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**HORMONAL SYNCHRONISATION AND SEQUENTIAL CHEMOTHERAPY IN ADVANCED BREAST CANCER.**

G. Grecchi[1], D. Perroni[1], P.La Ciura[2], G.La Grotta[2], A.Comandone[2]. [1]Divis.Medicina, Ospedale S.Groce, Cuneo and [2]Divis.di Oncologia, Ospedale S.Giovanni Vecchio, Torino.

In order to accertain the efficacy and tolerance of a scheduled sequential hormone-chemotherapy, a selected group of patients who had previously undergone treatment with hormones and chemotherapy and who were in a progressive phase of the disease, was treated with medium dosages of methotrexate (MTX, with folinic rescue), regularly timed, followed by 5-fluorouracil(5-FU) after 19 hours from the beginning; this phase-specific chemotherapy was preceded by a cellular synchronisation with low dosages of tamoxifen(TAM) and a subsequent stimulation in cycle with ethinyloestradiol (EE), as follows: TAM 10mg d 1-3;EE 1mg d 4-6;MTX 50mg/mq q 6 hrs x 4 d 7;5-FU 600 mg/mq d 8 at 19th hr:recycle every 21 days. Up to now 12 female patients aged from 45 to 75 years have been examined. All of them had advanced breast cancer with 2 or 3 metastatic sites and had been previously treated with hormones and various chemotherapies. The toxicity evaluation on a total of 76 cycles according to the WHO criteria gave the following results: gastroenteric tract:GR 1 mucositis in 14 cycles(18%); GR 1 nausea and vomit in 52 cycles (68%); haematological toxicity: GR 2 in 2 cycles;GR 4 in 1 cyle. The last three cases of toxicity were probably caused by poor hydratation: in fact the same patients did not show toxicity after adequate hydratation. At the moment the evaluation of this type of treatment can be done as follow: PR(partial response) 1/12; MR(minimal response) 4/12; SD(stable disease) 5/12; PD (progressive disease) 2/12. The limited number of patients cannot allow us to give a final evaluation, but the low toxicity of this schedule in heavily pretreated patients, the absence of "estrogenic escape" and the long interval of time for disease progression need further evaluation.

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**COMBINATION OF α-MSH AND IODOTHIOURACIL: A POSSIBLE ALTERNATIVE IN MELANOMA THERAPY**

A. van Langevelde, J. van der Plas, J.G. Journée-de Korver, S.T. Zegveld and E.K.J. Pauwels
Dept. of Pharmacology of the University of Leiden, P.O. Box 9503, 2300 RA Leiden, The Netherlands

Melanogenesis, a quality of melanocytes and melanoma cells, can be affected in in vitro and in animal experiments by α-MSH. 4-Norleucine, 7-D-phenylalanine-α-MSH (Nor-MSH) is an α-MSH analogue, resistant to degradation by enzymes and with a high biological activity. The properties favour the incorporation of 5-iodo-2-thiouracil (ITU) into melanin as a carrier molecule for targeting radioactive I (125-I or 131-I) in order to inhibit melanoma growth by endo-irradiation.

It has been shown that ITU is incorporated in newly synthetized melanin of hamster melanoma cells. This incorporation is completely tyrosinase-dependent and is stimulated by Nor-MSH. In hamster melanoma cell culture 0.1 μm Nor-MSH stimulated the ITU incorporation by 70%, whereas cell proliferation decreased significantly. The 125-I-ITU distribution was also measured after i.v. injection in hamsters with implanted melanoma. Single or repeated s.c. injections of 100 μg Nor-MSH before i.v. administration of labelled ITU did not show any significant effects on the ITU incorporation measured 24 h after ITU injection. When a constant supply of Nor-MSH was achieved by implanting osmotic pumps (delivery rate 1 μg/h for 24 h) in the abdominal cavity of tumour-bearing hamsters 24 h before ITU injection, an effect was found: necropsy 24 h after ITU injection showed an increase of ITU in the tumour to 250% of the controls, whereas uptake in other organs, also eyes and skin, was not affected.

The above experiments lead to the conclusion that hormonal manipulation of melanomas in combination with an appropriate radiopharmaceutical may lead to successful endo-irradiation of melanomas.