Neuroimmunomodulation in Medical Oncology: Application of Psychoneuroimmunology with Subcutaneous Low-dose IL-2 and the Pineal Hormone Melatonin in Patients with Untreatable Metastatic Solid Tumors

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Abstract. *Background: Anticancer immunity is under psychoneuroendocrine regulation, mainly via the pineal gland and brain opioid system, which may stimulate and inhibit antitumor immunity respectively. Cancer-related immuno-suppression does not depend only on functional damage of immune cells, but also on alterations of systems responsible for the neuroimmunomodulation, the most frequent of wich is a decline in blood levels of the pineal hormone melatonin (MLT). Patients and Methods: A study was performed to evaluate the influence of an exogenous administration of MLT alone or MLT plus subcutaneous (SC) low-dose interleukin-2 on tumor progression and survival time in patients with untreatable metastatic solid tumors. The study included 846 patients with metastatic solid tumor (non-small cell lung cancer or gastrointestinal tract tumors) randomized to receive the best supportive care only, supportive care plus MLT (20 mg/day, orally in the evening), or MLT plus SC low-dose IL-2 (3 MIU/day for 5 days/week, for 4 consecutive weeks). Results: The MLT alone was able to induce a significant increase of disease stabilization and survival time with respect to supportive care alone. The association of IL-2 with MLT provided a further improvement in the percentage of tumor regressions and of 3-year survival with respect to MLT alone. Conclusion: The administration of IL-2 and the pineal hormone MLT may induce control of neo1plastic growth and a prolonged survival time in patients with metastatic solid tumors, for whom no other conventional anticancer therapy is available.*

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Key Words: Cancer immunotherapy, IL-2, melatonin, neuro-immunomodulation.

Psychoneuroimmunology, also termed neuroimmunomodulation, is the medical science which studies the psychochemical mediation of the influence of emotions and consciousness states on the immune system. The application of psychoneuroimmunology to medical oncology does not relate only to therapy of cancer, but also to the physiopathological interpretation of the neoplastic disease and the mechanisms of its progression (1, 2). The existence of cancer-related immunosuppression has been demonstrated by several experimental and clinical observations (3-5). However, at the onset of neoplastic disease, the immunosuppressive status would not depend on the primary damage to immune cells but would be due to alterations of the psycho-neuroendocrine regulation of the anticancer immune response. In fact, recent advances in the psycho-neuroimmunology have demonstrated that the immune response is physiologically under a psychoneuroendocrine regulatory control. As far as anticancer immunity is concerned, it is mainly stimulated by the pineal gland and inhibited by the opioid system (6, 7). In fact, pinealectomy has been proven to reduce the IL-2-dependent anticancer immune response (6), with the subsequent stimulation of cancer progression (8), whereas stress-induced stimulation of cancer growth appears to be mediated by endogenous opioids and to be antagonized by the opioid antagonist naloxone (7). In addition, the progression of neoplastic disease has been shown to be associated with a progressive deficiency of the neuroendocrine systems responsible for the psychochemical stimulatory influence on anticancer immunity, in particular of the nocturnal production of the pineal immunomodulating oncostatic hormone melatonin (MLT) (9, 10), which would

play a role in determining the endogenous deficiency of interleukin-2 (11). In fact, MLT appears to stimulate IL-2 production by acting on specific MLT receptors expressed by TH1-lymphocytes (12). Therefore, progressive declines in IL-2 and MLT concentrations would represent the main immune and neuroendocrine deficiencies, respectively, characterizing the dissemination of the neoplastic disease. These findings would suggest the possibility of treating the human neoplasms by simply correcting the major cancer-related neuroendocrine and immune deficiencies, in particular those of IL-2 and MLT, in an attempt to counteract cancer cell proliferation by re-establishing the psychoneuroimmune biochemistry of the status of health, which is characterized by a natural resistance against cancer development and dissemination. Therefore, it is possible to propose a new rationale for the immunotherapy of human neoplasms consisting of the reconstitution of an effective anticancer immune response by acting not only on the immune cell, but also on the psychoneuroendocrine processes involved in the physiological regulation of the immune responses, including anticancer immunity, which aplpears to be essentially an IL-2-dependent phenomenon (13, 14). In contrast, the immunotherapeutic regimens available to date are generally developed on the basis of only empirical criteria, without taking into consideration the neuroimmune status of cancer patients themselves. Preliminary clinical data has already shown that the concomitant administration of the pineal hormone MLT may enhance IL-2-induced lymphocytosis and IL-12 production by dendritic cells in response to IL-2 (15, 16). Because of the occurrence of a pineal hypofunction during the clinical history of neoplastic disease (9, 10), the lower *in vivo* antitumor efficacy of IL-2 with respect to its *in vitro* activity could depend at least in part on pineal deficiency. Such deficiency which may be corrected by the exogenous administration of MLT itself (17), even though MLT is not the only molecule responsible for the antitumor activity of the pineal gland (18). On this basis, a study was performed in patients with untreatable metastatic solid tumors, who received best supportive care alone, supportive care plus MLT or supportive care plus MLT plus subcutaneous (SC) low-dose IL-2, in an attempt to evaluate the impact of the correction of the major immune and neuroendocrine deficiencies occurring with cancer progression on tumor growth and survival time.

Patients and Methods

The study included 846 patients with untreatable metastatic solid tumors, whose clinical characteristics are reported in Table I. Eligibility criteria were as follows: histologically proven metastatic non-small cell lung cancer or gastrointestinal tract tumors, measurable lesions, lack of available conventional treatments because of poor clinical status or progression in response to previous standard therapies, no double tumor, no brain metastasis, and no chronic treatment with immunosuppressive agents, such as corticosteroids or opioids. According to tumor histotype and sites of metastases, patients were randomized to be treated with the best supportive care alone, supportive care plus MLT or supportive care plus MLT plus (SC) low-dose IL-2. In accordance with findings showing its higher biological activity during the dark period of the day (19), MLT was given orally at 20 mg/day in the evening, every day without interruption. IL-2 was injected SC at a dose of 3 MIU/day in the evening for 5 days/week, for 4 consecutive weeks, corresponding to one complete immunotherapeutic cycle. A second cycle was repeated after a 21-day rest period. Patients then underwent a maintenance therapy consisting of 5 days every month, until disease progression or toxicity. The experimental protocol was explained to each patient and written consent was obtained. The clinical response was evaluated according to WHO criteria (20). The 3-year survival curves were plotted according to Kaplan-lMeier method. Data were statistically analyzed using the Chi-square test and log-rank test, as appropriate.

Table I. *Clinical characteristics of 846 patients with untreatable advanced solid tumors, who received supportive care alone, supportive care plus melatonin (MLT) or supportive care plus MLT + IL-2.*

Characteristic	IL-2+MLT	MLT	Supportive care
Number of patients	275	285	286
Gender male/female	141/134	156/129	155/131
Median/Age (years)	64 (42-77)	67 (48-75)	66 (45-78)
PS (Karnofsky)	80 (60-100)	80 (70-90)	80 (70-100)
Dominant metastasis sites			
Bone	41	44	45
Lung	93	91	95
Liver	62	69	66
Liver + lung	38	37	35
Pleura	11	13	14
Peritoneum	30	31	31
Previous chemotherapies	237 (86%)	241 (85%)	239 (84%)

Results

The clinical response is shown in Table II. No spontaneous tumor regression occurred in patients treated by the only supportive care. The treatment with MLT alone induced no complete responses (CR), whereas a partial response (PR) was achieved in 10/285 (4%) patients. In contrast, in the group concomitantly treated with IL-2 plus MLT, an objective tumor regression occurred in 51/275 (19%) patients, consisting of CR in 4 (2%) and PR in the other 47 (17%) patients. Stable disease (SD) was achieved in 16/286 (6%) patients treated with supportive care alone, in 79/285 (28%) patients treated with supportive care plus MLT and in 116 (42%) patients concomitantly treated with supportive care plus MLT plus low-dose IL-2. The percentage of disease control (DC: CR+PR+SD) obtained in patients treated with MLT plus IL-2 was significantly higher with respect to that achieved in both the other groups ($p<0.00$l). In the same way, the percentage of DC observed in patients treated with MLT was

Table II. *Clinical response (WHO criteria) in patients with advanced solid tumor treated with supportive care alone, supportive care plus melatonin (MLT) or supportive care plus neuroimmunotherapy with IL-2 plus MLT.*

Histotype	IL-2 + MLT						MLT						Supportive care					
	CR	*PR*	*CR+PR*	*SD*	*DC*	*PD*	*CR*	*PR*	*CR+PR*	*SD*	*DC*	*PD*	*CR*	*PR*	*CR+PR*	*SD*	*DC*	*PD*
Non-small cell lung cancer	0	17	17 (18%)	44	61 (66%)		0	3	3 (3%)	41	44 (46%)		7	0	0	7	7 (7%)	
Colorectal cancer	0	7	7 (14%)	19	26 (51%)		0	2	2 (4%)	14	16 (30%)		0	0	0	5	5 (9%)	
Gastric cancer	1	7	8 (24%)	13	21 (62%)		0	1	1 (3%)	6	7 (19%)		0	0	0	1	1 (3%)	
Pancreatic cancer	1	4	5 (11%)	17	22 (50%)		0	2	2 (4%)	11	13 (29%)		0	0	0	0	0	
Biliary tract cancer	0	1	1 (7%)	5	6 (36%)		0	0	0	2	2 (13%)		0	0	0	0	0	
Hepato carcinoma	2	11	13 (33%)	18	31 (79%)		0	2	2 (5%)	5	7 (18%)		0	0	0	3	3 (8%)	
Overall patients	4	47	51 (19%)*	116	167 (61%)**	108 (39%)	0	10	10 (4%)	79	89 (31%)+	196 (69%)	0	0	0	16	16 (6%)	270 (94%)

§CR: complete response; PR: partial response; SD: stable disease; DC: disease-control (CR + PR + SD); PD: Progressive disease. *$p<0.01$ *vs.* MLT, $p<0.001$ *vs.* Supportive care; **$p<0.001$ *vs.* MLT and Supportive care; +$p<0.005$ *vs.* Supportive care.

also significantly higher than that seen in patients who received only supportive care ($p<0.005$). The remaining 270/286 (94%) treated with supportive care alone, 196/285 (69%) treated with supportive care plus MLT and 108/275 (39%) treated with supportive care plus MLT plus IL-2 had a progressive disease (PD). The 3-year survival curves for the different groups of patients are illustrated in Figure 1. The survival time achieved in patients treated with MLT was significantly longer than that found in patients undergoing supportive care only ($p<0.05$), while that obtained in patients concomitantly treated with MLT and IL-2 was significantly longer with respect to both patients treated with MLT ($p<0.05$) and those with only supportive care ($p<0.001$). In more detail, no patient treated with the supportive care alone was alive at 2 years, whereas 2-year survival was achieved in 6/285 (2%) patients of the MLT group and in 29/275 (11%) patients treated with IL-2 plus MLT. Moreover, no patient treated with MLT alone was alive at 3 years, whereas 3-year survival was obtained in 13/275 (5%) patients concomitantly treated with MLT and IL-2. No MLT-related toxicity was observed, nor was any important clinical complication seen in patients concomitantly treated with IL-2, since the only side-effect observed was fever less than 38˚C during the first days of injection.

Discussion

This study confirms in a great number of patients with untreatable metastatic cancer that biological therapeutic approaches may counteract the clinical evolution of the neoplastic disease and prolong the survival time. This evidence demonstrates that cancer-related neuroimmune alterations do not constitute a simple epiphenomenon, but could be involved in the physiopathological mechanisms responsible for cancer progression, which would be at least in part a consequence of the disruption of the psychoneuroimmune functional status occurring in the neoplastic disease. The simple administration of the pineal hormone MLT, in an attempt to correct the main cancer-related endocrine deficiency, appears to be able to prolong the survival time, which may be further improved by the correction of the major cancer-related immune deficiency, namely the progressive decline in the endogenous production of IL-2. It is thus probable that more interesting therapeutic results may be achieved by the correction of other important neuroendocrine alterations, such as diminished activity of the endocannabinoid system (21), and immune anomalies, such as IL-12 secretion following the diminished activity

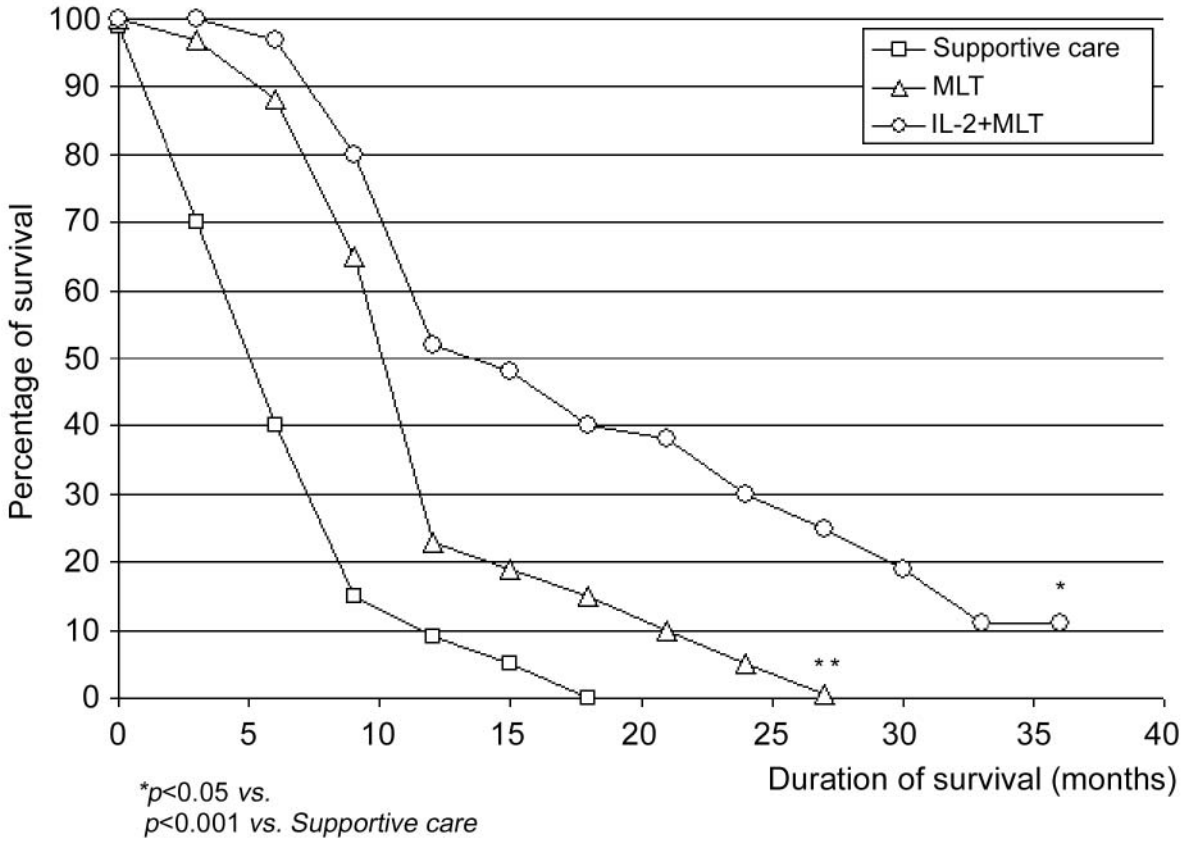

Figure 1. *Three-year survival curves of patients with untreatable metastatic solid tumors receiving supportive care alone, supportive care plus the pineal hormone melatonin (MLT) or supportive care plus neuroimmunotherapy with subcutaneous low-dose IL-2 plus MLT.*

of dendritic cells (22, 23). Finally, further more promising results may be achieved through an intermittent and more prolonged administration of IL-2, as demonstrated by other authors (24). This study suggests that future immunotherapies of cancer will need to be designed and established not only in an empirical manner (25-27), but also on the basis of the psycho-neuroimmune physiopathological alterations occurring in cancer that are responsible for the evolution of the neoplastic disease until the death of the patients.

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Received October 15, 2007
Revised December 15, 2007
Accepted February 8, 2008