

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Evaluation of the potential immunomodulating benefit by the application of retinoic acid in chemoImmunotherapy of metastatic melanoma

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Purpose: Considering contradictory reports regarding the potential beneficial therapeutic effect of 13-cis-retinoic acid (RA) in combined chemoimmunotherapy trials for metastatic melanoma (MM), the aim of this study was to perform detailed immunological evaluation of patients undergoing different chemoimmunotherapeutic regimens with or without RA.

Methods: 35 MM patients were treated with DTIC, 800 mg/m2/day and interferon alpha-2a (IFN), 5x106 IU/m2/day s.c., during 5 days (group A) and 35 MM patients received the same regimen, supplemented with RA, 60 mg/day, during 10 days (group B), and compared to 39 healthy controls. Peripheral blood lymphocytes (PBL) NK cell activity, PHA-induced proliferation (LTT), CD4+ and CD8+ T cell and NK cell subsets wereanalysed on day 1, 6 and 28 of the first three therapy cycles. The same parameters as well as the dynamics of IRF-1 transcription were evaluated on in vitro treated PBL with IFN, RA and IFN+RA.

Results: Predictive in vitro treatments of PBL showed a significant synergy in the expression of IRF-1 mRNA, and all the other evaluated parameters in combined IFN + RA treatments. However, immunological monitoring showed only significant increase in NK cell activity on the day 6 of the 1st therapy cycle in both groups, and an increase in CD4+ T cells on day 6 of the 1st cycle in group A. In the expression of CD69 on CD56+ PBL and CD38 on CD8+ T cells there was a repeating pattern of increase on day 6 of each therapy cycle in both groups, contrary to the gradual increase in HLA-DR expression on CD3+ T cells in group A, and an early decrease in group B.

Conclusion: The obtained results suggest that contrary to the observed in vitro synergism between IFN and RA, there was no immunopotentiating, nor therapeutic benefit in the regimen that included RA.

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Isolated limb perfusion with fotemustine after chemosensitization with dacarbazine in melanoma

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Introduction: Isolated Limb Perfusion (ILP) with Melphalan continues to be the standard treatment for localised recurrent melanoma of the limbs (Stages III - M. D. Andersen). In terms of local and regional control with Melphalan, complete remission is achieved in about 40% of patients (pt), with frequent toxicity, causing significant short term disability in many and long term incapacity in a few. Since 1989, several studies report the success of the association of Fotemustine and Dacarbazine (DTIC) in the systemic treatment of disseminated melanoma, but serious lung toxicity limited its use. In 1995, we introduce a pilot study with systemic DTIC and using Fotemustine as the perfusion agent.

Patients and Methods: Twenty-eight pt (M-6; F-16) in stages IIIA and IIIAB were introduced in this study, making a total of 30 ILP. DTIC in a dose of 400 mg/m2 was administrated 4 hours before ILP and Fotemustine, in a dose of 100-150 mg/m2, was introduced in the arterial line when the subcutaneous temperature reaches 38°C. Drug perfusion lasts for one hour with local temperatures ascending to 40-41°C.

Results: Results were evaluated by: A - Response rate: Complete Response-16 (53,3%), Partial Resp.- 8 (26,7%), Local disease progression - 1 (3,3%); Local disease stabilization - 1(3,3%), N/evaluated - 2 (6,7%), Lost for follow-up - 2 (6,7%); B - Local toxicity (Wieberdink scale): I-30; C - Systemic toxicity (WHO scale): 0 - 13; I - 11; D - Late local toxicity: Fibrosis-3; Epidermolisis - 4.

Conclusion: Treatment was effective, with a response rate similar to that obtained with Melphalan, but with much lower early toxicity. Therefore, this protocol may represent an innovation in local and regional therapy that would be interesting to explore in order to optimise the technical conditions and outcomes.

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P21 ciclin-dependent kinase inhibitor (CKI) polymorphisms and malignant melanoma: a study of susceptibility and an analysis of clinico-pathological parameters

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Purpose: In malignant melanomas, G1/S checkpoint abnormalities are known to be of significant importance in the development of the disease. In this study, we examine the presence of two polymorphisms in the G1 CKI gene P21, and its association with melanoma risk, stage, recurrence and median age.

Methods: Blood samples were obtained from 124 patients with melanoma, diagnosed and treated at Instituto Português de Oncologia of Porto. Control subjects were 220 healthy individuals. The analysis of the P21 polymorphisms was performed with the RFLP (Restriction Fragment Length Polymorphism) technique.

Results: The polymorphisms were present in 12,9% of the melanoma patients and in 11,4% of the healthy controls (O.R.=1,16; p=0;673). The analysis of the melanoma cases was performed separating the patients by stage (O.R.=1,45; p=0,314), recurrence (O.R.=2,606; p=0,089) and median age (O.R.=1,23; p=0,617). No significant association was observed between any of this variables and the presence of the polymorphisms.

Conclusion: Our results indicate that these P21 polymorphisms may not be involved in the susceptibility and development of melanoma although they have been associated with the development of some types of cancer.

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Tumor thickness as a predictive parameter of occult metastasis in melanoma patients undergoing sentinel node biopsy

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Purpose: Sentinel node biopsy is minimally invasive procedure proposed as a diagnostic test to accurately stage nodal basins at the risk for occult metastases. The purpose of this study is to find an evidence regarding the relationship between tumor thickness and the rate of positive SNs and to estimate the power of tumor thickness to determine the likelihood of the presence of occult nodal metastases in melanoma patients stage I and II.

Methods: A systematic search was performed using Medline and Embase through March 2001. A manual reference search and a manual review of specialty journals also were performed. Our search was restricted to studies published in English language. Of 417 identified studies on sentinel node biopsy in melanoma, 22 studies met our inclusion criteria of whom 12 were included in the analysis.

Results: We summarised results from 12 retrieved studies. Total number of patients undergoing sentinel node biopsy for melanoma was 4218. An occurrence rate of SN metastasis was 17.8% (95% 16.7 to 19.0). The incidence rate of tumor positive SNs increases with tumor thickness: it was less than 1% for lesions <0.75 mm, 8.3% for 0.76-1.50 mm lesions, 22.7% for 1.51-4.0 mm lesions and 35.5% for lesions >4.0 mm in thickness. Statistical test for trend confirmed a strong positive correlation between tumor thickness and SN positivity.

Conclusions: There is a strong evidence that the tumor thickness has significant power to predicy metastasis in SNs in melanoma patients. The