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Research Article

A Phase-2 Study of High-dose Melatonin in Association with Active Hexose-correlated Compound (NK-Life) in Advanced Cancer Patients with Persistent Lymphocytopenia

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Abstract

Lymphocytopenia is something that cancer patients present with very often. Lymphocyte deficiency appears to be correlated with a worse prognosis. This experimental study emphasises how the combination of melatonin and AHCC in appropriate dosages can help counteract lymphopenia.

Keywords: Melatonin; Cancer; Lymphocytopenia; AHCC

Introduction

In addition to the efficacy of the different conventional anti-cancer therapies, including chemotherapy, targeted therapies, anti-angiogenic therapy, endocrine therapy and immunotherapy, the various complementary natural treatments could potentially contribute to the advances in cancer cure not only as a palliative therapy, but also to counteract cancer growth itself because of their potential effects on the biological! immune-inflammatory response [1]. Then, it becomes fundamental to investigate the effects of the various therapeutic natural agents from human body itself, plants or mushrooms on both cancer cell proliferation and the anticancer immunity. At present, the most known and investigate anticancer endogenous molecule is represented by the pineal hormone melatonin (MLT) [2], which is mainly produced during the night and whose production has been proved to progressively decline with cancer progression [3]. Then, pineal deficiency would constitute the main cancer-related endocrine deficiency [4]. MLT exerts its anticancer activity though multiple mechanisms, including possible direct cytotoxic action, anti angiogenic activity, anti-inflammatory action, bone marrow support activities in cancer patients [5] and stimulation of the anticancer immunity by promoting IL-2 secretion from TH1 lymphocytes [6] and inhibiting the production of IL-17 [7], one of the main cytokines provided by pro-tumoral activity [8]. *In vivo*, MLT anticancer activity has appeared to be a dose-dependent phenomenon [9]. At present, the only complementary therapy reported in the literature showing its impact on the survival time of untreatable cancer patients is that with high-dose MLT [10,11]. Moreover, this evidence would suggest that the best complementary natural anticancer therapy is that with anticancer molecules coming from human body itself. Then, all other complementary therapies with products from plants and mushrooms would have to include MLT, being the only natural anticancer therapy, which has appeared to be able to prolong the survival time in advanced cancer patients [12]. On the other side, other natural anticancer molecules could be associate with MLT to enhance the antitumor efficacy of MLT itself. Within the great

number of potential anticancer products from plants and mushrooms, most of them have been investigate for their only cytotoxic activity rather than for their action on the antitumor immunity, which is known to be mainly mediated by the lymphocytes after activation with IL-2 [11], whereas it is suppressed by macrophage-induced chronic inflammatory status [12]. Moreover, it has been shown that cancer progression has appeared to be associated with a progressive decline in lymphocyte-to-monocyte ratio (LMR) [13]. Therefore, LMR constitutes a fundamental and simple biomarker to monito the immune status of cancer patients, because of the evidence of the association between abnormally low values of LMR and a reduced survival in advanced cancer patients [13]. Within the group of potential anticancer mushrooms, some important antitumor immunomodulating activities would exert by active hexose correlated compound (AHCC) [14]. On these bases, a phase-2 study was planned to evaluate the effect of a natural regimen with high-dose MLT and AHCC on changes in LMR values in advanced cancer patients with persistent lymphocytopenia.

Patients and Methods

The study included 14 consecutive advanced cancer patients with persistent lymphocytopenia. Eligibility criteria were, as follows: histologically proven neoplastic disease, locally advance or metastatic disease, lymphocytopenia with lymphocyte count less than 1,300/mm^3 for at least 2 months, and no chronic therapy with steroids because of their immune suppressive effects. The experimental protocol was explained to each patient, and written consent was obtained. MLT was given orally at 100 mg/day during the dark period of the day, corresponding to the daily period of its maximal secretion, generally 30 minutes prior to sleep. AHCC was also given orally at 2,500 mg/day (600 mg at 8 AM and 1,900 mg at 8 PM). Patients were considered as fully evaluable when received the treatment far at least 1 month. Normal values of LMR observed in our laboratory (95% confidence limits) were more than 2.1.

Data were reported as mean +/- SE, and statistically analyzed by the chi-square test and the Student's t test, as appropriate (Figure 1).

		Lymphocytes [10^9/L]			Monocytes [10^9/L]		ratio lym/mon		
Patient	MLN [mg]	Start	After one month of therapy	increase %	Start	After one month of therapy	Start	After one month of therapy	increase %
1	100	1,27	1,57	+24%	0,18	0,22	7,06	7,14	+1%
2	100	0,77	1,18	+53%	0,45	0,5	1,71	2,36	+38%
3	100	1,79	2,08	+16%	0,74	0,6	2,42	3,47	+43%
4	100	0,8	0,87	+9%	0,27	0,27	2,96	3,22	+9%
5	100	1,1	1,5	+36%	0,5	0,4	2,20	3,75	+70%
6	100	0,77	2,63	+242%	0,4	0,45	1,93	5,84	+204%
7	100	0,3	0,52	+73%	0,6	0,6	0,50	0,87	+73%
8	100	1,15	1,22	+6%	0,53	0,49	2,17	2,49	+15%
9	100	1,46	2,3	+58%	0,47	0,6	3,11	3,83	+23%
10	100	0,87	1	+15%	0,6	0,6	1,45	1,67	+15%
11	100	0,9	0,92	+2%	0,5	0,45	1,80	2,04	+14%
12	100	1,2	1,21	+1%	0,6	0,6	2,00	2,02	+1%
13	100	treatment discontinued by the patient							
14	100	treatment discontinued by the patient							
	average	1,03	1,42	45%	0,49	0,48	2,44	3,22	42%

Figure 1

Results

The results of this preliminary study show that a neuroimmune regimen with the pineal hormone MLT plus AHCC may modulate the immune status of advanced cancer patients by enhancing lymphocyte count and reduce monocyte number, with a fallowing increase in LMR values. Because of the negative prognostic significance of low LMR [14], the increase in LMR values may impact on cancer growth and induce a stabilization of disease.

Discussion and Conclusion

The results obtained in this small pilot study are very encouraging.

Therefore, successive studies will be required to evaluate the influence of MLT plus AHCC regimen on the survival of cancer patients with very advanced disease. Finally, successive randomized studies with MLT alone versus MLT plus AHCC will be needed to

establish whether the concomitant administration of AHCC may increase the immunomodulating properties of MLT on cancer growth and on its prognosis.

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