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Biotherapy with the pineal hormone melatonin plus aloe and myrrh tincture in untreatable metastatic cancer patients as an essence therapy of cancer

Research Article

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Abbreviations: Melatonin (MLT), complete response (CR), partial response (PR), stable disease (SD), disease control (DC), progressive disease (PD), T helper lymphocytes (TH, $CD4^+$), T regulatory lymphocytes (T reg, $CD4^+$ $CD25^+$)

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Summary

Background: The recent advances in understanding the immunobiological interactions responsible for cancer progression have allowed us to define the mechanisms of action of some plants, whose antitumor properties were already known by the popular Medicine, in particular Aloe and Myrrha, whose mixture was already therapeutically utilized more than 2000 years ago by the Essence medicine. Moreover, some endogenous natural substances, namely the main hormone produced by the pineal gland melatonin (MLT) may also play anticancer activity. On this basis, a study was performed with a biological regimen consisting of MLT, Aloe and Myrrha in untreatable metastatic cancer patients with life expectancy lower than 1 year. Methods: The study included 35 patients. MLT was given orally at 20 mg/day in the evening and a mixed Aloe and Myrrha tincture was administered at a dose of 5 ml/thrice daily. Results: The clinical response consisted of complete response (CR) in 1, partial response (PR) in 2, stable disease (SD) in 19 patients, whereas the remaining 13 patients had a progressive disease (PD). Thus, a disease control (CR + PR + SD) was achieved in 22/35 (63%)patients. Moreover, a survival longer than 1 year was achieved in 17/35 (49%) patients. Finally, DC was associated with an evident improvement in the immune status, namely consisting of a decrease in the number of T regulatory lymphocytes, which are the main cells responsible for the suppression of the anticancer immunity. Conclusion: This preliminary study shows that a biological anticancer regimen consisting of the pineal hormone MLT in association with Aloe and Myrrha mixture, already known at the times of the Essence medical tradition, may induce a control of the neoplastic disease by stimulating the anticancer immunity, in a relevant percentage metastatic cancer patients, who did not respond to the conventional anticancer treatments and for whom no other standard therapy was available.

I. Introduction

The recent better definition of the biochemical mechanisms responsible for cancer cell proliferation and for immune system-mediated tumor cell destruction has allowed the possibility to establish the biochemical actions of several plants already known by the popular Medicine to be provided by empiristic potential anticancer properties, namely Aloe, Myrrha, Cannabis Indica, Turmeric and Hyssopus (Davis et al, 1991; Capasso et al,

1998; Vogler et al, 1999; Claeson et al, 1991; Qureshi et al, 1993; Blazquez et al, 2003; Grotenhermen et al, 2004; Aggarwall et al, 2003; Lodha et al, 2000). In more detail, the anticancer activity of Aloe is due to several therapeutically active molecules capable of inhibiting cancer cell proliferation, such as aloenine, aloesine and aloe-hemodin, or stimulating the anticancer immunity, such as acemannane and glycomannane (Davis et al, 1991; Capasso et al, 1998; Vogler et al, 1999). On the same way, the antitumor therapeutic properties of Myrrha extracts have been proven to exert both anticancer antiproliferative and immunostimulating effects, which are mediated by T-cadinol and muzumboic acid, respectively (Claeson et al, 1991; Qureshi et al, 1993). The therapeutic biological properties of a mixture of Aloe and Myrrha were well known by the Essence medical tradition at Qumran, near to the Death Sea, as reported by John's Gospel (John's Gospel), referring that men connected to the Essence community, such as Nycodemus and Joseph of Arimathea, prepared a mixture of Aloe and Myrrha for the burial of Christ. Together with the Ellenic medical sciences, the Essence medicine represented the most advanced medical tradition in the ancient world. With respect to the Ellenic medicine, which was founded by Hippocrates, the Essence medical science was more symbolic and spiritual, by considering the treatment of the human diseases as a simultaneous chemical, psychic and spiritual regeneration of man, mediated by humans, but originating from God. The Essence philosophy interpreted the Universe, the human History and the individual life of men and women as the expression of a war between two opposite principles, the Light and Dark, and the single human disease was considered to be the consequence of the prevalence of the principle of Darkness, as the unconscious aspect of the human life, on the principle of Light, which in contrast is the expression of the spiritual consciousness. The philosophic and spiritual characteristics of the Essence medical tradition were further amplified by the Islamic Medicine, by affirming the existence in the Nature of a therapeutic remedy for the overall human illnesses, as the manifestation of Love and harmonies of God. The fundamental importance of the light/dark circadian rhythm in regulating the living organisms, including humans, has been recently confirmed by the investigation on the physiology of the pineal gland, which has appeared to regulate the most important biological functions and systems, such as cell proliferation, DNA expression and immune reactions in relation to the light/dark rhythm through the circadian secretion of its most known hormone melatonin (MLT), with high production during the darkness and low secretion during the light period of the day (Iguchi et al, 1982; Attanasio et al, 1985; Jankovic et al, 1997; Brzezinski et al, 1997). As well as Aloe and Myrrha, MLT also has been proven to play an anticancer action and the antitumor properties of MLT have been confirmed by several experimental and clinical studies (Bartsch et al, 1981; Regelson et al, 1987; Lissoni et al, 2002; Sze et al, 1993). The anticancer action of MLT is due to both direct antiproliferative effects and stimulation of IL-2- dependent anticancer immunity (Maestroni 1993; Lissoni et al, 2008). Because of its dependency on the Light/Dark universal rhythm, whose importance was already known by the Essence tradition, the knowledgements of the functions of the pineal gland, including its anticancer fundamental role, may be considered as the last contribution of the Essence science to the treatment of the human diseases, namely cancer, since the Essence medicine was the first to discover the therapeutic properties of the mixture of Aloe and Myrrha. Moreover, preliminary data would suggest the possibility to amplify the anticancer action of MLT by Aloe extracts (Lissoni 2002). On these bases and in agreement with the well experimentally documented anticancer activity of its overall compounds (Davis et al, 1991; Claeson et al, 1991; Bartsch et al, 1981), in this preliminary study we have evaluated the clinical efficacy of a biological regimen, consisting of Aloe, Myrrha and the pineal hormone MLT, which could be symbolically defined as an Essence therapy, in the treatment of metastatic cancer patients, who failed to respond to the conventional antitumor therapies, including chemotherapy, endocrine therapy and anti-angiogenic treatment, or who were unable to tolerate the conventional therapies and for whom no other standard treatment was available. The objective of the study was to establish whether the association of other natural anticancer agents such as Aloe and Myrrh might further enhance the antitumor efficacy of MLT in the treatment of human neoplasm, with respect to the historical ones achieved with MLT alone.

II. Materials and methods

The study included 35 consecutive metastatic cancer patients, who were followed at the Institute of Biological Medicine of Milan. The therapeutic protocol was explained to each patient and informed consent was obtained. Eligibility criteria were, as follows: histologically proven metastatic solid tumor, measurable lesions, no double tumor, lack of response top the conventional anticancer therapies or poor clinical conditions unable to subtain a chemotherapeutic approach, a life expectancy less than one year, no chronic concomitant therapy with corticosteroids because of their immunosuppressive effects and a minimum follow-up of 12 months. The clinical characteristics of patients are reported in **Table 1**. The treatment consisted of MLT at 20 mg/day orally during the dark period of the day according to its light/dark circadian rhythm (Iguchi et al, 1982; Attanasio et al, 1985; Jankovic et al, 1997; Brzezinski et al, 1997), plus a mixture of Aloe Vera and Myrrha tincture, containing 60% of Aloe and 40% of Myrrha, which was administered orally at a dose of 5 ml thrice/day at 8- hour intervals. The treatment was continued until the progression of disease. Both MLT (Melaton-Med) and mixed Aloe and Myrrha tincture (Mirral) were supplied by Natur-Spiritual (Milan, Italy). The clinical response was evaluated according to WHO criteria. The treatment was also evaluated in relation to its possible immunomodulating effects on the anticancer immunity, by measuring the absolute number of the most important anticancer lymphocyte subset and that of the main immunosuppressive lymphocyte subpopulation, consisting of T helper lymphocyte (TH) and T regulatory lymphocyte (T reg), respectively (Shevach et al, 2002). Lymphocyte subsets were measured by a flow cytometric assay and monoclonal antibodies supplied by Becton-Dickinson (Milan, Italy). TH and T reg lymphocytes were identified as $CD4^+$ cells and $CD4^+$ $CD25^+$ cells, respectively. CD4/CD4CD25 cell ratio was also established. Normal values of CD4/CD4CD25 ratio observed in our laboratory (95% confidence limits) was

greater than 4.0. The immune analysis was made before the onset of treatment and after three months of therapy. Finally, patients were also clinically evaluated from a psychological point of view by the Rorschach test (Rorschach et al, 1921) and spiritually investigated by a specific patient spiritual questionnaire, previously reported in literature (Lissoni et al, 2008). Moreover, patients, who asked a psychospiritual therapeutic approach, were followed through a specific psychospiritual herapeutic method, consisting of an educational program carried out to stimulate the concomitant rediscovery of the perception of pleasure and the spiritual sensitivity. In more detail, according to previous studies (Lissoni et al, 2008), patients were stimulate to become conscious that both pleasure repression and self-punishment may suppress the anticancer immunity and promote cancer cell dissemination. Data were reported as mean ± SE and statistically analyzed by the chi-square test, the Student's t test and the analysis of variance, as appropriate. Moreover, the 1-year survival curves were plotted according to Kaplan-Meier method and statistically analyzed by the log-rank test.

Table 1: Clinical characteristics of 35 untreatable metastatic cancer patients.

Characteristics	**N**
Male / Female	19/16
Median age (year s)	63 (52-81)
Median Performance status (Karnofsky's score)	90 (70-100)
Tumor histotypes:	
Lung cancer	10
Nonsmall cell lung cancer	7
Small cell lung cancer	3
Colorectal cancer	5
Pancreatic cancer	4
Ovarian cancer	4
Prostate cancer	4
Gastric cancer	3
Biliary tract cancer	3
Malignant melanoma cancer	2
Dominant metastasis sites:	
Soft tissues	2
Bone	3
Lung	10
Liver	7
Lung + liver	5
Peritoneum	6
Brain	2
Previous Chemotherapies	31 / 35

Table 2: Clinical results in response to Melatonin plus Aloe and Myrrh in relation to tumor hitotypes.

Tumor Histotype	**N**	**CR**	**PR**	**CR+PR**	**SD**	**DC** (CR+PR+SD)	**PD**
Overall patients	35	1	2	3 (9%)	19 (54%)	22 (63%)	13 (37%)
Nonsmall cell lung cancer	7	0	0	0	5	5	2
Small cell lung cancer	3	0	0	0	2	2	1
Colorectal cancer	5	0	0	0	4	4	1
Pancreatic cancer	4	0	1	1	1	2	2
Ovarian cancer	4	0	0	0	2	2	2
Prostate cancer	4	0	0	0	2	2	2
Gastric cancer	3	0	0	0	2	2	1
Biliary tract cancer	3	0	1	1	1	2	1
Malignant melanoma cancer	2	1	1	1	0	1	1

III. Results

As shown in **Table 2**, an objective tumor regression was achieved in 3/35 (9%) patients, consisting of a complete response (CR) in one patient with node metastases due to malignant melanoma and 2 partial responses (PR), the former in a patient with liver metastases due to pancreatic adenocarcinoma and the latter in a patient with biliary tract cancer-induced liver involvement. The median duration of the response was 11 months (Aggarwall et al, 2003; Lodha et al, 2000; John's Gospel; Iguchi et al, 1982; Attanasio et al, 1985; Jankovic et al, 1997; Brzezinski et al, 1997; Bartsch et al, 1981). A stable disease (SD) was observed in 19/35 (54%) patients (non-small cell lung cancer: 5; small cell lung cancer: 2; colorectal cancer: 4; gastric cancer: 2; pancreatic cancer: 1; biliary tract cancer: 1; prostate cancer: 2; ovarian carcinoma: 2). Then, a disease control (DC), consisting of CR, PR and SD, was achieved in 22/35 (63%) patients. On the contrary, the remaining 13/35 (37%) patients had a progressive disease (PD). The median duration of DC was 8 months (Qureshi et al, 1993; Blazquez et al, 2003; Grotenhermen et al, 2004; Aggarwall et al, 2003; Lodha et al, 2000; John's Gospel; Iguchi et al, 1982; Attanasio et al, 1985; Jankovic et al, 1997; Brzezinski et al, 1997; Bartsch et al, 1981; Regelson et al, 1987). A survival longer than 1 year was achieved in 17/35 (49%) patients and the percentage of 1-year survival observed in patients with DC was significantly higher with respect to that found in those who had a PD (15/22(68%) vs 2/13(15%), $P < 0.01$). As far as the ratio was found in 21/35 (60%) patients. The mean numbers of TH and T-reg lymphocytes increased and decreased on therapy, respectively, without however statistically significant differences with respect to the pre-treatment values (TH: 592 ± 46 vs 544 ± 38/mm^3; T reg: 226 ± 28 vs 277 ± 22/mm^3). On the same way, CD4$^+$ /CD4$^+$ CD25$^+$ mean ratio increased on therapy, without however significant differences (3.1 ± 0.4 vs 2.8 ± 0.3). On the contrary, by evaluating the immune variations in relation to the clinical response, a significant decrease in T-reg mean number and a significant increase in CD4+ /CD4$^+$ CD25$^+$ mean ratio were observed in patients with DC (T-reg: 189 ± 14 vs 268 ± 217/mm^3, $p<0.05$; CD4$^+$ /CD4$^+$ CD25$^+$: 5.9 ± 0.3 vs 2.2 ± 0.4, $p < 0.01$), whereas T-reg mean count enhanced (309 ± 28 vs 284 ± 25/mm^3) and CD4+ /CD4$^+$ CD25$^+$ mean ratio diminished (2.6 ± 0.5 vs 2.9 ± 0.3) in patients with PD, even though none of these differences was statistically significant. TH means number enhanced (686 ± 38 vs 584 ± 41/mm^3) in patients with DC and decreased (576 ± 46 vs 598 ± 37/mm^3) in patients with PD, without however significant differences. A lack of both spiritual sensitivity and pleasure feeling at the Rorschach test was observed in 21/35 (60%) patients. Moreover, the percentage of DC obtained in patients expressing pleasure and spiritual sensitivity at the Rorschach test was significantly greater with respect to that achieved in patients with suppression of both pleasure and spirituality (12 /14(86%) vs 10/21(48%), $p<0.05$). On the same way, the mean values of the spiritual score were significantly higher in patients who achieved a DC than in those who had a PD (72 ± 4 vs 53 ± 3, $p<0.025$). The treatment was well tolerated in all patients. A mild transient diarrhoea, due to the laxative action of aloine, occurred in only 4/35 (11%) patients. Moreover, a clear improvement in the well being was reported in 14/22 (64%) patients with DC and in only 3/13 (23%) patients with PD. This difference was statistically significant ($P < 0.05$). Finally, in none of the patient the neoplastic cachexia occurred.

IV. Discussion

This preliminary biotherapeutic study shows that a biological strategy consisting of the pineal hormone MLT, Aloe and Myrrha, each of who has been proven to play antitumor activity (Davis et al, 1991; Claeson et al, 1991; Bartsch et al, 1981), may induce a control of the neoplastic growth in a relevant percentage of metastatic cancer patients, for whom no other standard antitumor therapy was available. Moreover, this study demonstrates that the control of the neoplastic disease achieved by this biological strategy may influence the clinical course of the neoplastic disease, a prolonged survival with respect to that observed in patients, who had no benefit from the treatment. In particular, by comparing these results with those historically obtained with MLT alone (Lissoni 2002; Maestroni 1993) it seems that Aloe and Myrrh association further amplify the anticancer action of MLT (Lissoni 2002; Maestroni 1993). Therefore these preliminary data would justify successive randomized trials with MLT alone vs. MLT plus Aloe and Myrrh to confirm the greater efficacy of a polytherapy with several biological natural agents, with respect to single agent. In addition, this study would suggest that the therapeutic efficacy of this natural biological regimen is mainly mediated by the immune system by piloting in an antitumor way the host immunobiological reaction and in particular it seems to be able to counteract advanced cancer-related abnormally enhanced function of T-reg cell system, which would represent the main cause responsible for the lack of an effective anticancer immune reaction in the disseminated neoplastic disease (Shevach 2002). Finally, this study would seem to suggest that the efficacy of an anticancer immunobiological regimen, consisting of MLT, Aloe and Myrrha, may be influenced by both psychological and spiritual status of patients and in particular the evidence of a suppression of both pleasure and spiritual feeling may predict a reduced efficacy of the treatment in terms of control of the neoplastic growth. Generally, the Oncologists subdivide the medical treatments of cancer into curative and palliative therapies, by commonly considering as antitumor curative drugs the only chemotherapeutic agents. From this point of view, a clinical approach with natural biological anticancer agents, which is generally considered as a complementary medicine, cannot be simply defined as palliative treatment, because of its capacity of counteracting cancer cell proliferation also in patients for whom there was no other standard anticancer therapy. Further promising results in terms of control of the neoplastic progression could be achieved by considering that MLT is not the only anticancer hormone produced by the pineal gland (Bartsch

et al, 1981; Regelson et al, 1987; Lissoni et al, 2002; Sze et al, 1993). In fact, at least another pineal hormone, the 5 -methoxytryptamine, may play an anticancer action, with in vitro antiproliferative effects superior to those of MLT itself (Sze et al, 1993). Retinoids play also anticancer effects through cytodifferentiating and anti-angiogenic activities. In addition, at least five other plants could be successfully employed in the treatment of human neoplasms (Blazquez et al, 2003; Grotenhermen et al, 2004; Aggarwall et al, 2003; Lodha et al, 2000), including Hyssopus, Cannabis Indica, Turmeric and Incense may play anticancer effects. Moreover, Hyssopus, whose potential anticancer activity would be due to diosmine, could be particularly useful in the treatment of lung cancer patients, because of its very potent expectorating activity (Lodha et al, 2000). Cannabis Indica contains several cannabinoid agents provided by direct anticancer antiproliferative and anti-angiogenic actions (Blazquez et al, 2003; Grotenhermen et al, 2004). Finally, according to preliminary studies (unpublished data), curcumin, the main active anticancer molecule produced by turmeric (Aggarwall et al, 2003), would be particularly useful in the treatment of cancer of pancreas. Therefore, further studies will be required to establish which may be the best biological natural anticancer combination, by considering the therapeutic and the supportive care effects, the toxicity and the social coast of the various potential both endogenous and exogenous natural antitumor substances.

References

Davis RH, Parker WL, Sampson RT, Murdoch DP. Isolation of a stimulatory system in an Aloe extract. J Am Pediatr Med Assoc 1991; 81:473-8.

Capasso F, Borrelli F, Capasso R, Di Carlo G, Izzo AA, Pinto L et al. Aloe and its therapeutic use. Phytother Res 1998; 12:124-7.

Vogler BK. Aloe Vera: a systematic review of its clinical effectiveness. B J Gen Pract 1999; 49:823-8.

Claeson P, Zygmunt P, Hogestatt ED. Calcium antagonistic properties of the sesquiterpene T- cadinol. Pharmacol Toxicol 1991; 69:173-7.

Qureshi S, Al-Harbi MM, Ahmed M, Raza M, Giangreco AB, Shah AH. Evaluation of the genotixic, cytotoxic and antitumor properties of Commiphora molmol using normal and Erlich ascites carcinoma cell-bearing Swiss albino mice. Cancer Chemother Pharmacol 1993; 33130-8.

Blazquez C, Casanova ML, Planas A, Del Pulgar TG, Villanueva C, Fernandez-Acenero MJ et al. Inhibition of tumor angiogenesis by cannabinoids. FASEB J 2003; 17:529-31.

Grotenhermen F. Pharmacology of cannabinoids. Neuroendocrinol Lett 2004; 25:14-23.

Aggarwall BB, Kumar A, Bharti AC. Anticancer potential of curcumin. Preclinical and clinical studies. Anticancer Res 2003; 23:363-98.

Lodha R, Bagga A. Tradictional Indian system of Medicine. Ann Acad Med Singapore 2000; 29:37-41.

John's Gospel 19,38-40.

Iguchi H, Kato KI, Ibayashi H. Age-dependent reduction in serum melatonin concentrations in healthy subjects. J Clin Endocrinol Metab 1982; 55:27-9.

Attanasio A, Borrelli P, Gupta D. Circadian rhythms in serum melatonin from infancy to adolescence. J Clin Endocrinol Metab 1985; 61:388-90.

Jankovic BD. Neuroimmunomodulation. Ann NY Acad Sci 1994; 741:3-38.

Brzezinski A. Melatonin in humans. N Engl J Med 1997; 336:185-95

Bartsch H, Bartsch C. Effects of melatonin on experimental tumors under different photoperiods and times of administration. J neural Transm 1981; 52:269-79

Regelson W, Pierpaoli W. Melatonin: a rediscovered antitumor hormone? Cancer Invest

1987; 5:379-85

Lissoni P. Is there a role for melatonin in supportive care? Supp Care Cancer 2002; 10:110-6.

Sze S, Ng T, Liu W. Antiproliferative effect of pineal indoles on cultured tumor cell lines. J Pineal Res 1993; 14:27-33.

Maestroni GJM. The immunoneuroendocrine role of melatonin. J Pineal Res 1993; 14:1-10.

Lissoni P, Brivio F, Fumagalli L, Messina G,Vigorè L, Parolini D et al. : Neuroimmunomodulation in Medical Oncology: application of Psychoneuroimmunology with subcutaneous low-dose IL-2 plus the pineal hormone melatonin in patients with untreatable metastatic solid tumors. Anticancer Res 2008; 28:1377-82.

Shevach EM. CD4+CD25+ suppressor T cells: more questions than answers. Nat Rev Immunol 2002; 2:389-400.

Rorschach H. Psychodiagnosytics. Ed HA Huber, Bern, Stuttgart, Toronto. Verlag, 1921.

Lissoni P, Messina G, Parolini D, Balestra A, Brivio F, Fumagalli L et al.:A spiritual approach in the treatment of cancer. In Vivo 2008; 22:557-82.

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