Pergamon

European Journal of Cancer Vol. 30A, No. 10, pp. 1424–1431, 1994

0959-8049/94 $7.00+0.00

0959-8049(94)00286-X

A Randomised Trial of MACC Chemotherapy With or Without Lonidamine in Advanced Non-small Cell Lung Cancer

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Combination chemotherapy with anti-proliferative agents is the usual treatment for patients with advanced non-small cell lung cancer (NSCLC), good performance status and no major clinical contraindications. Lonidamine (LND), a new drug with an innovative mechanism of action, might potentiate anti-cancer activity of conventional cytotoxic drugs, with no increase of specific toxicity. Following a pilot study of feasibility, we now report the results of a randomised trial evaluating MACC chemotherapy, as originally described, versus the same regimen + LND. 151 patients with advanced NSCLC were assigned at random to the two treatment arms. LND 150 mg was given orally three times daily. Treatment was continued until progression of disease, unacceptable toxicity or refusal by the patient (median number of cycles of MACC, three for both arms; median duration of LND administration, 8 weeks in the arm concerned). Actual dose intensities (DI) of MACC and LND were, respectively, 100 and 83% of those intended (median values). There was a negative correlation between duration of chemotherapy and the DI of MACC reached in each patient, but no correlation between the duration of treatment with LND and its DI. DIs of LND and MACC were not correlated with each other. In all, 15 objective responses (one complete and four partial responses in the MACC group, 10 partial responses in patients on MACC + LND) were observed. Median progression-free survivals were 20 weeks (confidence interval, CI 14–22) for the group on LND and 17 weeks (CI 12–17) for the control group (non-significant difference). Median overall survivals were, respectively, 30 weeks (CI 23–40) and 27 weeks (CI 22–34), P = non-significant. Toxicity was as expected by the use of MACC, and similar in both arms, except for more severe anaemia and gastric toxicity in the group on MACC + LND. Other uncommon side-effects, seen only in this latter group, were mild to moderate and reversible and included myalgia, asthenia, testicle pain, headache, visual troubles, incubi and dizziness. Subjective tolerance to the treatment, and perception of physical and psychological well-being were rated similarly by patients of both groups. MACC plus LND is a moderately active regimen in advanced NSCLC, with a foreseeable and reversible toxicity of low–medium grade. Potential enhancements of anti-tumour efficacy of chemotherapy, and possible host survival benefits derived from the use of LND are not substantiated by the results of this trial.

Key words: non-small cell lung cancer, combination chemotherapy, MACC chemotherapy, lonidamine, phase III study

Eur J Cancer, Vol. 30A, No. 10, pp. 1424–1431, 1994

INTRODUCTION

METASTATIC OR locally advanced non-small cell lung cancer (NSCLC) is notoriously difficult to treat. Although radiotherapy has a palliative effect and cytotoxic combination chemotherapy produces a number of objective responses, clinical benefits, if any, have short duration. The pessimism on the efficacy of current therapeutic choices and, particularly, on the value of chemotherapy for the treatment of inoperable disease is understandable, even though not completely justified [1]. Certainly, a vigorous search for more active drugs is necessary.

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Revised 9 May 1994; accepted 17 May 1994.

Lonidamine (LND), a 1-[(2,4-dichlorophenyl)methyl]-1H-indazol-3-carboxylic acid, was first recognised as the most powerful anti-spermatogenic derivative of a series of indazole carboxylic acid [2]. Subsequent studies led to the discovery that LND has embryotoxic and anti-tumoral effects and that the mechanism of its pharmacological properties lies in the inhibition of cellular respiration [3–5]. Mitochondria were considered the primary intracellular targets of this drug [5, 6]. *In vitro* studies showed that LND inhibits energy-dependent repair of potentially lethal damage caused by hyperthermia [7], radiation [8], doxorubicin [9], and of a number of aklylating agents, including cyclophosphamide and nitrosoureas [10, 11]. Lonidamine has already undergone phase II and III clinical testing in several human cancers [12]. In NSCLC, it has modest anti-tumour

activity, typical reversible side-effects of mild or moderate intensity, and nearly no myelosuppression [13–16]. In combination with a standard regimen of chemotherapy, it may increase response rate and/or survival of patients, with no additional haematological toxicity [13, 17–19].

In the 1970s, several chemotherapy programmes, containing both cyclophosphamide and doxorubicin, were tested for treatment of NSCLC [20]. We have been interested in the combination of methotrexate, doxorubicin, cyclophosphamide and CCNU (MACC) since the early 1980s. Using this combination, we reported the rather disappointing response rate of 10% or less, but also acceptable toxicity, fair subjective tolerance and historical evidence of survival prolongation [21–23]. In 1989, in order to improve upon these results, we decided to exploit the addition of LND, which, as previously mentioned, acts synergically with two or three drugs of the combination [9–11]. In a recently reported phase II study, we described the feasibility of the concurrent administration of LND and MACC chemotherapy [24]. The level of activity of this therapeutic association justified a comparison with MACC alone in a phase III study, and such a trial is reported here.

PATIENTS AND METHODS

Eligibility

Patients were eligible for the trial if they had a cytological or histological proof of NSCLC (mixed histologies with small cell features were not acceptable [25]), and if they had received no prior chemotherapy. Patients should have locally advanced, metastatic, or recurrent disease, Karnofsky performance status (KPS) [26] > 50, normal blood cell count, normal hepatic and renal functions (bilirubin < 2 mg/dl and creatinine < 1.5 mg/dl). Exclusion criteria included age > 75 years, active cardiac disease, serious intercurrent medical illness or a history of a prior malignant tumour. Patients with a single, small, inoperable cancer lesion (maximum diameter < 4 cm) were ineligible, if they were suitable for small-field radical radiotherapy. Prior surgery or irradiation were not considered criteria of exclusion, provided that a recurrence had been pathologically documented, and at least 3 months had elapsed since completion of radiotherapy (or 4 weeks after an exploratory intervention). All patients should have measurable or evaluable sites of disease, other than those previously treated. Patients who participated in the study were assessed initially with clinical history and physical examination, complete blood cell count, serum chemistry, bronchoscopy, chest X-rays and tomograms, computed tomography of the thorax, brain and upper abdomen. Patients with dubious metastatic involvement were further investigated with appropriate imaging studies, biopsies or needle aspirations. In the absence of other inoperability criteria, any radiological finding equivocal for nodal mediastinal involvement was considered an indication to mediastinoscopy.

After completion of diagnostic tests, informed oral consent was obtained from all patients who fulfilled study requirements and consenting individuals were eligible for this study. The protocol received the approval from the ethical committee of our institution.

Study design

Eligible patients were randomised to MACC chemotherapy or MACC plus LND. Prior to randomisation, patients were stratified for stage of disease and performance status.

Treatment was started within 1 day of registration and randomisation. As originally described [27, 28], the MACC regimen consisted of methotrexate 40 mg/m^2 intravenously (i.v.); doxorubicin 40 mg/m^2 i.v.; cyclophosphamide 400 mg/m^2 i.v. and lomustine 30 mg/m^2 orally (p.o.), administered together on day 1 and repeated every 3 weeks. Doses were adjusted on the basis of the day-of-treatment count, according to predefined haematological criteria. Namely, 50% of the projected dose of each drug was given if leucocytes and/or thrombocytes fell below, respectively, 4000/mm^3 and 100 000/mm^3. If leucocytes were under 2000 and/or platelets under 50 000/mm^3, treatment was delayed for weeks, until the blood cell count became normal again. Patients also had a precycle blood chemistry and urine analysis, an electrocardiogram and were asked about oral and gastrointestinal troubles, nausea and vomiting. Dose reduction by 50%, withdrawal of single cytotoxic agents, and even weekly delays of the planned chemotherapy were applied for cardiac, hepatic, renal and gastrointestinal toxicity, or in case of stomatitis, anaemia, and cystytis. Doxorubicin was withdrawn when a maximum cumulative dose of 450 mg/m^2 was reached.

Lonidamine (Doridamina R, 150-mg tablets; Angelini S.p.A, Rome, Italy) was given orally, starting 7 days before the first cycle of MACC, at a total dose of 225 mg (half a table three times a day) for 2–3 days, escalating by 75 mg daily up to the dose of 150 mg three times daily, which was considered the optimum dosage in fully compliant patients. Dose increases were suspended temporarily (and definitively after a second unsuccessful attempt) if moderately disturbing side-effects occurred, which interfered with daily activities. However, the initiation of MACC chemotherapy was not delayed if patients were unable to escalate to the full dose of 450 mg. If severe toxicity from lonidamine administration occurred, which was not relieved by symptomatic treatment and dose reductions, the drug was temporarily discontinued. It was also suspended if a foreseeable MACC toxicity of grade 3 or 4 [29] persisted after the MACC cessation. After resolution of the toxicity, a second and final attempt, starting with the lowest dosage, was performed.

Patients were maintained on chemotherapy until disease progression, unacceptable toxicity, severe subjective side-effects, no compliance with the protocol requirements or treatment refusal (in patients assigned to the experimental therapeutic association, only the treatment responsible for toxicity or intolerance was suspended; in other words, the definitive withdrawals of MACC and LND were not necessarily concurrent). After cessation of MACC, no second-line chemotherapy was given to any patient. There were no limitations on symptomatic medications and/or palliative irradiation, prescribed at the discretion of the attending physician. However, irradiated sites were not considered in the evaluation of tumour response.

End-points of study

Evaluations were made for dose intensity, toxicity, subjective tolerance, physical and psychological well-being, response to treatment and survival.

The evaluation of tumour response required at least a complete physical examination with blood chemistry and chest X-rays. It was performed after a minimum of two courses of chemotherapy, and then at 3-week intervals, just before the next cycle of MACC. CT scans and other diagnostic tests that were initially abnormal, were repeated every 2 months or more frequently, if clinically indicated. Rebronchoscopy was not a requirement for the assessment of response. Standard definitions of complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were used [29]. A significant tumour volume reduction, which did not fulfill the criteria of at least PR, was

declared minor regression (MR), defined as a <50% and >25% reduction in the product (sum of the products) of the longest perpendicular diameters of the indicator lesion (lesions). CR, PR and MR had to be proved on at least two consecutive evaluations, 3 weeks apart.

Drug toxicity was graded, according to Miller and colleagues [29], before each chemotherapy cycle. For uncommon side-effects of LND, an *ad hoc* scale of subjective tolerance was developed as follows: grade 0 = no side-effect; grade 1 = mild and transient side-effects not interfering with daily activities; grade 2 = moderately disturbing side-effects not requiring symptomatic treatment or reduction of the dose of LND; grade 3 = seriously disturbing side-effects, controlled by symptomatic treatment and/or dose reduction; grade 4 = severe side-effects, requiring therapy suspension.

A quality-of-life (QL) instrument was administered to all patients, prior to each course, including the first. Patients were required to participate actively in this part of the study. However, not all patients agreed, or were able to reply to the questionnaire correctly, in any phase of their treatment. The questionnaire included multiple categoric and visual analogue self-assessment scales [30]. Herein, we report the analysis of the three fundamental questions concerning treatment tolerance, general physical well-being and mood.

The dose intensity (DI) is defined as the total amount of drug given, divided by body surface and the time taken to administer it. This definition implies that both dose reductions and treatment delays affect the calculated DI. Actual and projected DI for each drug, average DI for the drugs included in the MACC regimen and summary statistics for all patients were calculated following the examples given by Longo and colleagues [31]. In this study, DI were referred to the entire duration of treatment and reported as percentages of the intended DI (DI%) for both LND and MACC (this last percentage was the mean of the DI% of the four cytotoxic drugs). Medians and ranges of the DI% for the two groups of patients were also reported.

Statistical analysis

A target sample of 183 patients (119 events) was set for this study. Accepting a 5% rejection error, this sample enables the detection of a 45% 1-year survival rate at the power of 0.9 (1-tailed test) [32]. We felt a 45% 1-year survival rate clinically important (approximately 20% above the one obtained with MACC alone [21]). Survival time was measured from the beginning of therapy until death or last follow-up, and progression-free survival was measured from the beginning of therapy to the date of disease progression. Progression-free and survival analyses were based on the Kaplan–Meier product-limit estimates of the distribution [33]. Differences between actuarial curves were tested using either the Mantel–Cox log rank test or the Breslow–Gehan test, offered by the BMDP programme [34]. A Cox proportional hazards model [35] was used to adjust for and to determine the significance of prognostic variables in the treatment comparison of survival. Non-parametric tests [36] were used to test correlations between DI and between DI and time (Spearman rank tests), and to evaluate the statistical significance of differences in medians and proportions among the two groups (rank sum and χ^2 tests, as appropriate). A P value of less than 0.05 was set as significant. All tests were two-sided. The BMDP package (Statistical Software, Los Angeles, California, U.S.A.) and the Statistix package (NH Analytical Software, St Paul, Minnesota, U.S.A.) were used for data processing.

RESULTS

Characteristics of patients

Between April 1990 and October 1992, a total of 151 patients were enrolled into the trial, from either our institution or a few collaborating hospitals of the Cuneo province. The study was closed to further accrual before reaching the target sample of 183 because the number of patients first enrolled, who had already died, was higher than the expected number of 119 [32]. No interim analysis was performed.

Table 1 shows the distribution of the study sample by treatment and prognostic factors. Information about sex, age, KPS, Eastern Cooperative Oncology Group (ECOG) [37] performance status, weight loss and histology were collected from all 151 randomised patients. The serum concentration of two prognostically important tumour markers, i.e. carcinoembryonic antigen (CEA) and tissue polypeptide antigen (TPA) [38, 39], were obtained in only 137 and 132 patients, respectively. The randomisation achieved a good balance on the items that were stratified, although subjects on MACC + LND had a trend (statistically non-significant) toward less favourable performance status, as well as towards more advanced disease. The only imbalance (nearly significant) was in weight loss and TPA, favouring again the control arm. Median age was 63 years. 7 patients from the MACC group and 4 from the arm on

Table 1. Patients' characteristics

	Treatment group		Rank sum/χ^2 test (P-value)
	MACC	MACC + LND	
No. of patients	76	75	
Sex (male/female)	71/5	71/4	0.8964
Median age, years (range)	62 (33–74)	63 (45–75)	0.2374
Median Karnofsky performance status (range)	75 (50–100)	70 (60–100)	0.2529
ECOG performance status (0/1/2)	5/44/27	7/34/34	0.2994
Median percentage weight loss in 6 months (range)	0 (0–30)	4 (0–22)	0.055
Median CEA, ng/ml (range)	3 (0–390)	3 (1–1140)	0.5334
Median TPA, U/l (range)	152 (38–1300)	190 (40–1960)	0.0999
Histology (squamous/adeno-/large cell/mixed or unclassified)	51/11/7/7	50/13/10/2	0.3237
Stage of disease (IIIa/IIIb/IV/recurrent disease)	20/11/38/7	15/18/38/4	0.3596
Prior treatment (none/surgery/radiotherapy)	69/3/4	71/3/1	0.4021

Table 2. Delivery of chemotherapy

	Treatment group MACC	Treatment group MACC + LND	Rank sum test (*P* value)
No. of patients	76	75	
MACC chemotherapy			
Courses given, total	283	265	
Courses given, median (range)	3 (1–13)	3 (1–10)	0.7084
Weeks of delay, total	10	57	
Weeks of delay, median (range)	0 (0–7)	0 (0–14)	0.1257
Courses given with reduced doses, total	22	14	
Courses given with reduced doses, median (range)	0 (0–3)	0 (0–2)	0.4055
Percent projected dose intensity, median (range)*	100 (43–100)	100 (43–100)	0.7293
Lonidamine			
Weeks of treatment, total		838	
Daily dose, median mg (range)		450 (75–450)	
Per cent projected dose intensity, median (range)		83 (3–100)	

*Average of the percentage projected dose intensities of the four drugs of the regimen.

MACC + LND had previous pulmonary resection or thoracic irradiation.

11 of the 151 patients died within 7 weeks of the beginning of chemotherapy (6 in the MACC arm, 5 in the MACC + LND group). Before receiving the second course of MACC, another 14 patients (6 in the MACC arm, 8 in the other group) refused the allocated therapy, or requested a change of treatment, or were no longer compliant with protocol requirements. Thus, there were 126 patients evaluable for tumour response, and 133 evaluable for toxicity to MACC (7 of the 14 patients, who withdrew their consent after the first cycle of chemotherapy, could not be seen and assayed for toxicity at the planned time). All 75 patients randomised to the experimental arm were evaluated for toxicity to LND.

Delivery of treatment

The median number of cycles of chemotherapy received by patients in the two arms was identical (three in both arms, ranges 1–10 and 1–13). 112 patients received at least two cycles (60 in the MACC group, 52 in the other), while 36 completed a minimum of six courses of chemotherapy (17 and 19 in the two arms, respectively). In the 75 evaluable patients, the median daily dose of LND (defined as the maximum dose reached after the initial tolerance test) was 450 mg (range 75–450). 2 patients received a maximum dose of LND 75 and 150 mg per day, 21 received a dose between 225 and 300 mg, 52 the full dose of 450 mg per day. The median duration of therapy with LND was 8 weeks (range 1–46), but only 49 patients of 75 received the drug continuously for at least 1 month. In 16 patients, LND was suspended, before MACC, between the first and the 24th week of treatment. The cycles of MACC given at either full or reduced doses (total number, median and range), the weeks of delay (total, median and range), and the median dose intensity of MACC are summarised in Table 2, according to the treatment plan. Similar information concerning LND is given for patients randomised on MACC + LND.

As shown in Figure 1, we found an inverse, statistically significant relationship between number of cycles and the DI% of MACC reached in each patient. This was significant both in patients allocated in the MACC arm, and in patients assigned to the MACC + LND group. Thus, the tolerance to chemotherapy was negatively affected by the duration of the treatment itself and worsened progressively with time, irrespective of the contemporary administration of LND. This did not apply to LND (Figure 1). On the contrary, in the MACC + LND group a trend towards a positive correlation between DI% and treatment duration was seen (this was probably due to the lower average dose of LND assumed by patients who did not tolerate the drug and soon discontinued the treatment).

Figure 2 confirms the theoretical assumption that the use of LND does not affect the possibility of delivering cytotoxic chemotherapy; in fact, we found no correlation at all between DI% of MACC and LND in patients who received both treatments.

Toxicity

Toxicity experienced by our patients is summarised in Tables 3 and 4. In all, three drug-related deaths from myocardial

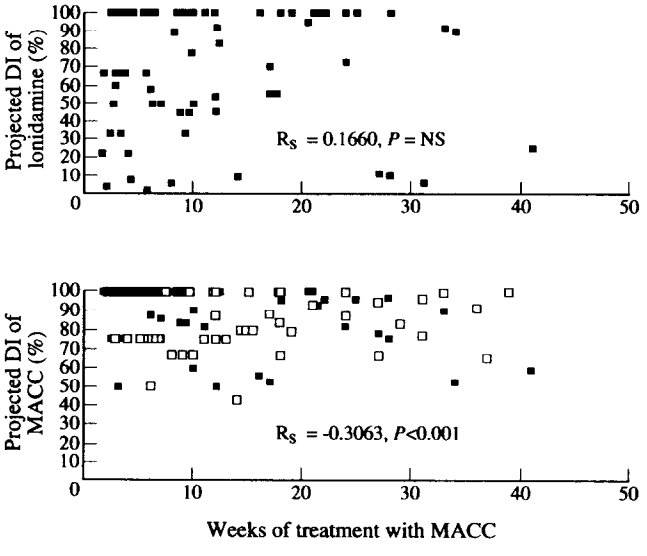

Figure 1. Relationship between treatment duration and the actual dose intensity of LND (as % of the projected dose) and MACC (as average % of the projected dose of the four drugs). Treatment duration is expressed as number of cycles of MACC. Statistical analysis by the Spearman rank correlation.

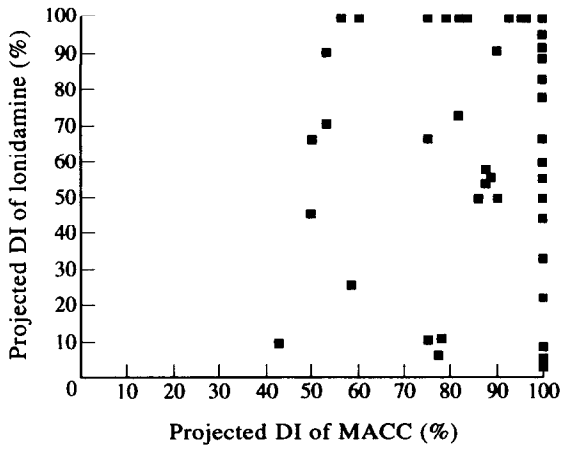

Figure 2. Relationship between MACC and LND dose intensities (both expressed as % of the projected dose). Statistical analysis by the Spearman rank correlation. Rs = *−0.0203*, *P* = NS.

infarction, fatal bleeding in severe thrombocytopenia (MACC + LND group) and neutropenic sepsis with pneumonia, (MACC group) occurred; another five deaths occurred unexpectedly at home and could have been related to the treatment. Patients on MACC + LND had a significantly more severe anaemia, and complained of more frequent nausea and vomiting (Table 3). Other toxicity phenomena were well balanced between the two groups. In particular, toxicity of grade 3 and 4 was haematological (in both arms, 10 cases with anaemia, 10 with leucopenia and 6 with platelet toxicity), oral (6 cases), gastric (16 cases), renal (1 case), hair-related (39 cases) and cardiac (1 case).

No toxicity correlated to LND was life-threatening. Side-effects from this drug were always reversible, but in 16 patients they were severe enough to cause early suspension (Table 4). Patients who discontinued the drug complained of grade 4 myalgia (6 patients), asthenia (2), testicle pain (2), gastric intolerance (1), visual troubles (1), dizziness (1) or multiple grade 4 side-effects (3 patients). Other side-effects of LND were headache and nightmares.

Assessment of subjective tolerance to treatment, physical and psychological well-being

The number of patients who completed the QL instrument at 6, 12 and 18 weeks was 56, 32 and 19, respectively (32, 16 and 8 from the MACC group, and 24, 16 and 11 from the MACC + LND arm). All patients had also had a QL evaluation performed prior to initiating treatment. This permitted a comparison with their baseline status. In general, patients who continued to respond to QL questionnaires did not experience a

Table 3. Worst toxicity experienced (toxicity grades according to Miller and colleagues [30])

Treatment group	MACC chemotherapy						MACC + LND chemotherapy						χ^2 test (*P*-value)
No. of patients with toxicity	0	1	2	3	4	Total	0	1	2	3	4	Total	
Haematological													
Haemoglobin	54	5	5	2	1	67	34	16	9	6	1	66	0.0093
Leucocytes	52	8	3	2	2	67	47	13	0	2	4	66	0.2769
Platelets	62	2	1	1	1	67	58	2	2	0	4	66	0.5154
Gastrointestinal													
Oral	56	3	5	3	0	67	54	7	2	3	0	66	0.4005
Nausea/Vomiting	40	6	11	10	0	67	27	18	15	6	0	66	0.0175
Hepatic													
SGOT/SGPT	62	5	0	0	0	67	65	1	0	0	0	66	0.0985
Renal													
Creatinine	60	7	0	0	0	67	59	5	1	1	0	66	0.506
Hair	12	18	18	19	0	67	17	10	19	20	0	66	0.3628
Cardiac	61	6	0	0	0	67	62	2	1	0	1	66	0.2614

Number of evaluable patients = 75.

Table 4. Uncommon side-effects of lonidamine (worst toxicity experienced, ad-hoc scale: see text for definition)

No. of patients with toxicity	1	2	3	4	Toxicity Total (%)	
Myalgia	7	0	1	8	16	(21)
Asthenia	4	1	1	3	9	(12)
Testicle pain	5	0	0	3	8	(11)
Gastric intolerance	3	0	1	2	6	(8)
Headache	2	1	0	0	3	(4)
Visual troubles	0	0	1	1	2	(3)
Nightmares	1	0	0	1	2	(3)
Dizziness	0	0	1	1	2	(3)

Number of evaluable patients = 75.

Table 5. Variations of subjective status at 6, 12 and 18 weeks of treatment

	MACC chemotherapy group				MACC + LND chemotherapy group				χ^2 test (*P*-value)
	Improvement	No change	Deterioration	Total	Improvement	No change	Deterioration	Total	
Chemotherapy tolerance									
At 6 weeks	8	14	10	32	6	12	6	24	0.8595
At 12 weeks	4	8	2	14	8	7	1	16	0.4477
At 18 weeks	1	2	4	7	3	7	1	11	0.0849
Physical well being									
At 6 weeks	13	16	3	32	5	14	5	24	0.2112
At 12 weeks	10	4	2	16	6	7	3	16	0.3646
At 18 weeks	4	3	1	8	1	7	3	11	0.1335
Mood									
At 6 weeks	11	15	6	32	3	16	5	24	0.1632
At 12 weeks	4	8	4	16	5	9	2	16	0.6582
At 18 weeks	2	4	2	8	2	7	2	11	0.8381

constant deterioration of their subjective status. This observation is subject to bias since it is limited to the small number of patients who were fully collaborating for a time after their registration into the study. Of course, patients who refused or were unable to complete the QL instrument (because of disease progression or toxicity) would have responded in a different way. Nevertheless, the comparison between replying patients gave homogeneous outcomes, and is of some value. It shows that there was no significant difference at any time and for any type of psychological evaluation between treatment arms (Table 5).

Tumour response and survival

126 patients had a minimum of 6 weeks of follow-up with no major protocol violation and were assessable for response (Figure 3). There were, in total, 1 CR and 14 PR (1 CR and 4 PR in patients on MACC, 10 PRs in the group on MACC + LND) for an overall response rate of 12% [95% confidence limits (CL), 6–18%], a MACC response rate of 8% (95% CL, 1–14%), and a MACC plus LND response rate of 16% (95% CL, 7–25%). Using the total number of patients entered as the denominator, on an "intent-to-treat basis", corresponding rates would be 7% (95% CL, 1–12%) for the MACC group, and 13% (95% CL, 7–20%) for the MACC plus LND arm. 20 patients achieved some form of tumour volume reduction which fulfilled the criteria of a minor response (14 cases in the MACC + LND group). Another 50 subjects had stable disease (NC), while 41 progressed at their first restaging evaluation.

No patient was lost to follow-up. Actuarial curves for time to progression and survival duration are given according to the treatment plan in Figure 4 and 5, respectively. Median time to progression for the MACC group was 17 weeks (95% CL, 12–17), as compared to 20 weeks for patients on MACC + LND (95% CL, 14–22). This difference was not statistically significant. Survival probability was also similar within the two arms, the median being 27 weeks (95% CL, 22–34) for patients on MACC, and 30 weeks (95% CL, 23–40) for patients on MACC + LND. A Cox's multivariate analysis of survival could be performed on 139 patients. It took into account the following factors: age, sex, Karnofsky and ECOG performance status, weight loss, histology, T classification, N classification, M classification, stage of disease, location of the metastatic disease (0 if absent) and treatment plan. The resulting regression equation included as significant variables the type of metastatic disease [improvement of χ^2 (ICS): 15.612, $P = 0.000$], the extent of the nodal disease (ICS = 10.423, $P = 0.000$) and KPS

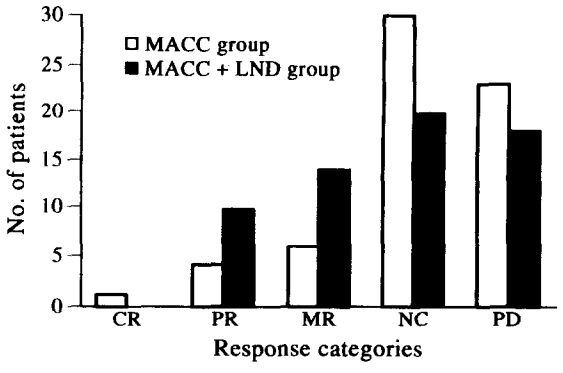

Figure 3. Best objective response according to the treatment group.

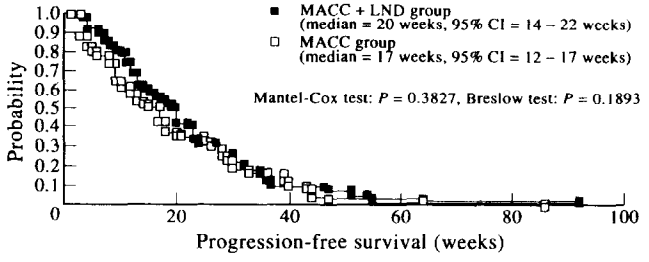

Figure 4. Probability of progression-free survival according to the treatment group.

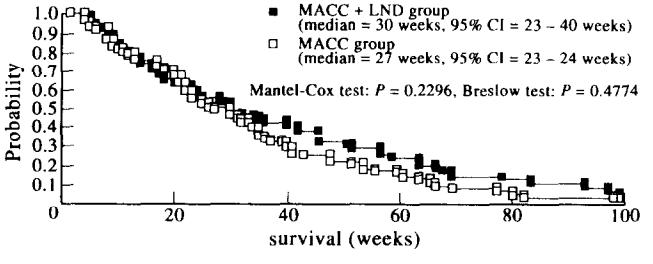

Figure 5. Probability of survival according to the treatment group.

(ICS = 5.726, $P = 0.017$). Also in this analysis, the treatment allocation was an insignificant determinant of the patients' survival.

DISCUSSION

Approaching the new millenium, we still do not know with certainty which is the best therapeutic choice for advanced NSCLC patients. For example, there is no agreement on whether to offer chemotherapy to out-of-protocol patients, and if so, what kind of chemotherapy to offer [40–42]. Although it is probably true that regimens containing cis-platinum have the highest and most reproducible response rates [43, 44], several studies suggest a lack of correlation between response and survival [45]. Increases in anti-proliferative efficacy are usually accompanied by similar increases in toxicity. Toxicity may prove to be the real limiting factor for survival, and the final balance between greater tumour cell killing and greater toxicity may be a net zero. In NSCLC, regimens with modest anti-tumour activity and mild to moderate toxicity are not necessarily inferior to more active and toxic regimens. Our previous experience seems to confirm this hypothesis [21–23, 46]. In our hands, the MACC regimen was able to ensure significant life prolongation [23], in spite of a disappointing response rate of 8% [21]. Survival benefits were already reported with the same programme [47] and nearly half a century ago, with the today abandoned nitrogen mustard [48]. In constrast, a number of studies of platinum-based regimens were not capable of substantiating a similar survival advantage [49–52]. Planning this study, we had in mind all the above considerations. We thought that the prolongation of the duration of response or even the maintenance of a condition of stable disease might be as important as the very rate of response in determining the final outcome of patients. Consequently, we decided to maintain our old MACC programme, and simply test the addition of LND in a pilot phase II study [24] and then in a randomised phase III trial.

In clinical studies, lonidamine alone, used in doses between 450 and 1050 mg per day, was reported active against NSCLC in 3 to 11% of patients [13–16]. Patients with less advanced disease and patients with squamous cell carcinoma responded better in one study [15]. Side-effects were mild to moderate, promptly reversible with the suspension of treatment, and devoid of the toxicity commonly encountered with other cytotoxic drugs [13–16]. In particular, no haematological toxicity was ever observed [13–15], except for mild to moderate anaemia in one study [16]. Daily doses above 450 mg induced more severe side-effects without therapeutic advantage [15]. The addition of LND to a conventional treatment of chemotherapy has been attempted in two phase II studies of advanced NSCLC [17, 24] and in three previous controlled trials [13, 18, 19]. Preliminary feasibility studies indicated the potential interest of combining LND with a conventional polychemotherapy regimen (in our case, the MACC regimen [24]), but phase III studies are still rather limited in number. According to the study by Battelli and colleagues [18], LND should not significantly potentiate the effects of chemotherapy [18]. The authors used the same regimen (i.e. MACC) and the same dosages and schedule of LND administration that we used. The major limitation was the small number of patients enrolled. Gallo-Curcio and coworkers randomised 164 patients with inoperable non-metastatic patients to receive radiotherapy (split course) and chemotherapy (cisplatin and etoposide), with or without LND, 450 mg daily [19], and response rates, median times to progression and survivals were substantially unchanged. LND did not give rise to serious additional toxicity. 184 patients were randomised by Gatzemeier and associates to receive either LND alone, 600 mg daily, or a two-drug chemotherapy (i.e. mitomycin C and vindesine), or the same regimen plus LND [13]. Again, there were no major differences in response rate, global survival, toxicity and subjective tolerance, but a significant increase in the proportion of patients living after 12 months from the beginning of the combined ttreatment (chemotherapy plus LND) was observed.

The major findings of the current study can be summarised as follows: (i) MACC plus LND, 150 mg three times daily, orally, is a moderately active combination chemotherapy for NSCLC, with a foreseeable and reversible toxicity of low–medium grade and an acceptable subjective tolerance. Diverse, often mild side-effects of a subjective nature may result. Tolerance to MACC worsens progressively with the continuation of treatment. In contrast, the continuous administration of LND does not reduce the tolerance to the drug itself, and does not impede the continuation of chemotherapy. Therapy is easy to deliver on outpatient basis, with all drugs administered concurrently every 3 weeks or continuously by the oral route. These results totally confirm our previous phase II study [24]. (ii) The addition of lonidamine to MACC might improve response rate and survival at expense of a certain increase of toxicity (namely, anaemia and gastric upset), while quality of life remains unchanged. Improvements are possible, but remain unproven by current data, since differences in outcomes were never statistically significant, in spite of the acceptable statistical power of the trial.

We were unable to substantiate meaningful benefits from the addition of lonidamine to a standard combination chemotherapy. Accordingly, we do not recommend further clinical exploration of this drug in NSCLC; however, the path opened by lonidamine (i.e. the sensitisation of tumour cells to cytotoxic agents obtained by affecting their damage-repair ability), is stimulating theoretically, and needs further basic research that could be advantageously translated in future clinical practice.

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Acknowledgements—The authors wish to thank Mrs Monica Viale, nurse of the out-patient unit of our hospital, and Mrs Anna Cerchietti, English teacher.