Anti-Cancer Drugs 1997, **8**, pp. 459–465

Effect of medroxyprogesterone acetate on the quality of life of the oncologic patient: a multicentric* cooperative study

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Anorexia and cachexia, major problems in patients with cancer, lead to decreased caloric intake and weight loss. Successful treatment of these conditions has a positive effect on patients' quality of life. Among the pharmacologic treatments, partial effects have been observed following administration of corticosteroids, anabolizing drugs and synthetic progestogens such as megestrol acetate and medroxyprogesterone acetate (MPA). The aim of the present study was to evaluate whether MPA is able to influence the quality of life of neoplastic patients undergoing different chemotherapeutic regimens and/or radiotherapy for different tumor types. A series of 279 cancer patients undergoing either chemotherapy and/or radiotherapy treatment for different tumor types was randomly allocated to receive either MPA or no treatment. We explored the effect of MPA oral suspension at the daily dose of 1000 mg for 12 weeks (group A) or no treatment (group B). Our data show an increase of body weight in group A patients and improvement in performance status. The outcome of the present study strongly demonstrates that therapy with MPA plays a fundamental role in ameliorating the complex symptomatology of cancer patients in intermediate or advanced stage of the disease undergoing casual treatment with chemotherapy and/or radiotherapy.

Key words: Medroxyprogesterone acetate, quality of life, randomized study, solid tumor.

Introduction

The evaluation of quality of life has become, in recent years, a parameter of paramount importance in the frame of patients' management: this concept particularly applies to cancer patients in whom a risk/benefit balance strongly depends upon the toxicity of chemotherapy.[1,2] The term 'quality of life' is sometimes not completely clear and not fully understood, and there is no doubt that it assumes different shades closely bound up with different individuals, their experiences and their expectancies, and with the choice of a suitable 'questionnaire', which should be short, understandable, not irksome and adequately validated by psychometric tests.[3–5] From the clinical point of view, the question arises as to whether therapeutic intervention is possible on the quality of life of the oncologic patient during administration of chemotherapy. The most simple response is that an improvement of the quality of life can be achieved by controlling the symptoms induced by the disease (pain, nausea/vomiting, dyspnea, weakness, insomnia, etc.) or the undesirable effects caused by the treatment itself. Among the pharmacologic treatments, partial effects have been observed following administration of corticosteroids,[6–10] anabolizing drugs (testosterone, ACTH, GH) and synthetic progestogens, such as megestrol acetate and medroxyprogesterone acetate (MPA).[11–15] The latter has been widely investigated over many years in the management of cancer patients and it has shown, besides a specific antineoplastic activity in hormone-dependent tumors, a clear cut activity on myelodepression induced by chemotherapy as well as an efficacy on anorexia and cachexia.[16–18] The aim of the present study was to evaluate whether MPA is able to influence the quality of life of neoplastic patients undergoing different chemotherapeutic regimens and/or radiotherapy for different tumor types. For the evaluation of quality of life, the Therapeutic Impact Questionnaire (TIQ), specifically designed and validated for oncologic patients, has been adopted.

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Patients and methods

Patients

From February 1993 to January 1995, a series of 279 cancer patients undergoing either chemotherapy and/or radiotherapy treatment for different tumor types, all of whom gave their informed consent, was randomly allocated to receive either MPA or no treatment. According to the same experimental protocol, the study was carried out in 24 oncology departments scattered throughout Italy. Baseline eligibility criteria included both sex cancer patients with a life expectancy higher than 3 months, performance status greater than 60 (Karnofsky) or 0–2 (ECOG) and able to guarantee an adequate follow-up. Patients necessitating hormonal therapeutic treatment for neoplastic disease or using growth factors for aggressive therapeutic regimens as well as those receiving corticosteroids for palliative purposes were excluded from the study. In addition, the history of intercurrent or previous thromboembolic diseases, serious cardiovascular diseases, arterial hypertension, uncontrolled diabetes mellitus, and impaired renal, hepatic and thyroid functions were considered criteria for exclusion.

Treatment

Treatment consisted of MPA oral suspension at the daily dose of 1000 mg for 12 weeks (group A) to be started concomitantly with chemotherapy and/or radiotherapy, or no treatment (group B): the assignement of patients to the two experimental groups was made in the ratio of 2:1 according to Peto *et al.*[19] who state the validity of this approach whenever the treatment is expected to be more efficacious than control. Assessments were carried out at the baseline and every 4 weeks after the initiation of treatment, and included physical examination, evaluation of response to chemotherapy and/or radiotherapy treatment during the period of MPA administration, performance status, body weight, hemogram, blood chemistry, serum electrolytes, blood arterial pressure, and the evaluation of quality of life using the TIQ questionnaire. The latter was also utilized by patients who were asked to carry out at home a self-assessment every week.

Safety

All adverse events spontaneously reported by the patients or detected by the investigator were recorded. Particular attention was given to those related to MPA and already known from the literature, such as thromboembolic disorders, hypertension, water retention, impaired glucose metabolism, Cushing syndrome, cramps, vaginal spotting, fine tremors, perspiration, nausea/vomiting and hypothyroidism: for each of them, the date of onset, the duration and the outcome were recorded.

TIQ questionnaire

The TIQ is a self-rating, cancer-specific, concise and highly reproducible questionnaire, developed and validated in 1987 at the National Cancer Institute of Milan by Tamburini *et al.*,[20] that is able to assess functional, physical, psychological and social conditions of the patient, as well as global health. The questionnaire had to be completed, from the baseline up to the 12th week, weekly by the patient as a 'self-assessment' and every 4 weeks by the physician. The TIQ is composed of 36 items which assess both disease and therapy impact according to four dimensions that operationally define quality of life: physical symptoms (24 items), functional status (three items), concomitant emotional and cognitive factors (six items), and social interaction (two items). According to the authors' validation of the questionnaire, only eight out of 24 items belonging to the group of physical symptoms are considered essential for a reliable and correct evaluation. A global judgement expressed as 'have you been feeling ill' further completes the TIQ. Patients assess the degree of discomfort experienced using a verbal Likert scale with four possible answers (not at all, slight, a lot and very much) for each item to which a given coefficient is applied. This procedure identifies seven groups of scales (second level scale) which describes fatigue (four items), GI symptoms (four items), global health status (one item), functional impairment (three items), emotional status (four items), cognitive status (two items) and social interaction (two items). Since these seven scales represent an imperfect indicator, they have been pooled into two more general scales (third level scale): the physical symptoms scale which includes the first three scales of the above series and the so-called Therapy Impact Index which includes the remaining ones.

Statistical analysis

Data processing was carried out by SAS (Statistical Analysis Systems). All variables have been described

(frequency, mean, SE and SD) as distribution of frequency according to treatment. For each TIQ item and for the two levels of scales identified, the analysis of variance according to a parallel group design was performed.

Results

Two hundred and seventy nine patients entered the study: however, only 246 (168 in arm A and 78 in arm B) were considered suitable for the evaluation of the activity since 33 of them had to be excluded for reasons such as protocol violation, early refusal and early loss to follow-up. They were 110 males and 136 females with a median age of 62 years (range 30–85). One hundred and twenty four of them (58.5%) were under chemotherapy treatment, the latter consisting of the most common and standard combination chemotherapy regimens; 61 (24.8%) were under radiotherapy treatment; and 41 (16.7%) were receiving both chemotherapy and radiotherapy simultaneously. Patients were affected by a large variety of tumors: however, the major incidence was represented by breast cancer in 71 cases (28.7%), GI tumors in 59 cases (23.9%), lung cancer in 46 (18.7%), urological tumors in 17 (6.9%) and ovarian cancer in 12 (4.9%). In the majority of cases (139), the tumor stage was III and IV. The main characteristics of the patients distributed according to the treatment arms are reported in Table 1. Two hundred and twenty five patients (153 in arm A and 72 in arm B) completed the treatment up to the 12th week as scheduled in the experimental protocol: 21 (15 and six in arm A and B respectively) went off the study because of death from progressive disease (eight patients), progression of the disease (five patients), loss to follow-up or refusal (five patients), adverse reactions (two patients) and other reasons (one patient) (Table 1). Results following the treatment with MPA (arm A) in comparison with no treatment (arm B) are reported in Tables 2–5. In patients treated with MPA the Karnofsky index increased from the mean value of 76.52 at the baseline to 79.80 after 12 weeks of treatment (+4.3%), while in those with no treatment this value decreased during the same time span from 77.14 to 74.51 (−3.4%) ($p = 0.001$) (Table 2). Among the series of objective parameters evaluated, i.e. body weight, blood arterial pressure, hemogram and blood chemistry, no major changes were observed except for the following (Table 3):

(i) An increase of 3.16% of body weight in patients treated with MPA as compared to a decrease (−3.12%) in untreated patients ($p = 0.001$).
(ii) An increase of both systolic and diastolic blood pressure in treated patients (+4.46 and +3.6%, respectively; $p = 0.1$) versus a decrease in untreated patients (−2.9 and −2.7%, respectively; $p = 0.7$).
(iii) Serum blood glucose, even if not exceeding the upper limit of the normal value, showed a positive trend in treated patients (+6.3%) versus a negative trend in untreated patients (−4.0%) ($p = 0.013$).

The TIQ questionnaire for the evaluation of quality of life was compiled both by physicians and patients in 236 cases since 10 patients did not fill it in at all or adequately. A complete evaluation up to the 12th week is available in 225 cases (153 and 72 in arms A and B, respectively). Table 4 reports the results of the analyses carried out at the 'second level scale' and at the 'third level scale'. At the 'second level scale' it appears that MPA is active in

Table 1. Patient characteristics

Characteristic	MPA	No treatment
Patients		
entered	168	78
males	73	37
females	95	41
median age (range)	62 (30–85)	60 (38–81)
Treatments		
chemotherapy	101	43
radiotherapy	44	17
chemotherapy + radiotherapy	23	18
Main tumor types		
breast	52	19
GI	42	17
lung	30	16
urological	9	8
ovary	5	7
III and IV stage tumor	100	39
Treatment completed according to protocol	153	72

Table 2. Karnofsky index

Treatment		Weeks			
		0	4	8	12
MPA	score	76.52	77.86	78.66	79.80
	variation (%)	—	+1.75	+2.80	+4.30
No treatment	score	77.14	76.16	75.59	74.51
	variation (%)	—	−1.26	−2.00	−3.40

Time per treatment: $p = 0.001$

Table 3. Objective parameters (weight, blood pressure, serum glucose)

Parameter		Weeks				*p*
		0	4	8	12	
Weight						
MPA	score	60.61	60.90	61.44	62.53	
	variation (%)	—	+0.47	+1.70	+3.16	0.001
no treatment	score	62.96	62.08	61.36	60.99	
	variation (%)	—	−1.40	−2.50	−3.12	
Systemic BT						
MPA	score	133.07	138.34	138.14	139.01	
	variation (%)	—	+3.96	+3.81	+4.46	0.1
no treatment	score	133.55	132.13	132.50	129.79	
	variation (%)	—	−1.06	−0.78	−2.90	
Diastolic BT						
MPA	score	79.49	83.32	80.98	82.35	
	variation (%)	—	+4.81	+1.87	+3.60	0.7
no treatment	score	79.67	79.73	79.19	77.54	
	variation (%)	—	+0.07	−0.60	−2.70	
Serum glucose						
MPA	score	96.44	97.14	100.54	102.57	
	variation (%)	—	+0.72	+4.25	+6.35	0.013
no treatment	score	102.44	102.25	98.72	98.52	
	variation (%)	—	−0.37	−3.81	−4.01	

reducing and ameliorating at a significant level all of the parameters linked with the psycho-cognitive sphere except for the social interaction item in which, notwithstanding an improvement in the subjects treated with MPA in comparison with no treatment, patient evaluation does not reach significance. Similar considerations can be made as far as physical symptoms are concerned. On the contrary, no significant differences were observed in the functional impairment score. The analysis at the 'third level scale' showed a definite activity of the treatment with MPA both when we consider physician opinion and patient opinion. Eighty five adverse events related to the treatment with MPA have been recorded in 60 patients: they were hypertension (20 episodes), water retention (20 episodes), fine tremors (15 episodes), cramps (11 episodes), perspiration (11 episodes), vaginal spotting (six episodes), thrombosis (one episode) and Cushing syndrome (one episode). They required dose reduction of MPA in 14 patients and treatment discontinuation in two patients.

Discussion

The outcome of the present study strongly demonstrates that therapy with MPA plays a fundamental role in ameliorating the complex symptomatology of cancer patients in an intermediate or advanced stage of the disease undergoing causal treatment with chemotherapy and/or radiotherapy. The first evidence of this activity is supported by an improvement of the Karnofsky index in patients treated with MPA as compared with a worsening in the untreated ones. Similar considerations can be done as far as the weight gain is concerned; in this case, the question arises whether this increase is ascribable to a higher food intake rate of the patients followed by an increase of the muscle mass and of the fat body mass or to fluid retention as a consequence of the steroidal effect of MPA itself. The observation that the mean values of systolic and diastolic blood pressure did not increase at a significant level in patients treated with MPA ($p = 0.1$ and $p = 0.7$ for systolic and diastolic, respectively) should exclude the hypothesis of an effect of the treatment on the hydrosaline balance. This is in keeping with the results of a study carried out by Lelli *et al.*[21] in 10 patients with advanced stage tumors treated for 30 days with oral MPA at doses higher than 500 mg/day. At the end of the treatment period, no alterations of the exchanger sodium pool, of the plasma and urinary sodium levels, and of arterial blood pressure had been observed. An increase of serum glucose was also observed in patients treated

Table 4. TIQ scores—second level evaluation

Items	Scale	Compiler	Treatment	Baseline	12 weeks	*p*
Insomnia	Fatigue	Physician	MPA	44.42	39.75	0.0017
Fall asleep difficulty			no treatment	44.55	46.57	
Weakness		Patient	MPA	45.01	41.60	0.0001
Feeling tired			no treatment	44.98	48.18	
Nausea	GI symptoms	Physician	MPA	32.80	30.49	0.048
Vomiting			no treatment	33.37	36.14	
Stomach ache		Patient	MPA	33.91	31.25	0.006
Indigestion			no treatment	35.16	36.93	
Been feeling ill	Global health status	Physician	MPA	63.73	54.04	0.007
			no treatment	51.69	61.64	
		Patient	MPA	64.27	54.08	0.5 NS
			no treatment	61.67	59.11	
Difficulty to work	Functional impairment	Physician	MPA	44.16	34.97	0.1 NS
Difficulty with usual free-time activities			no treatment	41.03	41.90	
Help to eat, get dressed or go to the toilet		Patient	MPA	45.74	36.13	0.5 NS
			no treatment	40.63	41.82	
Sad or depressed	Emotional status	Physician	MPA	45.30	43.23	0.014
Anxious or scared			no treatment	41.60	45.53	
Nervous, restless or irritable		Patient	MPA	46.43	43.08	0.0001
Unsure			no treatment	44.26	45.52	
Difficulty concentrating	Cognitive status	Physician	MPA	37.89	34.84	0.036
Difficulty relaxing			no treatment	38.46	40.46	
		Patient	MPA	37.75	36.09	0.019
			no treatment	36.83	40.45	
Arguments with the family	Social interaction	Physician	MPA	31.59	29.98	0.003
Felt isolated			no treatment	29.17	31.34	
		Patient	MPA	31.20	30.88	0.6 NS
			no treatment	30.36	33.64	

Table 5. TIQ scores—third level evaluation

Second level scale	Third level scale	Compiler	Treatment	Baseline	12 weeks	*p*
Fatigue	Physical symptoms scale	Physician	MPA	45.69	40.74	0.005
GI symptoms			no treatment	46.64	48.13	
Global health status		Patient	MPA	46.74	41.84	0.011
			no treatment	47.76	47.98	
Functional impairment	Therapy impact index	Physician	MPA	42.25	36.50	0.014
Emotional status			no treatment	39.94	41.92	
Cognitive status		Patient	MPA	43.19	37.60	0.022
Social interaction			no treatment	40.07	41.99	

with MPA (treated versus untreated: $p = 0.013$). This is an expected finding closely linked to a well known glucoactive effect of MPA; however, even though at a significant level, it must be pointed out that the final mean values recorded in the treated patients (102.52 mg/dl) were slightly beyond the upper limit of the normality. The choice of the TIQ seems to have fulfilled the requirements for a correct and comprehensive evaluation of the quality of life. In fact, it takes into consideration the psychometric properties, and assesses functional, physical, psychological and social conditions of the patient, as well as global health. The analysis of the results shows that in the majority of cases there was a good

agreement between the assessment of the physician and that of the patient. At the 'second level scale', only in two cases was a discrepancy between the evaluation of the physician and that of the patient observed: it concerns the scale of the global health status and the social interaction where, even with an improvement following treatment with MPA, the judgement of the patient did not reach significance. To this purpose, it must be borne in mind that the cancer patient is strongly and continuously psychologically conditioned by his striking situation, and even a good supportive care therapy able to improve or to relieve his illness will never help him to completely forget his real condition. However, from the analysis of the results at the 'second level scale', it appears that the treatment did not modify the outcome of the functional impairment neither from the physician nor from the patient view point. This finding is justified by the fact that the growth of primary tumor mass and, particularly, the spreading of the metastases can give rise to different levels of pain, often compromising the function of organs or the articular motion of body segments. In such situations only a specific analgesic therapy is warranted. However, the final analysis at the 'third level scale' gives evidence that both physicians and patients recognize the usefulness of the treatment with MPA. Lastly, the side effects that emerged were taken into consideration: all of them seemed presumable ascribable to the use of MPA, and their incidence and severity did not appear higher than that normally detected with other treatments with MPA. The results obtained appear satisfactory and MPA seems to positively respond to the objective of the study. Quality of life is now an established part of clinical oncology both in research and in practice. This is a need which dates back to the mid-1980s when the attitude of oncologists moved from a palliative chemotherapeutic approach to a more aggressive one, mainly consisting in the administration of higher doses of chemotherapy. This approach, whose outcome has given encouraging results in terms of responses and survival, strict monitoring of the patients, and the availability of a supportive treatment that is safe, easy to administer and definitely active, places MPA as one of the best candidates.

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(Received 27 March 1997; accepted 10 April 1997)