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+)

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 untreated 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,}
Because of its dependency on the Light/Dark universal rhythm, whose importance was already known by the Essence tradition, the knowledge 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 Myrrha might further enhance the antitumor efficacy of MLT in the treatment of human neoplasms, 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 to the conventional anticancer therapies or poor clinical conditions unable to sustain 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 antitumor 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 therapeutic 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.

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

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

<table>
<thead>
<tr>
<th>Tumor Histotype</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>CR+PR</th>
<th>SD</th>
<th>DC (CR+PR+SD)</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients</td>
<td>35</td>
<td>1</td>
<td>2</td>
<td>3 (9%)</td>
<td>19 (54%)</td>
<td>22 (63%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Nonsmall cell lung cancer</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Biliary tract cancer</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Malignant melanoma cancer</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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; Grotinhermen 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 pretreatment values (TH: 592 ± 46 vs 544 ± 38/mm³; T-reg: 226 ± 28 vs 277 ± 22/mm³). 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/mm³, 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/mm³) 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/mm³) in patients with DC and decreased (576 ± 46 vs 598 ± 37/mm³) 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 antitumor 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 antitumor immune reaction in the disseminated neoplastic disease (Shevach 2002). Finally, this study would seem to suggest that the efficacy of an antitumor 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 countering 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 cost of the various potential both
endogenous and exogenous natural antitumor substances.

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