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FOTEMUSTINE IN THE TREATMENT OF DISSEMINATED MALIGNANT MELANOMA : A RETROSPECTIVE ANALYSIS

D. KHAYAT (1), M.F. AVRIL (2), GERARD B. (3), J.P. BIZZARI (3)
(1) : Hôp. Pitié Salpétrière, Paris - (2) : Inst. Gustave Roussy, Villejuif - (3) : IRI SERVIER, Courbevoie - France

We have evaluated the efficacy and the toxicity of the nitrosourea fotemustine (F) in the treatment of disseminated malignant melanoma (DMM) and results according to various protocols are summarized below.

DRUG	EVALUABLE PATIENTS	MEDIAN RESPONSE RATE (range)
F alone	315	24.2 % (16.7 - 27.5)
F + DTIC (non sequential)	148	26.7 % (14.0 - 38.5)
F + DTIC (sequential)	184	24.0 % (0 - 41.0)
F + IFN	49	32.0 % (0 - 37.5)
F + DTIC + IFN	29	23.1 %
F + DTIC + VDS	51	40.0 % (40.0 - 43.0)
Other combinations	93	25.0 % (10.0 - 40.0)
Local route	7	100 %
Intra arterial route	29	43.8 % (43.8 - 61.5)

Overall analysis will be presented and a strategy in using F according to various metastatic sites (i.e. cerebral, visceral or non visceral) will be outlined.

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BIOCHEMOTHERAPY WITH DTIC AND THYMOSIN-α1 (TA1) + INTERLEUKIN-2 (IL-2) IN PATIENTS (PTS) WITH METASTATIC MELANOMA (MM)

S Carpano, S Santini, P Del Medico, M Vercillo, F Valente, L Di Lauro, T Gionfra, M Lopez
Regina Elena Institute, Rome, Italy

The combination of TA1, a synthetic polypeptide of thymic origin, and IL-2 with chemotherapy has been reported to be highly effective in experimental studies. In October 1990 we began a phase II trial of biochemotherapy in pts with MM. Schedule: DTIC 850 mg/m^2 iv d 1 + TA1 2 mg sc d 4 to 7 + IL-2 18 MUI/m^2/d by CIV d 8 to 12 q 3 weeks. There were 1 CR and 14 PR in 43 evaluable pts (RR= 35%). Median duration of response was 5 months. 6 pts had stable disease. Sites of response: soft tissue in 5 pts, visceral metastases in 10 pts. Median survival was 12.5 months in responding and 6.3 months in non responding pts (P=0.004). There was no statistical difference between responding pts and those with stable disease. Toxicity: fever (100%), hypotension G2-3 (96%), diarrhea (39%), N/V (35%), nephrotoxicity (20%) and thrombocytopenia (13%). This combination is generally well tolerated and should be considered for further investigations in metastatic melanoma.

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COMBINED TREATMENT OF METASTATIC MELANOMA WITH DACARBAZINE AND RECOMBINANT ALPHA 2b INTERFERON: RESULTS OF A MEXICAN STUDY.

Palma F, Lira-Puerto V, Silva A, Martínez R, Zepeda G, Labastida S.
Servicio de Oncología Médica, Hospital de Oncología, IMSS, México, D.F.

Twenty two patients suffering from histologically proven metastatic melanoma were treated with a combination of DTIC (600 mg/m^2 IV every 21 days) and recombinant alpha 2b interferon (Intron A) 5 x 10^6 3 times a week subcutaneously. Treatment was carried out for a period of 12 months unless progressive disease was noted after 3 months. Among the 20 evaluable, 2 achieved a complete response (CR) and 4 a partial response (PR) (response rate, 30 %). These responses ocurred in patients with cutaneous (2 cases) or lymph node metastases (2 cases) but 2 responses included visceral sites: lung (1CR) and liver (1PR). Average response duration was 12.3 months (range 6-24 months). The time required for objective response can be up to 6 months, which suggests that treatment should receive a reasonable trial period (at least 3 months). Clinical toxicity consisted mainly of a flu-like syndrome, anorexia and fever, and ocurred in more than 30 % of patients; hematologic and hepatic toxicities required a dose reduction in 20 % of patients but in no case did treatment have to be terminated because of this. Within the patients with response 5 are still alive, 3 with metastases and 2 without metastases (follow-up period: 24 months). Conclusion: A combined regimen of interferon alpha 2b (Intron A) and dacarbazine is effective in treating patients with metastatic melanoma with acceptable toxicities and a reasonable quality of life. The objective response rate was 25 %.

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PHASE III TRIAL OF CISPLATIN(DDP),DACARBAZINE(DTIC),BCNU, INTERFERON-ALFA-2A(IFN) AND TAMOXIFEN(TAM) IN THE TREATMENT OF DISEMINEATED MALIGNANT MELANOMA(MM).

CA.GALVEZ;M.BONAMASSA;R.PIRE.
DEPARTMENTS OF ONCOLOGY,CENTRO MEDICO CHACABUCO,CLINICA 25 DE MAYO;HOSPITAL UNZUE;CLINICA CENTRO DE PERGAMINO: Prov. De Buenos Aires.R.ARGENTINA.

The combination of DTIC/BCNU/DDPand TAM has resulted in overall response rate of 53% in pts. with MM(ASCO: 8;1098,89).Recent clinical trials have shown that a combination CT agents and IFN may be synergistic in Advanced malinancies.To date 27 Pts. with MM have been treated with a sequence of CT and IFN as follow DTIC: 250mg/sm,iv,dl-3;DDP: 25mg/sm,iv,dl-3;BCNU:120mg/sm dl,every 28 days,TAM 10mg po bid,continuosly and IFN: 5x 10^6,sc 3 times a week.Median age of pts. was 51(r:26-75); male:female was 16/11;PS was: 0(19),1(8)pts..Sites of metastatic disease included,liver(17);lung(6),subcutaneous sites(18) and limph nodes(24).Pts. with brain metastases were not elegible for the study..The response rate with this regimen was 48.1%(CR: 7.4%(2);PR:40.7%(11),SD 14.8% and PD:37%(10).Median follow-up on the study is 15m Median time to progression was 8.7months and median survival was 11 months for responders.Hematology toxicity (G3) included neutropenic 13/27pts.;thrombocytopenia 15/27pts.10 Pts. have been neutropenic fever.We conclude that this regimen has manageable toxicity,especially since the introduction of ondansetron and GM-CSF.TAM appears to contribute to response.

Sarcomas

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LONG TERM OUTCOME IN PATIENTS WITH AGGRESSIVE FIBROMATOSIS. A SINGLE INSTITUTION ANALYSIS OF 172 CONSECUTIVE CASES

Quagliuolo V., Fissi S., Garbuglia A., Azzarelli A, Clemente C.
Istituto Nazionale Tumori, Via Venezian 1, 20133 Milano - Italy.

From 1965 to 1992, 172 patients with aggressive fibromatosis were treated in our Institute. Male/female ratio 0.4, average age 30.6 years. 86 (50.5%) were located in the trunk or head & neck, 85 (49.5%) in the extremities. 60 (42%) patients presented a recurrent lesion at entry in our Institute. 30 cases were not considered for surgery and were treated with RT and/or chemo or hormono-therapy. 142 (82.6%) were operated. Surgery was considered radical in 6 (4.2%) patients, wide in 90 (63.4%), marginal in 40 (28.2%) and intralesional in 6 (4.2%). The overall recurrence rate was 32.7 at 5 years, 28.0% for radical+wide operations, and 43.2% for not adequate operations (P=0.3). According to the recurrence rate by site, no difference was documented between lesions of the trunk versus those of the extremities. No patient developed distant metastases. Only 5 pts died:3 for local progressive disease and 2 for causes not related to disease. The 10-year survival was 85%. Also patients considered not operable had a fair good prognosis: 75% at 10 years. Survival according to the site of the primary was 95% for extremities and 80% for the trunk at 10 years (p=0.3). The quality of surgery is determinant in fibromatosis as for any soft tissue sarcoma, nevertheless in our series the incidence of local failure after adequate surgery is higher (28%) than expected, and the same incidence after not adequate operations is lower (43%). It suggests that this low grade malignant disease has a natural history poorly modified by our treatments. ASIso patients not amenable with surgery have a fair prognosis with few deaths due to disease, and for that patients can be sometimes only observed and eventually considered for alternative treatments, as for endocrine therapy, chemotherapy + radiotherapy.

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SMALL ROUND BLUE CELL MALIGNANT TUMORS OF SOFT TISSUES AND BONE IN ADULT PATIENTS. Casali P, Mastore M, Bertulli R, Lombardi F, Gandola G, Navarria P, Azzarelli A, Quagliuolo V, Santoro A, Bonadonna G. *Istituto Nazionale Tumori, Milan, Italy.*

Small round blue cell malignant tumors include Ewing's sarcoma, peripheral neuroepithelioma, and rhabdomyosarcoma. From June 1988 we have prospectively studied a consecutive series of 36 adults (mean age = 27 yrs; range = 16-55) with such tumors arising from soft tissues (30 pts) or bone (6 pts). A combined approach was used in 30 pts, including primary chemotherapy with epirubicin 90 mg/sqm, ifosfamide 7500 mg/sqm, and vincristine 2 mg every 3 wks for 4-6 courses. Surgery followed in conservatively resectable patients. Radiotherapy (45-60 Gy) was given in combination with cisplatin 90 mg/sqm for 2 courses. Consolidation was performed with 4 courses of ifosfamide 7500 mg/sqm, actinomycin-D 1.5 mg/sqm, and dacarbazine 900 mg/sqm every 3-4 wks. Six pts had chemo-radiotherapy following surgery done elsewhere.

Primary chemotherapy achieved CR or PR in 83% of the 30 pts with measurable lesions (CI: 65% to 94%). Overall, FFP was 40% at 3 yrs. In the subgroup of 20 pts with only local-regional disease, DFS was 60% at 3 yrs. All 10 pts with metastatic disease relapsed, progressed or died. Three of the other 6 pts who received their treatment as an adjuvant to surgery relapsed at ≤14 mos.

We conclude that chemotherapy is highly active in adults with small cell sarcomas. These sarcomas are aggressive tumors deserving combined treatment and, possibly, new approaches in high risk patients. In particular, both in clinical trials and in clinical practice these histotypes should be distinguished from classical adult soft tissue sarcomas.