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A Randomized Study of Chemotherapy *Versus* Biochemotherapy with Chemotherapy plus *Aloe arborescens* in Patients with Metastatic Cancer

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Abstract. *Background: The recent advances in the analysis of tumor immunobiology suggest the possibility of biologically manipulating the efficacy and toxicity of cancer chemotherapy by endogenous or exogenous immunomodulating substances. Aloe is one of the of the most important plants exhibiting anticancer activity and its antineoplastic property is due to at least three different mechanisms, based on antiproliferative, immunostimulatory and antioxidant effects. The anti-proliferative action is determined by anthracenic and antraquinonic molecules, while the immunostimulating activity is mainly due to acemannan. Patients and Methods: A study was planned to include 240 patients with metastatic solid tumor who were randomized to receive chemotherapy with or without Aloe. According to tumor histotype and clinical status, lung cancer patients were treated with cisplatin and etoposide or weekly vinorelbine, colorectal cancer patients received oxaliplatin plus 5-fluorouracil (5-FU), gastric cancer patients were treated with weekly 5-FU and pancreatic cancer patients received weekly gemcitabine. Aloe was given orally at 10 ml thrice/daily. Results: The percentage of both objective tumor regressions and disease control was significantly higher in patients concomitantly treated with Aloe than with chemotherapy alone, as well as the percent of 3-year survival patients. Conclusion: This study seems to suggest that Aloe may be successfully associated with chemotherapy to increase its efficacy in terms of both tumor regression rate and survival time.*

The recent formulation of chemo-biochemotherapeutic regimens could represent a very simple but promising strategy in the treatment of human neoplasms (1-3). The chemo-biochemotherapeutic combinations have been developed to associate the cytotoxic action of cancer chemotherapy with molecules capable of modulating the antitumor biological response and to counteract the suppressive effect of cancer chemotherapy on host immunobiological responses, which plays a fundamental role in the control of tumor progression and dissemination (4-7). Hence, the rationale of the association between cancer chemotherapy and biological response modifier agents consists of the prevention of chemotherapy-induced damage of host anticancer immunobiological reaction. A great variety of natural molecules with immunostimulatory activity have been isolated from plants commonly used in traditional medicine in an empirical manner, in particular from Aloe, *Cannabis indica* and myrrh (8-10). The immunobiological information available up to now may justify the clinical use of these three plants in the palliative therapy of human neoplasms, at least to improve the efficacy and tolerability of the common standard anticancer therapies, including chemotherapy and radiotherapy. Despite differences in the chemical structure of their molecules, the anticancer activity of aloe, cannabis and myrrh is based on very similar mechanisms, consisting of antiproliferative, immunostimulatory, anti-inflammatory and antioxidant effects (8-10). In cannabis and myrrh, both the antiproliferative and immunoinflammatory-modulating effects are attributed to the same molecules, tethrahydrocannabinol and cannabinol for cannabis (11) and the sesquiterpene T-cadinol for myrrh (12). On the contrary, the antiproliferative and the immunomodulating effects of aloe are mediated by separate molecules. More specifically, the antitumor and antiproliferative effects of aloe are mainly exerted by aloenin-like substances, namely aloe-emodine, whose oncostatic action has been shown to be particularly evident against neuroendocrine cancer cell lines (13). On the other hand, the immunostimulatory properties of aloe are mainly dependent on acemannan and glycomannan (14), whose stimulatory action on anticancer immunity is mediated, at least in part, by the inhibibition of interleukin (IL)-l0 secretion, with a resulting increase in the production of IL-2, which plays a fundamental role in the generation of the anticancer immunity

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(15). The anticancer properties of aloe have been confirmed by several experimental *in vitro* and *in vivo* studies (16, 17), revealing that the anticancer activity of aloe does not depend only on its immunomodulatory effect, as believed until recently, but also on a direct inhibition of cancer cell proliferation through aloenin-like molecules.

This finding is not surprising, since aloenin and other similar molecules may be classified within the group of anthracenic and anthraquinonic substances, whose antiproliferative cytotoxic effects are well known. A considerable number of clinical investigations with aloe extracts have been performed, however, these have yelded controversial results. Aloe therapy has been particularly investigated in the treatment of psoriasis, hyperlipidemia and diabetes mellitus (18-21) and it may exert anticholesterolemic and antidiabetic effects (18). Moreover, it stimulates wound repairing, however, no efficacy has been observed in the treatment of radiotherapy-induced skin damage (21).

Finally, aloe has been used for the tratment of human neoplasm (22), although only preliminary data are available. Despite all of this work, most studies are very limited from a methodological point of view, due to the low number of patients and lack of randomization. Therefore, the present study was planned in an attempt to investigate the influence of a concomitant aloe administration on the efficacy and tolerability of chemotherapy in patients with advanced cancer and poor clinical status.

Patients and Methods

Patients. The study included 240 consecutive patients with metastatic solid tumor, who were treated with chemotherapy with or without aloe treatment. The study was performed by using the variety *Aloe arborescens*. Eligibility criteria were as follows: histologically proven metastatic solid tumor; histological diagnosis of lung cancer or gastrointestinal tract tumor; measurable lesions, no previous chemotherapy for the metastatic disease; no possibility to tolerate the most aggressive polychemotherapies because of low performance status (PS), age and/or concomitant important medical illnesses other than cancer; no brain metastasis and no double tumor. The metastatic disease was established by CT scan and/or NMR or PET. Moreover the diagnosis of poor clinical status was established on the basis of low PS and/or concomitant relevant medical diseases other than cancer. The experimental protocol was explained to each patient, and written consent was obtained.

Treatments. According to tumor histotype, sites of metastases and type of chemotherapy, patients were randomized to receive chemotherapy alone or chemotherapy plus aloe. Chemotherapy consisted of cisplatin (CDDP) plus etoposide (VP16) or weekly vinorelbine (VNR) for non-small cell lung cancer (NSCLC) in patients with good or poor clinical status respectively; CDDP plus VP-16 for small cell lung cancer (SCLC); low-dose oxaliplatin (OXA) plus 5-fluorouracil (5-FU) for colorectal cancer; weekly 5-FU for gastric cancer, and weekly gemcitabine (GEM) for pancreatic adenocarcinoma.

Table I. *Clinical characteristics of 240 evaluable patients withs metastatic solid tumors treated with chemotherapy (CT) alone or CT plus aloe.*

Characteristics	CT	CT + Aloe
No.	121	119
Male/female	67/54	65/54
Median age (years)	64 (61-77)	65 (58-79)
Median performance status (Karnofsky's score)	80 (60-100)	80 (60-100)
Dominant metastasis sites:		
Soft tissues	7	6
Bone	20	16
Lung	26	25
Liver	37	35
Liver + lung	24	25
Liver + peritoneum	7	12

CDDP and VP-16 were given *i.v.* at 20 mg/m^2 and at 100 mg/m^2 for 3 consecutive days every 21 days, corresponding to one complete chemotherapeutic cycle. OXA was given *i.v.* at 85 mg/m^2 on days 1 and 8, in association with 5-FU and folates (FA) at a dose of 500 mg/m^2 and 10 mg/m^2 respectively, at days 18 and l5, by repeating the cycle every 28 days. VNR was given weekly at 25 mg/m^2. Weekly 5-FU consisted of 375 mg/m^2, in association with FA at a dose of 10 mg/m^2.

Finally, GEM was given weekly at 1,000 mg/m^2. *Aloe arborescens* was given orally at a dose of 10 ml thrice daily of a mixture consisting of 300 g of Aloe fresh leaves in 500 g of honey plus 40 ml of 40% alcohol, every day without interruption, either during or after chemotherapy, until the progression of disease, starting 6 days prior to the onset of chemotherapy. Aloe mixture was supplied by Deca (Isernia, Italy). The clinical response and toxicity were assessed according to WHO criteria. PS was evaluated by Karnowsky's score. The clinical responses were radiologically evaluated after at least three cycles of chemotherapy by repeating the same radiological investigation used prior to the onset of chemotherapy, including CT scan, NMR and PET. Patients were monitored weekly by routine laboratory tests. Lymphocyte counts were determined by hemochromocytometric analysis. The evaluation of subjective symptoms, such as fatigue and asthenia, was assessed by an individual report.

Statistical analysis. The results were statistically analyzed by the chi-square test, Student's *t*-test and analysis of variance, as appropriate.

The survival curves were plotted by the Kaplan-Meier method and statistically evaluated by the log-rank test. The differences were considered to be statistically significant when p-values were <0.05.

Results

The clinical characteristics of patients are reported in Table I. As shown, the two groups of patients treated with chemotherapy alone, or chemotherapy plus aloe were well comparable for the main prognostic variables, including

Table II. *Clinical response (WHO criteria) in 240 metastatic solid tumor patients treated with chemotherapy (CT) or CT plus Aloe.*

Histotypes	CT							CT + ALOE						
	n	CR	PR	CR+PR	SD	DC	PD	n	CR	PR	CR+PR	SD	DC	PD
Small cell lung cancer														
CDDP/VP16	22	2	6	8 (36%)	7	15 (68%)	7	23	6	8	14 (61%)*	4	18 (78%)**	5
Non-small cell lung cancer	36	1	6	7 (19%)	11	18 (50%)	18	38	4	8	12 (32%)	14	26 (68%)	12
Weekly VNR	17	0	3	3 (18%)	4	7 (41%)	10	17	2	3	5 (29%)	6	11 (65%)	6
CDDP/VP	19	1	3	4 (21%)	7	11 (58%)	8	21	2	5	7 (33%)	8	15 (71%)	6
Colorectal cancer														
OXA/5-FU/FA	21	1	5	6 (29%)	8	14 (67%)	7	21	2	6	8 (38%)	7	15 (71%)	6
Gastric cancer														
Weekly 5-FU/FA	22	0	0	0	9	5 (28%)	13	19	0	3	3 (16%)	7	10 (59%)	9
Pancreatic adenocarcinoma														
Weekly GEM	20	0	2	2 (7%)	10	8 (50%)	8	18	0	3	3 (17%)	8	11 (73%)	7
Overall	121	4	19	23 (19%)	37	60 (50%)	61	119	12*	28	40 (34%)**	40	80 (67%)**	39

CDDP: Cisplatin; VP16: etoposide; VNR: vinorelbine; OXA: oxaliplatin; 5-FU: 5-fluorouracil; FA: folinic acid; GEM: gemcitabine; CR: complete response; PR: partial response; SD: stable disease; DC: disease control (CR+PR+SD); PD: progressive disease. *p<(0.025 *vs*. CT; **p<0.01 *vs*. CT

histotype, sites of metastasis, PS and age. The observed clinical response in the two groups of patients are reported in Table II.

By considering the overall tumor histotypes, the percentages of complete responses (CR) and partial responses (PR) achieved in patients concomitantly treated with aloe were significantly higher than in those who received chemotherapy alone (40/119 (34%) *vs*. 23/121 (19%), p<0.01). A CR occurred in 12/119 (10%) patients concomitantly treated with aloe and in only 4/121 (3%) patients treated with chemotherapy alone. This difference was statistically significant (p<0.01). Stable disease (SD) was achieved in 37/121 (31%) patients treated with chemotherapy alone and in 40/119 (34%) patients who received a concomitant aloe administration. The disease control (DC=CR+PR+SD) obtained in patients concomitantly treated with aloe showed a significantly higher percentage than that found in patients who received chemotherapy alone (80/119 (67%) *vs*. 60/121 (50%), p<0.0l).

As far as the clinical response in relation to tumor histotype is concerned, the objective tumor response rate (CR+PR) achieved in the group of SCLC patients concomitantly treated with aloe was significantly higher than that found in the group of chemotherapy alone (14/23 (61%) *vs*. 8/22 (36%), p<0.05). Moreover, the percentage of CR was also significantly higher in SCLC patients concomitantly treated with aloe (6/23 (26%) *vs*. 2/22 (9%), p<0.05). Similarly, the objective tumor response (CR+PR) observed in the remaining tumor histotypes, including colorectal cancer, gastric cancer and pancreatic adenocarcinoma, was consistently higher in patients concomitantly treated with aloe, without statistically significant differences.

Figure 1 illustrates the 3-year survival curves achieved in patients treated with chemotherapy alone or chemotherapy plus aloe. As shown, the percentage of 3-year survival obtained in patients concomitantly treated with aloe was significantly higher than that found in the group of chemotherapy alone (p<0.0l). As far as the survival in relation to tumor histotype are concerned, the percentage of 3-year survival achieved in both SCLC and NSCLC patients concomitantly treated with aloe was significantly higher than that obtained in those treated with chemotherapy alone (p<0.05). The survival was also longer in all other tumor histotypes treated with chemotherapy plus aloe, without statistically significant differences. Aloe was well tolerated in all patients and no metabolic undesirable effects were observed. In addition, no aloe-related toxicity occurred, including vomiting and diarrhoea.

From an immunobiological point of view, mean numbers of lymphocytes decreased and increased after chemotherapy in patients treated with chemotherapy alone or chemotherapy plus aloe, respectively, even though none of these differences were statistically significant. However, as illustrated in Figure 2, the mean lymphocyte mean number observed after therapy in patients concomitantly treated with aloe was significantly higher than that observed in the group treated with chemotherapy alone (p<0.05), while no difference was seen before the onset of treatment.

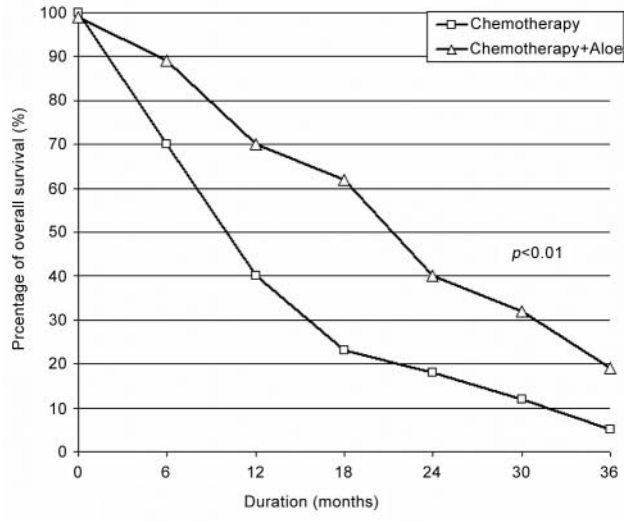

Figure 1. *3-Year survival curves observed in 240 patients with metastatic solid tumor treated with chemotherapy alone or chemotherapy plus aloe.*

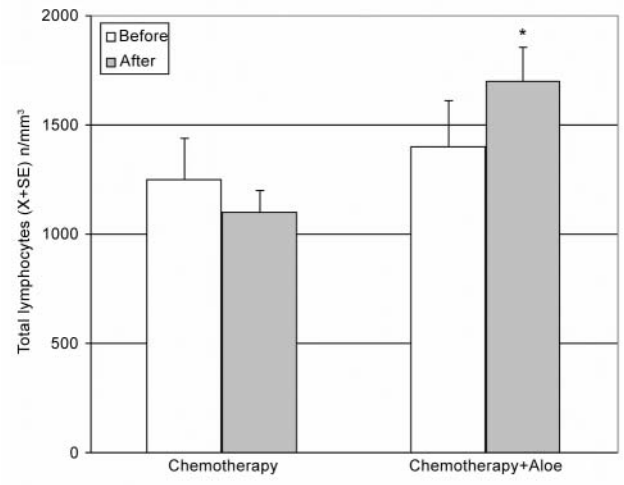

Figure 2. *Mean number of lymphocytes observed before and after the chemotherapeutic treatment in 240 patients with metastatic solid tumor treated with chemotherapy alone or chemotherapy plus aloe. *p<0.05 vs. Chemotherapy.*

Finally, chemotherapy was substantially better tolerated in patients concomitantly treated with aloe. In particular, the occurrence of asthenia and/or fatigue was significantly less frequent in patients concomitantly treated with aloe than in those who received chemotherapy alone (31/119 (26%) *vs.* 56/121 (46%), $p<0.01$). Similarly, VNR-induced constipation was significantly less frequent in the aloe group than in patients treated with VNR alone (3/17 (18%) *vs.* 12/17 (71%), $p<0.0l$). In addition, OXA-induced neurotoxicity, with paresthesic disturbances, was also less frequent in patients who received aloe with respect to those treated with chemotherapy alone (6/21 (29%) *vs.* 9/21(43%)), without statistically significant differences. No other important difference in the occurrence of side-effects was found.

Discussion

The results of this study confirm previous preliminary clinical investigations which had already shown the efficacy of aloe extracts in the palliative therapy of patients with untreatable metastatic cancer, either to improve their quality of life, or to prolong the survival time (22). In addition to these previous results, this study demonstrates the efficacy of aloe in association with cancer chemotherapy, at least in patients with poor clinical status because of low PS or important medical diseases, in whom the therapeutic activity of chemotherapy alone is generally low.

Thus, aloe extracts may exert not only a direct oncostatic effect, but also enhance the efficacy of chemotherapy in terms of both tumor regression rate and survival time as well as reducing some toxicities. Moreover, aloe-induced prolonged survival time was constantly associated with a better quality of life, at least in terms of relief of asthenia and fatigue. Aloe-induced increase in chemotherapy cytotoxic efficacy appear to be particularly evident in SCLC, because of its neuroendocrine nature. This evidence is not surprising, since experimental studies had already shown that the oncostatic properties of aloe substances are more pronounced against neuroendocrine cancer cell lines (13). In any case, aloe-induced increase in chemotherapy anticancer efficacy would depend not only on molecules provided by antiproliferative action, but also on the activity of immunomodulating substances, such as acemannan (8, 14). A particularly interesting combination could be represented by the association between VNR and aloe in the treatment of NSCLC, since aloe seemed either to increase VNR cytotoxic potency, or to correct the most frequent side-effect of VNR, that of severe constipation. The biochemotherapeutic combination of VNR plus aloe could thus constitute a very well tolerated and active therapy for NSCLC patients, including those with poor clinical status. Obviously, the low number of patients for the single tumor histotype does not allow definitive conclusions to be drawn in the treatment of the various solid tumor histotypes by aloe and chemotherapy combination therapy. The relatively low percentage of responses shown by this study for a single histotype with respect to that reported in the literature could depend on the poor clinical status of patients. In any case, further studies will be required to better investigate the real impact of a concomitant aloe therapy on the life of chemotherapy-treated patients with advanced cancer by using more appropriate scales for the quality of life. Moreover, since the study was not blinded, multiple bias may occur. Hence, double-blind randomized studies will be necessary to

confirm these promising results. Finally, further studies should be performed to establish whether aloe extracts may also enhance the efficacy of chemotherapy in patients with good clinical status. Future clinical studies with single aloe molecules, such as aloe-emodine and acemannan for their immunomodulating and antiproliferative properties, respectively, could allow further benefits in the treatment of human neoplasms. Several recent studies (23-27) have contributed to better define the mechanism of the anticancer activity of aloe. However, the exact mechanism of its immunomodulatory antitumor effect has still to be established in detail. Hence, successive studies, by evaluating the most important immune biomarkers, namely IL-2, IL-12, IL-6, IL-10, TGF-β and T regulator lymphocytes, will be essential to establish the influence of aloe on the anticancer cytokine network.

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