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Originals

Megestrol acetate in neoplastic anorexia/cachexia: clinical evaluation and comparison with cytokine levels in patients with head and neck carcinoma treated with neoadjuvant chemotherapy

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Summary. The aim of our study (clinical phase II open pilot study) was to evaluate the toxicity of megestrol acetate and its ability to increase appetite and body weight in patients with advanced-stage (III–IV) primary head and neck squamous cell carcinoma treated with neoadjuvant (primary) chemotherapy. Serum levels of interleukin-1α and β, interleukin-2 and 6, tumor necrosis factor-α, and the soluble receptor for interleukin-2 were evaluated before and after megestrol acetate treatment. The same cytokines and soluble interleukin-2 receptor were also measured in culture medium of peripheral blood lymphocytes from the same patients after stimulation with phytohemagglutinin. From April 1993 to February 1994, 11 male patients were enrolled in our study: their mean age was 57.8 years (range 43–69 years). Megestrol acetate was administered at a dose of 320 mg/day in the interval between chemotherapeutic cycles for a total of three consecutive cycles; 9 of the 11 patients could be evaluated (81.8%). Except for the performance status according to Karnofsky, all parameters were increased after megestrol acetate treatment. The average weight increased by 6.3 kg (13.2%), appetite by a score of 2.4 (38.6%) and the Spitzer's quality of life index by a score of 2.4 (36.2%). The performance status according to Karnofsky decreased in only 1 patient, remained the same in most patients, and in 2 patients was slightly improved. No significant side effects were observed during treatment. Serum levels of interleukin-1α and β, interleukin-2 and 6, tumor necrosis factor-α, and soluble interleukin-2 receptor were significantly higher than in normal subjects, prior to treatment with megestrol acetate. These levels dropped after megestrol acetate treatment with a statistically significant decrease for interleukin-1α and β and tumor necrosis factor-α. There were no significant differences in the production of cytokines by peripheral blood lymphocytes stimulated with phytohemagglutinin from patients before megestrol acetate treatment and normal subjects, with the exception of interleukin-6 (higher in patients) and of soluble interleukin-2 receptor (lower in patients). There was no significant difference in the cytokines and soluble interleukin-2 receptor produced in culture before and after megestrol acetate treatment, except for interleukin-6 which decreased after treatment.

Key words: Cytokines – Soluble interleukin-2 receptor – Head and neck carcinoma – Megestrol acetate – Neoplastic anorexia/cachexia

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Introduction

The anorexia/cachexia syndrome is the most common single cause of death documented in cancer patients [1]. The term "cachexia" derives from Greek *kakòs* which means bad and *hexis* meaning condition. Anorexia, loss of body weight accompanied by a decrease in muscular and adipose mass, increased susceptibility to infections, and a decreased response to anti-neoplastic therapy are the major clinical features of this condition [2,3]. The nutritional deficiency and the hormonal and metabolic modifications which characterize neoplastic/host interactions are the factors which eventually determine neoplastic anorexia/cachexia (NAC) [4].

Anorexia is one of the main features of the cachectic syndrome and may be so great that spontaneous nutrition is totally inhibited. The etiopathogenesis of anorexia is most certainly multifactorial: it seems at least in part attributable to intermediary metabolites which accumulate along an abnormal metabolic pathway in cancer patients (lactate, ketones, oligonucleotides) or other substances released by the tumor itself or by the host in response to the tumor, particularly the cytokines [3], which affect the medial hypothalamic regions. However, anorexia cannot by itself explain the complex organic alterations seen in NAC patients. Alongside the reduced food intake, important changes in energy metabolism have been observed, which may account for the cachectic syndrome.

It can therefore be hypothesized that NAC may result from the production of cytokines of a lymphomonocytic origin [5]. Experimental and clinical support for this etiopathogenetic theory is becoming ever more frequent in the literature, and it seems that a central role is played by interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor (TNF) [6, 7]. High serum levels of IL-1, IL-2, IL-6 and TNF have been found in cancer patients, and the levels of these cytokines seem to correlate with the progression of the tumor [8]. The chronic administration of these factors in man, either alone or in combination, is capable of reproducing the different features of NAC [7–11]. Animals passively immunized with specific antibodies directed against certain cytokines, particularly TNF and IL-6, do not present symptoms of cachexia [12, 13]. Moreover, there is no clear evidence that any one specific cytokine is chiefly responsible for NAC. Therefore, a hypothetic etiopathogenetic mechanism of NAC is the release of cachectic cytokines by neoplastic and/or immunocompetent cells and even cells of other compartments of the neoplastic patient.

From a clinical viewpoint, the degree of NAC accounts for the cancer mortality rate by itself, whatever the cause. The correction of NAC would therefore improve both the prognosis and quality of life of the neoplastic patients, especially in an advanced stage of disease. To control NAC and the corresponding weight loss, a possible approach consists of supporting forced feeding (impractical and/or ineffective due to altered metabolic processes together with nausea and vomiting) and drug administration. Among the drugs capable of stimulating appetite, progestins have been demonstrated to have a positive effect on appetite, food intake, and body weight [14]. In particular, megestrol acetate (MA), and active oral synthetic derivative of the natural steroid progesterone, has been shown to be well tolerated and to increase calorie intake and body weight [14–19], mostly due to an increased deposition of fat [20]. The effect of MA on NAC induced by different neoplasias [15–19, 21] or by the acquired immunodeficiency syndrome [22, 23] has previously been studied, but data are lacking on the effect of MA on the appetite and nutritional state of patients with advanced head and neck squamous cell carcinoma (HNC), undergoing chemotherapy or chemotherapy combined with radiation therapy. Among neoplastic patients, those affected by primary HNC represent a group in which the loss of appetite, the difficult alimentation due to anatomical factors, weight loss, and the more or less serious state of malnutrition (often already present before diagnosis of the neoplasia) associated with the bad habits of these patients (they are nearly always heavy smokers and/or drinkers), eventually made worse by the effects of anti-neoplastic chemotherapy, induce a severe NAC in a relatively early stage of the neoplasia, so much so as to represent a paradigmatic pattern of this type of cancer.

The aim of our study was to evaluate the effect of MA in inducing an increased appetite and body weight in HNC patients in an advanced (III–IV) stage of the disease treated with cisplatin-based neoadjuvant chemotherapy. Serum levels of the cytokines involved in NAC, IL-1α and β, IL-2, IL-6, TNFα, and the soluble receptor for IL-2 (sIL-2R), were evaluated in all patients before and after MA treatment. The same cytokines and sIL-2R were also measured in the culture medium of peripheral blood lymphocytes (PBMC) from the same patients after stimulation with phytohemagglutinin (PHA) (1 day for the cytokines and 7 days for sIL-2R), before and after MA treatment.

Patients and methods

Patients

From April 1993 to February 1994, 11 male patients were enrolled in our study: their mean age was 57.8 years (range 43–69 years). The patients were considered eligible according to the following criteria: locally advanced head and neck carcinoma treated with neoadjuvant chemotherapy, age 40–75 years, expected life span >4 months, weight decrease ≥10% of the ideal or customary body weight, geographic accessibility, and informed oral consent. Patients with a performance status according to Karnofsky (PSK) <40, unable to ingest food orally, obstruction or dysfunction of the alimentary tract, gastroduodenal ulcer, congestive heart failure, serious metabolic disorders, in particular diabetes mellitus and hypertension, impossible to control by therapy, a history of thrombophlebitis or thrombosis, bone metastases, ascites, or a serious edematous condition, concomitant treatment with corticosteroids, androgens or opioids were excluded from the study.

Ten patients were treated with MA during neoadjuvant chemotherapy, while 1 patient was treated with MA during definitive loco-regional radiation therapy administered at the end of primary chemotherapy. The neoadjuvant chemotherapy consisted of either the Al-Sarraf's regimen (treatment A) [24]: cisplatin 100 mg/m^2 i.v. on day 1 plus fluorouracil (5-FU) 1,000 mg/m^2 per day i.v. continuous infusion on days 1–5, repeated every 3 weeks, or the same drugs plus vinorelbine (treatment B): cisplatin 80 mg/m^2 i.v. on day 1, 5-FU 600 mg/m^2 i.v. 4-h infusion on days 2–5, and vinorelbine 20 mg/m^2 i.v. 20-min infusion on days 2 and 8. Five patients were given treatment A and 6 patients treatment B.

Since the patients underwent a cisplatin-based highly emetogenic chemotherapy, anti-emetic coverage was administered both for acute and delayed nausea and vomiting. The anti-emetic schedule was based for each patient on one of the three most widely used 5-hydroxytryptamine$_3$ receptor antagonists, i.e., Granisetron, Ondansetron, or Tropisetron, at the recommended doses. Consequently, nausea and vomiting were very well controlled and the patients did not suffer anorexia during the chemotherapeutic cycles.

Clinical parameters

The following clinical and immunological parameters were evaluated in all patients included in the study.

Clinical response to chemotherapy after three cycles was evaluated as complete response (CR) and partial response (PR).

Body weight was measured at enrolment, at the end of each cycle of chemotherapy (every 21 days), and at the end of the study, i.e., after 3 months.

Appetite was evaluated using a visual analogue scale calibrated from 0 to 10, at enrolment, at the end of the first cycle, and at the end of the study, i.e., after 3 months. All the above assessments were carried out at the same time for the patient treated with radiation therapy.

Complete hematological analysis was performed at enrolment, at the end of each cycle of chemotherapy, and at the end of the study.

Development of edema was assessed using the scale of Tchekmedyian et al. [21] at the end of each cycle.

PSK score (0–100) was assessed at enrolment and at the end of the study.

Quality of life index. Spitzer's quality of life index (QLI) [25], which is useful for the objective evaluation of the impact of treatment on the well-being of a patient, was assessed at enrolment and at the end of the study.

Immunological parameters

Serum levels of the cytokines IL-1α and β, IL-2, IL-6, TNF-α, and sIL-2R were evaluated at enrolment and at the end of the study and compared with a group of 7 age-/sex-matched normal individuals as well as a control group of 4 HNC patients treated with the same chemotherapeutic regimens but without MA.

The production in culture of the same cytokines and of sIL-2R by PBMC of patients after stimulation with PHA (1 day for cytokines and 7 days for sIL-2R) was evaluated at enrolment and at the end of the study (i.e., before and after treatment with MA) and compared with the group of 7 normal individuals and the control group of 4 HNC patients.

Treatment protocol

MA (Megestil, Boehringer-Mannheim, tablets of 160 mg) was administered at a dose of 320 mg/day (2 tablets: 1 tablet before each of the 2 main meals) during the interval between cycles of chemotherapy, starting from the 3rd day after the end of therapy until the day before the next cycle, for a total of three consecutive cycles. After the first cycle of MA treatment, appetite was again evaluated. In patients with an increased appetite, treatment was continued at the same dosage while in the remaining patients it was increased to 480 mg. The changes in appetite were not taken into consideration during the subsequent cycles of MA treatment and patients continued the assigned treatment until the end of the second cycle. At the end of the second cycle weight increase was evaluated and, if it was higher than 10% of pre-treatment weight, MA was administered for another 15 days at 160 mg/day and then stopped. If the weight increase was less than 10% or if no increase was registered, MA was administered at a dose of 320 mg/day for 15 days and then stopped. In patients receiving 480 mg/day, if the weight increase was ≥10%, treatment was continued with 320 mg/day, while if the weight increase was <10%, MA was administered at 480 mg/day for 15 days and then stopped. All patients gave their oral informed consent prior to enrolment in the study.

Results

Of the 11 enrolled patients, 9 could be evaluated (81.8%). Two patients could not be evaluated due to major protocol violations (drug intake <90% of that programmed). The characteristics of the 9 patients, including tumor site, stage of disease, and clinical response to chemotherapy, are reported in Table 1. They started MA therapy at a dose of 320 mg/day and, following evaluation after the first cycle, 8 continued treatment with 320 mg/day until the end of the second cycle and then the dose was reduced to 160 mg/day for the last 15 days of treatment. One patient did not show a weight increase and therefore continued treatment with 320 mg/day for the last 15 days.

Table 1. Clinical characteristics of patients treated with chemotherapy and megestrol acetate (MA)

No. of patients	%	Tumor site	Stage		Clinical response	
			III	IV	CR	PR
2	22.2	Oral cavity	1	1		2
2	22.2	Oropharynx	1	1		2
3	33.4	Hypopharynx	2	1	1	2
2	22.2	Larynx		2		2

CR, Complete response; PR, partial response

Table 2. Evaluation of clinical parameters in patients treated with chemotherapy and MA

	Treatment with MA		Mean increase	[%]
	Before Mean (range)	After Mean (range)		
Weight (kg)	47.3 (34–63)	53.6 (28.5–70)	+6.3	13.2
Appetite (score)	6.3 (2–9)	8.7 (6–10)	+2.4	38.6
PSK (score)	96.7 (90–100)	94.4 (50–100)	−2.3	−2.3
Spitzer's QLI (score)	6.4 (5–9)	8.8 (6–10)	+2.4	36.2

QLI, Quality of life index

Table 3. Comparison of objective clinical response and changes in clinical parameters in patients treated with chemotherapy plus MA and those treated with chemotherapy alone (controls)

	Stage		Clinical response		Mean increase					
					Weight		PSK		Spitzer's QLI	
	III	IV	CR	PR	kg	%	score	%	score	%
MA	4	5	1	8	6.3*	13.2	−2.3	−2.3	2.4	36.2
Controls	4	5	–	9	0.3	0.5	1.1	1.2	1.1	17.5

* $P = <0.05$, MA vs. controls

Clinical parameters

The clinical parameters before and after treatment with MA are reported in Table 2. Except for PSK, all the parameters show an increase following treatment with MA. In particular, average body weight increased by 6.3 kg (13.2%), appetite by a score of 2.4 (38.6%), and the Spitzer's QLI by a score of 2.4 (36.2%). PSK was decreased in only 1 patient, while most patients maintained the initial score, and 2 patients showed a slight improvement.

Table 3 shows the objective clinical response to tumor and the change in clinical parameters of patients treated with chemotherapy and MA and a group of 9 HNC patients comparable with the above patients for stage of disease and treated during the same period with chemotherapy

Table 4. Serum levels of interleukin-1 (IL-1)α, IL-1β, IL-2, IL-6, tumor necrosis factor-α (TNF-α), and soluble IL-2 receptor (sIL-2R) in patients treated with chemotherapy plus MA and 7 normal subjects (normals)

Cytokines	Patients before treatment with MA		Normals		P
	Mean ± SD (pg/ml)	Range	Mean ± SD (pg/ml)	Range	
IL-1α	14.3 ± 10.6	(1–31)	11 ± 3	(7–15)	NS
IL-1β	31.3 ± 18.8	(1–55.1)	6 ± 1	(5–8)	<0.001
IL-2	15.7 ± 14.6	(1–34.3)	2 ± 1	(1–4)	<0.05
IL-6	15.9 ± 10.6	(4–28)	3 ± 1	(2–4)	<0.01
TNF-α	57.3 ± 27.4	(30–89)	0		<0.001
sIL-2R	2,826.6 ± 1,692.6	(210–4,662)	1,848 ± 672	(1,344–3066)	NS

Serum levels of IL-1α, IL-1β, IL-2, IL-6, TNF-α, and sIL-2R in patients treated with chemotherapy plus MA (before and after MA treatment)

Cytokines	Patients treated with MA				P
	Before		After		
	Mean ± SD (pg/ml)	Range	Mean ± SD (pg/ml)	Range	
IL-1α	14.3 ± 10.6	(1–31)	4.5 ± 3.10	(4–8)	<0.05
IL-1β	31.3 ± 18.8	(1–55.1)	11.5 ± 10.5	(2–28.8)	<0.05
IL-2	15.7 ± 14.6	(1–34.3)	12.1 ± 15.6	(1–41)	NS
IL-6	15.9 ± 10.6	(4–28)	7.7 ± 9.5	(1–25)	NS
TNF-α	57.3 ± 27.4	(30–89)	39.3 ± 27.8	(1–77)	NS
sIL-2R	2,826.6 ± 1,692.6	(210–4,662)	1,638 ± 1,066.8	(210–5,376)	NS

Serum levels of IL-1α, IL-1β, IL-2, IL-6, TNF-α, and sIL-2R in the control group of 4 patients treated only with chemotherapy (before and after chemotherapy)

Cytokines	Patients treated with chemotherapy				P
	Before		After		
	Mean ± SD (pg/ml)	Range	Mean ± SD (pg/ml)	Range	
IL-1α	0		0		NS
IL-1β	557 ± 112.3	(439–653)	928.2 ± 536.6	(377–1,523.9)	NS
IL-2	254.7 ± 201.6	(33–516)	243 ± 188.2	(22–481)	NS
IL-6	16.2 ± 3.8	(11–20)	22.2 ± 12.7	(13–41)	NS
TNF-α	0		0		NS
sIL-2R	3,013.5 ± 1,169.3	(1,428–4,242)	6,741 ± 5,032	(1,890–13,776)	NS

alone (controls). This comparison was carried out to demonstrate that the weight gain was due to MA and not to the clinical response induced by chemotherapy. While the clinical response was quite similar in the two groups, the weight gain of controls was very small (0.3 kg) and significantly lower than that of the group treated with MA (6.3 kg).

Hematological parameters did not show any significant changes during MA treatment. Only 1 patient presented with edema (grade I, involving only the ankle) which persisted for 7 days and was treated with diuretics. Another patient presented with mild palpebral edema which regressed in a few days without treatment. No relevant side effects were observed during treatment.

Immunological parameters

The serum levels of IL-1α and β, IL-2, IL-6, TNF-α, and sIL-2R in patients were significantly higher before MA treatment than in normal subjects (Table 4). Levels of all cytokines decreased after treatment and the decreases in IL-1α and β were statistically significant. The serum levels of the cytokines in a control group of 4 HNC patients treated only with chemotherapy are also reported in Table 4. There were no significant changes after chemotherapy for all the cytokines studied.

The production in culture of the same cytokines and of sIL-2R by PBMC (after stimulation with PHA) from patients before MA treatment was not significantly different

Table 5. Production in culture of IL-1α, IL-1β, IL-2, IL-6, TNF-α (1 day), and sIL-2R (7 days) by peripheral blood lymphocytes (PBMC) stimulated with phytohemagglutinin from patients treated with chemotherapy plus MA and 7 normal subjects (normals)

Cytokines	Patients before treatment with MA		Normals		P
	Mean ± SD (pg/ml)	Range	Mean ± SD (pg/ml)	Range	
IL-1α	487.6 ± 319.2	(221–930)	565 ± 198	(284–667)	NS
IL-1β	2,795.6 ± 2,108.9	(1,050–6,725)	3,310 ± 133	(3,116–3,490)	NS
IL-2	1,936.3 ± 901.2	(120–2,508)	1,798 ± 319	(1,302–2,185)	NS
IL-6	2,344.6 ± 321.9	(1,950–2,806)	1,770 ± 662	(988–2,536)	<0.05
TNF-α	1,034.4 ± 537.9	(389–1,778)	1,183 ± 161	(956–1,305)	NS
sIL-2R	14,326.2 ± 1,220.7	(4,200–39,060)	23,268 ± 2730	(18,816–26,166)	<0.05

Production in culture of IL-1α, IL-1β, Il-2, IL-6, TNF-α (1 day), and sIL-2R (7 days) by PBMC stimulated with PHA from patients treated with chemotherapy plus MA (before and after treatment)

Cytokines	Patients treated with MA				P
	Before		After		
	Mean ± SD (pg/ml)	Range	Mean ± SD (pg/ml)	Range	
IL-1α	487.6 ± 319.2	(221–930)	502.3 ± 234.2	(202–1,056)	NS
IL-1β	2,795.6 ± 2,108.9	(1,050–6,725)	3,338.7 ± 864.2	(1,404–3,857)	NS
IL-2	1,936.3 ± 901.2	(120–2,508)	2,450.7 ± 149.5	(2,213–2,611)	NS
IL-6	2,344.6 ± 321.9	(1,950–2,806)	1,309.4 ± 529.7	(941–2,279)	<0.001
TNF-α	1,034.4 ± 537.9	(389–1,778)	1,291.1 ± 334.1	(922–1,793)	NS
sIL-2R	14,326.2 ± 1,220.7	(4,200–39,060)	13,519.8 ± 8,259.7	(5,040–25,284)	NS

Production in culture of IL-1α, IL-1β, IL-2, IL-6, TNF-α (1 day), and sIL-2R (7 days) by PBMC stimulated with PHA from the control group of 4 patients treated only with chemotherapy (before and after chemotherapy)

Cytokines	Patients treated with chemotherapy				P
	Before		After		
	Mean ± SD (pg/ml)	Range	Mean ± SD (pg/ml)	Range	
IL-1α	737.2 ± 502	(64–1,182)	364 ± 251.3	(144–714)	NS
IL-1β	1,898.7 ± 1,305.2	(258–3,028)	1,478.2 ± 1,093.4	(236–2,532)	NS
IL-2	513.2 ± 367	(251–1,057)	1,947 ± 3,354.1	(250–6,978)	NS
IL-6	2,261.5 ± 159.6	(2,127–2,481)	2,286.3 ± 162.7	(2074–2,462)	NS
TNF-α	910.2 ± 386.7	(469–1,252)	643.7 ± 280.3	(269–881)	<0.05
sIL-2R	11,917.5 ± 3,798.5	(8,526–15,372)	11,770.5 ± 5,425.1	(4,410–16,338)	NS

from normal subjects, except for IL-6, which was higher in patients, and sIL-2R, which was lower in patients (Table 5). There were no significant differences in cytokine production before or after MA treatment, except for IL-6, which decreased after treatment (Table 5). The production in culture of cytokines in a control group of 4 HNC patients treated only with chemotherapy is also reported in Table 5: this did not change significantly after chemotherapy except for TNF-α which was decreased (Table 5).

Discussion

Among the drugs with proven efficacy in NAC, the most useful are metoclopramide, dexamethasone, MA, and delta-9 tetrahydrocannabinol. For our study we chose MA, a highly effective drug, very well tolerated and with acceptable side effects compared with the other drugs, considering that it was to be administered to male patients with advanced HNC and severe malnutrition. MA is a synthetic progestagen commonly used in hormonal treatment of advanced breast cancer which has been shown to have the main side effect of inducing an increase in weight, appetite and well-being without interfering with the anti-neoplastic effect [26]. The percentage of patients responding to therapy was 30% at a standard dose of 160 mg/day [27], rising to 96% at 10 times the dose [18], with a median weight gain at the highest dose of 5.1 kg. In a group of patients with different tumor histology accompanied by anorexia who had lost 10% of their body weight, 27% gained

more than 2.2 kg after treatment with standard doses of MA [28]. These data suggest a dose-dependent effect of the drug. A double-blind, placebo-controlled trial in advanced hormone-insensitive cancers was carried out by Loprinzi et al. [15]. In this study 133 patients were randomized to receive placebo or MA (800 mg/day orally); 16% of patients on MA had a weight gain greater than 6.8 kg over baseline compared with the placebo group (2%). Many other clinical studies of MA for the treatment of NAC have been published [3, 19, 29–31] and report very few and mild side effects, especially at the lower doses (160–320 mg/day). The currently recommended dose of MA for use in NAC is 160–320 mg/day, which allows for a good quality of life compared with the high doses of the drug (800–1,600 mg/day) [32].

The results obtained in our study confirm the previously published data. MA administered at a dose of 320 mg/day in the intervals between chemotherapy was capable of increasing appetite (average increase in score was 2.4, 38.6% compared with the initial score), body weight (average weight increase of 6.3 kg, 13.2% compared with the initial weight), and the well-being of the patients (average increase in Spitzer's QLI score of 2.4, 36.2% compared with the initial score), without producing any relevant side effect. The patients were given effective anti-emetic therapy during the chemotherapeutic cycles and hence nausea/vomiting and anorexia were not relevant symptoms. In our study the score for PSK was slightly decreased: being unchanged in most patients, slightly improved in 2, and in 1 patient (the same patient who had to continue MA at a dose of 320 mg/day for the last 15 days of treatment for not having achieved a weight increase) markedly decreased. One out of the 2 patients not evaluable due to major protocol violations, decided to stop therapy himself as his appetite increased so much that it made him feel uncomfortable.

Despite the small number of patients included, we believe our study is important because of: the very homogeneous patient population (all patients had head and neck carcinomas, stage III–IV) and the very strong correlation between this type of tumor, even at an early stage, and NAC. Moreover, not only did we evaluate strictly physical aspects (appetite, weight increase, PSK), but also the quality of life (Spitzer's QLI). We have also attempted to correlate the changes in clinical parameters with some relevant immunological parameters, i.e., the cytokines IL-1α and β, IL-2, IL-6, TNF-α, and sIL-2R, which are closely associated with the pathogenesis of NAC.

We also compared patients treated with MA with a group of 9 patients treated in our hospital and comparable for age, disease (HNC in advanced stage), cachectic situation, and anti-neoplastic treatment but not treated with MA (Table 3). These patients showed a clinical response similar to that obtained in patients treated with chemotherapy and MA, but a minimal insignificant weight increase (0.3 kg, i.e., 0.5% of initial body weight). This suggests that weight gain is due to MA treatment and not to the clinical response induced by chemotherapy. The mechanisms by which MA increases body weight are still unknown and cannot completely be explained by its ability to stimulate appetite. It is possible that MA antagonizes the anorectic/cachectic activity of the cytokines produced by the tumor itself and/or by the host immune system and promotes differentiation of the adipocytes [33]. Several studies have demonstrated that MA antagonizes the TNF-α-induced inhibition of adipocyte differentiation and that several factors, including TNF, can interfere with adipocyte maturation, by reducing the synthesis and activity of key enzymes of liposynthesis [34, 35].

The synergistic action of certain cytokines, especially IL-1α and β, IL-6, and TNF-α, is currently considered the mechanism most likely responsible for NAC: many clinical and experimental studies seem to support this hypothesis. An association between serum levels of TNF and the degree of NAC has been demonstrated in both animals [36, 37] and man [38]. Injection of TNF induces weight loss, although by itself it is incapable of producing NAC, and anti-TNF antibodies antagonize the NAC induced in this way [39]. Moreover, synthetic progestagens such as MA which stimulate appetite inhibit the weight loss induced by TNF [40]. Experiments have been carried out which demonstrate the direct interaction of progestagens with specific receptors of immunocompetent cells. These drugs inhibit intracellular levels of the RNA messenger for IL-1, which leads to the reduced synthesis and release of cytokines [41, 42].

In our study serum levels of IL-1β, IL-2, IL-6, and TNF-α were significantly higher in patients than in normal subjects, but these levels decreased after MA treatment, with statistical significance for IL-1α and β. Data from a control group of patients treated with the same chemotherapeutic regimen but not with MA (Table 4) suggested that decreases in cytokine levels were due to MA and not the chemotherapeutic regimen. However, the production in culture of the same cytokines and sIL-2R by stimulated PBMC from patients, which, except for IL-6 and sIL-2R, was in the normal range before MA treatment, did not significantly change after MA therapy, except for IL-6, which significantly decreased. The production of the cytokines in culture did not change significantly in the control group after chemotherapy (Table 5).

Our immunological data therefore seem to be consistent with previous reports and suggest an important role for certain cytokines in the pathogenesis of NAC. They support the hypothesis that the beneficial therapeutic effects of MA in NAC may at least in part be due to its ability to interfere with the synthesis and release of these key cytokines, blocking the cascade of events responsible for NAC. These cytokines could initially play an important role in controlling neoplastic proliferation but, in more advanced stages of disease, could eventually induce a chronic state of malnutrition and wasting, leading to the final stage of cachexia [43].

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