Phase I Trial of an Infrared Pulsed Laser Device in Patients with Advanced Neoplasias

Luis A. Santana-Blank, Elizabeth Rodríguez-Santana, Fernando Vargas, Heberto Reyes, Pablo Fernández-Andrade, Saide Rukos, and Karin E. Santana-Rodríguez

ABSTRACT

Purpose: The objective of this study was to evaluate the toxicity/radiant exposure/time relationship of an infrared pulsed laser device (IPLD) treatment in patients with advanced neoplasias. Karnofsky performance status (KPS), Spitzer quality of life index (QLI), and potential antitumor activity, if any, were also assessed.

Experimental Design: Seventeen patients (n = 17) received a daily IPLD radiant exposure of 4.5 × 10^5 J/m^2 (904 nm pulsed at 3 MHz) under a one-dose schedule and procedure design. Toxicity was evaluated under the parameters of the WHO; indirect toxic ocular effects were also monitored. KPS and QLI measurements were conducted before treatment and at six 3-months intervals. Scores for the seventh interval are the last available (range, 19–39 months). For statistical purposes, patients were classified into group 1, those alive at the end of the study, and group 2, those who had died.

Results: Dose-limiting toxicity was not observed. Five patients (n = 5) reported occasional headaches (grade 2), and four (n = 4) referred local pain (grade 2). In group 1 (n = 7), statistically significant increases in KPS and QLI were observed in all of the follow-up intervals compared with pretreatment values. One patient had a complete response, 1 a partial response, 4 stable diseases ≥12 months, and 1 progressive disease. In group 2 (n = 10), statistically significant increases in QLI were observed during the first two intervals. Eight patients had stable disease ≥6 months and 2 had uninterrupted progressive diseases.

Conclusions: The IPLD treatment studied is safe for clinical use and may have potential effects on KPS, QLI, and antitumor activity in patients with advanced neoplasias.

INTRODUCTION

Radiation therapy has been used in the treatment of certain types of cancers for decades. Generally, this treatment modality aims at inflicting sufficient genetic damage to kill tumor cells directly or activate apoptosis. Thus, powerful x- and γ-rays together with high-energy protons and neutrons constitute the mainstay of radiation therapy. Conversely, less energetic forms of radiation have been scarcely studied as possible anticancer treatment options. One possible reason for this has been the belief that, to affect biological systems, EM^3 signals must ionize matter, that is, cause molecules to gain or lose electrons. Another has been a poor understanding of so-called “athermal” processes induced by low-energy irradiation.

Yet, in other disciplines, research on the interaction between nonionizing EM signals and biological processes has increased exponentially (1). The reason for this interest is simple. Living organisms are complex electrochemical systems that rely on weak EM interactions to perform all of their activities, from pumping ions, ferrying materials, and creating proteins to conducting nervous system function and cellular communication (2). Ideally, scientists would like to be able to use external EM signals to selectively enhance or interfere with such biological functions. Although the field is still in its infancy, studies already suggest that weak external EMFs of different characteristics can modulate T-cell proliferation in vitro (3), promote nerve regeneration (4), and even act as adjunctive treatment for certain malignant tumors (5).

Several forms of radiation can create weak EMFs. Among them, low-energy bosons (i.e., photons, pions, and α particles) have the potentially attractive property of obeying statistical rules that permit any number of such particles to occupy the same quantum state. This quality allows bosons to conform energy packets that can interact more effectively with biological structures than fermions (i.e., electrons, protons, and neutrons) of the same energy level. Among bosons, photons offer other potentially desirable characteristics. For instance, streams of photons can be made into laser beams that are easy to modulate and have well-defined frequency-dependent absorption spectra. Thus, laser beams can be configured into precise EM signals that can prod specific molecular targets in biological systems. In experimental physics, this quality has allowed increasingly accurate experiments on the “control” of matter using high-energy lasers (6).

Recent controlled studies indicate that low-energy lasers...
can induce stimulation of keratinocyte proliferation in cell culture (7), skeletal muscle cell activation (8), attenuation of infarct size in rats and dogs after myocardial infarction (9), and effects on cell attachment (10). Increased natural antitumor resistance level, reduction of intoxication severity, and augmented organism tolerance to irradiation and polychemotherapy have also been reported with adjuvant low-energy laser therapy (11). It is now well known that the above laser effects depend primarily on the frequency, radiant exposure, and modulation (if any) used. Santana-Blank et al. (12) have additionally proposed that the initial metabolic state of the target tissue, the noise:signal ratio established, and the duty cycle and wave-shape of the beam are also crucial to the biological outcome obtained. Advances have also been made toward the understanding of primary and secondary mechanisms of action of low energy laser irradiation on biological systems (13, 14).

An IPLD of novel characteristics (15) was used in the present Phase I trial. Theoretical (16, 17), experimental (12), and clinical (18, 19) results suggest that the said IPLD photoinduces chaotic dynamics that can modulate complex physiologically reparative bioeffects. The objective of this trial was to evaluate the toxicity/radiant exposure/time relationship of an IPLD treatment in patients with advanced neoplasias. PS, QOL, and potential antitumor activity, if any, were also investigated.

PATIENTS AND METHODS

Ethical Normative. The present investigation was conducted between October 1989 and December 1992 in Caracas-Venezuela. The Helsinki Declaration was followed, and legal authorizations from patients and their families were obtained. The ethical normative and scientific bases of the present Phase I trial were approved by the appropriate Venezuelan regulatory agencies: Ministry of Health No. 497, and Ministry of Science and Technology (CONICIT) No. 013–298. Complementarily, the following domestic institutions were notified of the research protocol: Venezuelan Medical Federation, Venezuelan Society of Oncology, Venezuelan Society of Radiotherapy, Padre Machado Oncological Hospital, and Luis Razetti Institute of Oncology. In the United States, the research protocol was presented to the Director of Radiation Therapy and the Associate Director of the Radiation Research Program of the American Cancer Society, the Associate Director for International Affairs of the NIH-National Cancer Institute, and the Food and Drug Administration.

Eligibility. Patients of either sex with histological evidence of advanced neoplasias and clinical evidence of progressive disease (TNM/Unio Internationale Contra Cancrum) after treatment with any regimen of proven therapeutic benefit were eligible for entry onto this Phase I trial. Eligibility criteria at the time of entry also included: a Karnofsky status ≥80, a life expectancy ≥12 weeks, age ≥18, an interval ≥6 months since any prior radiation therapy, an interval ≥6 weeks since any prior chemotherapy, hormone therapy, or major surgery, no current steroid treatment, adequate bone marrow function (WBC >5000/µl, hemoglobin >10 g/dl, platelets >100,000/µl), adequate hepatic function (total bilirubin <2.0 mg/dl, aspartate ami- notransferase ≤90 IU/liter (normal 15–45 IU/liter), adequate renal function (creatinine ≤2 mg/dl), absence of major cardiac arrhythmia or severe conduction blockage, no mental illness, and adequate social/family support.

Study Group. Eighteen patients were admitted onto this trial. One week after entry, a male patient (ADC lung) voluntarily withdrew because of a family crisis not foreseeable at the time of admission. Consequently, the study group consisted of 17 patients (n = 17), 8 males and 9 females, with an average age of 47 years (range, 25–72 years). Patient characteristics are listed in Table 1.

Patient Entry and Follow-Up. Patients entered onto this trial underwent a complete history, physical examination, as well as bi- and tridimensional tumor documentation by MRI.

<table>
<thead>
<tr>
<th>Patient ID no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Previous treatment(s)</th>
<th>TNM</th>
<th>IPLD treatment (months)</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>54</td>
<td>ADC colon</td>
<td>SU, CH</td>
<td>IV</td>
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<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>45</td>
<td>Malignant meningioma (R)</td>
<td>SU, CH, RT</td>
<td>IV</td>
<td>39</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>34</td>
<td>Chondrosarcoma</td>
<td>SU, RT</td>
<td>III</td>
<td>24</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>29</td>
<td>Osteoblastoma (R)</td>
<td>SU</td>
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</tr>
<tr>
<td>5</td>
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<td>ADC parotid (R)</td>
<td>SU, RT</td>
<td>IV</td>
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</tr>
<tr>
<td>6</td>
<td>F</td>
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<td>M</td>
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<td>NHL (R)</td>
<td>CH</td>
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<tr>
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</tr>
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<td>F</td>
<td>56</td>
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<td>9</td>
<td>M</td>
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<td>SU</td>
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<td>F</td>
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<td>11</td>
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<td>Dead</td>
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<td>Dead</td>
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<tr>
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<td>35</td>
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</tr>
<tr>
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<td>IV</td>
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<td>Dead</td>
</tr>
<tr>
<td>16</td>
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<td>52</td>
<td>ADC colon</td>
<td>SU, CH, RT</td>
<td>IV</td>
<td>8</td>
<td>Dead</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>59</td>
<td>ADC colon</td>
<td>SU, CH, RT</td>
<td>IV</td>
<td>19</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*ADC, adenocarcinoma; NHL, Non-Hodgkin’s lymphoma; SU, surgery; CH, chemotherapy; RT, radiation therapy; R, recurrent.

*Benign tumor that importantly affected survival.
Ultrasound and/or x-ray measurements were obtained when necessary to complement diagnostic images. In addition, a pretreatment clinical ophthalmologic evaluation, including a fluorescein angiography and/or other complementary tests, was performed at least 2 weeks before the start of IPLD irradiation to determine the initial ophthalmologic state of patients.

Monitoring was performed as follows: (a) clinical evaluations were conducted daily during the first 48 h of IPLD irradiation, weekly during the remainder of the first month, every other week from the second until the third month, and monthly thereafter. The evaluations regularly included an eco-sonogram, a Doppler exam, an electrocardiogram, and, when applicable and possible to obtain, a spirometer; (b) control MRIs were obtained approximately every 60 days; (c) tumor biopsies were taken approximately every 180 days and were correlated with control MRIs; (d) sequential immune studies were performed approximately every 30 days to evaluate serum levels of TNF-α, sIL-2R, and distribution of peripheral lymphocyte subsets; (e) sequential chemical screens and complete blood counts were performed approximately every 30 days; and (e) control clinical ophthalmologic evaluations were performed after 3 and 12 months of IPLD treatment, on referral after clinical evaluations, or earlier if patients reported adverse ocular symptoms.

Study Design. Dose escalation was not used because this trial evaluated the effects of a specific daily radiant exposure of IPLD irradiation. All of the patients were irradiated with the IPLD under a one-dose schedule and procedure design. Toxicity was determined as recommended by the WHO (20, 21) and classified as follows: (a) acute toxicity, during the first 30 days; (b) subacute toxicity, from days 31 to 90; and (c) chronic/fate toxicity, after 90 days.

Although patients did not receive IPLD irradiation directly on their eyes, indirect toxic effects were monitored. Grading of ocular toxicity was determined as suggested by Ajani et al. (22) and was classified as above. The maximum tolerated radiant exposure was defined as the number of treatment programs in which grade 3 toxicity was present in two of three consecutive clinical evaluations. Patients with objective response or stable disease continued to receive IPLD irradiation until evidence of tumor progression, and deterioration of KPS and QLI values were documented, requested to be withdrawn from study, or had been clinically determined to be disease-free for 24 months. The duration of the study was lengthened to a maximum follow-up period of 39 months to additionally examine any chronic/fate toxicity and to observe whether the effects induced, if any, might be reversible (23). The long-term evolution of patients after the end of the study is described in “Results.”

PS and QOL. Three trained physicians evaluated independently PS and QOL. The former was measured through the KPS (24), and the latter was assessed using the Spitzer QLI (25).

Measurements were conducted before treatment and at seven follow-up intervals (in months): first: 0–3; second: 4–6; third: 7–9; fourth: 10–12; fifth: 13–15; sixth: 16–18; and seventh: 19–39. Scores reported for the last period comprise those of the last available follow-up by the end of the trial.

Antitumor Activity. Antitumor activity was evaluated at 3-month intervals or earlier if there was suggestion of tumor progression using the conventional response criteria developed by Hetzel et al. (26). Objective response was determined clinically, hematologically, immunologically, biochemically, by MRI tumor documentation, and by cytomorphologic restaging.

Laser Device and Treatment Regimen. The modulated wave of the IPLD (prototype LASB Laser; Ref. 15) is composed of two superposed waves: a carrier wave (λ 100 nm, 3 MHz, 10−8 eV) and a drive force wave in the near infrared (λ 904 nm, 1014 Hz, 0.27 eV). This modulated beam can also be described as a 904-nm wave pulsed at 3 MHz. A relatively low duty cycle was used to avoid excess thermal energy. The average peak power in this study was 35 mW. The IPLD has a convex lens with an UV filter to block unwanted harmonic byproduct. To ensure the desired optoelectronic characteristics, the IPLD was calibrated before the start of treatment and each month thereafter. The IPLD (15) was manufactured by Luis Carlos Rodriguez-Molero, Micro Mac C.A. (Valencia, Venezuela), exclusively for research projects under license from LASB Laser Corp. (Miami, FL).

Patients were trained to follow the treatment schedule and to use daily a tester incorporated to the device (15). Extreme care was placed on instructing patients not to expose their eyes directly to the IPLD. The treatment program was defined as the consecutive fractioned application during the daytime hours of a the total daily radiant exposure. The assigned radiant exposure of 4.5 × 105 J/m2/day (laser field intensity/power density, 4.5 × 107 mW/cm2) is in the intermediate level between values reported to produce stimulating/proliferating biological effects (107–109 J/m2) and those reported to produce inhibitory effects (107 J/m2; Refs. 27, 28). The IPLD was applied using a 2 mm-high top hat with a 10-μm diameter and placed at right angles to the surface of the patient’s skin in previously determined areas of closest proximity to the biologically closed electric circuits and the vascular interstitial closed circuit that would most efficiently carry the laser energy to the target tissues (15, 29).

Adjuvant Treatment. After ~3 months of IPLD treatment, patients whose physical state allowed a surgical intervention were eligible to undergo metastasectomies as adjuvant treatment to reduce the tumor:host ratio and the high risk of relapse associated with advanced neoplasias.

Compliance. Patients were asked to keep a journal for the length of their time in the trial, and to record the time and duration of each IPLD application as well as any sign, symptom, or problem/side effect experienced. This information was collected and verified during programmed clinical evaluations.

Statistical Analysis. A descriptive study of the toxicity induced in organ systems, if any, was performed. When appropriate, the data were expressed as the mean ± SD; the significance was analyzed using the Student t test. For the analysis of QOL, KPS, and antitumor activity data, patients were divided into two groups: group 1 consisting of all of the patients who were alive at the end of the study, and group 2 including all of those who had died by the end of the study. For group 2, the evaluation closest to at least 2 months before death was the last taken into account. The significance and correlation between QLI and KPS data were evaluated by the Wilcoxon matched-pairs signed-rank test and Spearman rank correlation coefficients, respectively. The significance level selected was P ≤ 0.05.
RESULTS

Systemic Toxicity. Except for one occasion in which a patient received acetaminophen as described in the “Pain” section, no patient required physical or pharmacological therapy because of fever, malaise, chills, allergy, rigo, anorexia, or constipation resulting from the application of the IPLD nor was evidence found of dose-limiting acute, subacute, or chronic/late systemic toxicity.

Pain. Twenty-nine percent of patients (n = 5) reported occasional generalized pulsating headaches (grade 2) after IPLD application during the first 2 weeks of treatment. The headaches lasted only few minutes and disappeared spontaneously without the use of medication, except for one occasion in which a patient (hard palate) was administered 2 tablets of acetaminophen. The said headaches became less frequent and milder with time, and patients did not experience this symptom after the second week of IPLD treatment. In addition, after a range of 1–3 months of IPLD treatment, 24% patients (n = 4) referred local pain (grade 2) in areas where the IPLD had been applied in the proximity of peripheral nerves. The pain was reversible and ceased without need for medication when the point of IPLD application was relocated.

Gastrointestinal Toxicity. Oral toxicity, nausea, vomiting, or diarrhea attributable to the use of the IPLD were not observed. Although this study population consisted mainly of TNM IV patients (n = 14), and ~53% of them (n = 9) had hepatic metastasis confirmed by MRI, no hepatic toxicity attributable to IPLD irradiation was observed.

Hematologic Toxicity and Biochemical Variables. The Student t test did not reveal statistically significant changes in hemoglobin, leukocytes, lymphocytes, platelets, creatinine, and glycemia attributable to the use of the IPLD.

Ophthalmologic Toxicity. For ethical reasons, ophthalmologic evaluations were performed when patients were able to tolerate them. Thus, of the 17 patients in this trial (n = 33 eyes), 4 (n = 8 eyes; ADC esophageal, hard palate, lung cancer, and osteoblastoma) could not be evaluated, and 2 (malignant meningioma and ADC parotid) could not be assessed before the start of IPLD treatment (n = 3 eyes). In total, 11 patients (n = 22 eyes) were sequentially monitored. In the initial clinical ophthalmologic evaluation (n = 22 eyes), 5 patients were found to be emmetropic, and 6 were ametropic. Of the latter, 2 used contact lenses and 4 spectacle glasses. For distance vision, the best corrected visual acuity (OU) measured using the Snellen eye chart was 20/20 in average (range, 20/15–20/20). Incipient anterior subcapsular peripheral cataracts were observed in 2 patients [breast cancer (OS) and transitional meningioma (OD)].

None of the 17 patients in the trial were referred for ophthalmologic consultation after clinical evaluations. In those monitored, no ocular trauma caused by ultrasonic action, hyperthermia, or other effects associated with infrared irradiation were detected clinically. No patient experienced changes in visual acuity or intraocular pressure, loss of vision, ocular discomfort, or any other eye symptoms that could be attributable to the IPLD. Although patients did not develop opacities in their transparent media, the pre-existing cataract (OD) of 1 patient (transitional meningioma) was observed to become denser and slightly smaller at the 3-month ophthalmologic evaluation and remained unchanged by the 1-year evaluation. The OS lens of the same patient remained unaffected. The other patient (breast cancer) with a pre-existing cataract (OS) did not present changes (OU) after 3 months of IPLD treatment and died before the 1-year ophthalmologic evaluation.

The latest post-treatment evaluation of the 2 patients that could not be assessed before the start of IPLD treatment showed in 1 case (malignant meningioma) a visual acuity of 20/20 (OD) after 2 years of IPLD treatment and in the other (ADC parotid) a 20/20 (OU) visual acuity 10 years after IPLD treatment. There were no evidences of opacities in their transparent media or of any other ocular abnormality attributable to the IPLD irradiation.

Other Toxicity. A review of multiple potential toxic effects including pulmonary, cardiac, cutaneous, renal, and neurological toxicity showed no evidence of a relationship with the radiant exposure administered nor potential cumulative effects.

Adjuvant Treatment. One patient (malignant meningioma) underwent six metastectomies as reported in the evolution of the case in Table 2.

Compliance. Patients reported completing treatment programs regularly except for days in which lengthy control studies or surgical interventions were scheduled. In total, 96% of daily treatment programs were reported to have been conducted as prescribed.

QOL and PS. In group 1, a statistically significant increase in QLI values was observed in all seven of the intervals in comparison with pretreatment values. The increase was highly significant during the first three intervals (P < 0.02, P < 0.02, and P < 0.03) and borderline for the following four intervals (P < 0.05). A statistically significant increase in KPS was also observed. The increase was highly significant during the first four intervals (P < 0.02, P < 0.02, P < 0.03, and P < 0.02) and borderline for the following three intervals (P < 0.05; Fig. 1).

In group 2, a statistically significant increase of QLI values was observed only during the first two intervals (P < 0.02 and P < 0.02). The change in QLI values of the following five intervals was not statistically significant. KPS data were not significant (Fig. 2).

The correlation between QLI and KPS data from the 17 patients, evaluated using Spearman rank correlation coefficient, was highly significant: Spearman rank = 0.827 (P < 0.0001).

Antitumor Activity. Evidence of antitumor activity was observed in 88.23% of patients (n = 15); results were classified as follows.

For group 1, living patients (n = 7), the group consisted of 5 males and 2 females with an age average of 37.85 years (range, 25–54 years); average time under treatment was 24.57 months (range, 12–39 months). One patient had a complete response, 1 a partial response, 4 stable disease ≥12 months, and 1 progressive disease.

For group 2, patients who died before the end of the trial (n = 10), the group included 3 males and 7 females with an average age of 52.6 years (range, 35–75 years); average time under treatment was 9.7 months (range, 4–19 months). Eight patients had stable disease ≥6 months and 2 had uninterrupted progressive disease.

Tables 2 and 3, respectively, provide a brief clinical report
Table 2  Clinical report of the antitumor response of group 1 patients

<table>
<thead>
<tr>
<th>Antecedents</th>
<th>Post IPLD antitumor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No. 1: ADC colon with a surgically irremovable liver metastasis adhered to the inferior vena cava.</td>
<td>(SD) The patient’s disease remained stable for 17 months, and she was able to reassume her professional activities.</td>
</tr>
<tr>
<td>Case No. 2: recurrent papillary meningioma of the left intraorbital region. After a left orbital exenteration, the patient received radiotherapy (5220 rads) and chemotherapy. When the disease progressed to surrounding regions (left temporal and infra temporal fossas, supraciliiar orbit, orbital root, and cheek), the patient refused radical surgical intervention.</td>
<td>(PD) The patient underwent local metastectomies after 5, 9, 17, 32, 35, and 38 months. After the fourth procedure, the disease spread to the left lower mandible and lateral cervical region possibly because the encapsulated left cheek mass was sectioned during the operation and viable tumor cells were exuded into peripheral areas.</td>
</tr>
<tr>
<td>Case No. 3: Chondrosarcoma of the posterior fossa with compression of the brainstem. The patient had undergone surgery and radiotherapy and presented dysphagia, dysphonia, and severe central vertigo.</td>
<td>(SD) At 3 months, neurological symptoms disappeared without the use of any steroid treatment. After 8 months, control MRIs showed a tumor of which the size was unchanged but emitted a stronger T2-weighted signal as evaluated by microdensitometry, indicating a significant change in the tumor’s apparent diffusion coefficient (ADC) of water. By the end of the study, the patient had been asymptomatic for 21 months, and lead a normal personal and professional life.</td>
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<tr>
<td>Case No. 4: recurrent osteoblastoma of the thoracic spine. After three laminectomies, tumor growth had impinged on the spinal cord and caused progressive quadriplegia. The patient rejected radiotherapy as a last resort, and was removed from a rehabilitation center because of the progressive and irreversible nature of his disease. By the start of IPLD treatment, the tumor had doubled in size during the previous year and involved spinal elements on the right from C4–T3.</td>
<td>(SD) At 1 month, the patient regained sphincter control. At 8 months, he showed marked and progressive improvements in mobility, muscle strength and mass, and in profound and superficial global sensitivity with predominance in the lower and upper left extremities. By the end of the trial, tumor size had remained stable for 24 months. Although external tumor fibrosis prevented the use of fine-needle aspiration biopsies for control pathologic assessments, MRI studies showed an increase in hypointense signals and greater tumor heterogeneity suggestive of calcification.</td>
</tr>
<tr>
<td>Case No. 5: recurrent acinic cell ADC of the left parotid with neural infiltration, preceded by multiple benign neoplasias</td>
<td>(CR) At 6 months, complete disappearance of disease was documented by MRI, fine-needle aspiration biopsies did not find atypical cells, and immune values were normal. The patient received 24 months of IPLD treatment without developing symptoms of recurrence.</td>
</tr>
<tr>
<td>Case No. 6: transitional meningioma, with hemiparesis, severe headaches, and seizures.</td>
<td>(SD) At 9 months, the patient showed a marked improvement in neurological symptoms and seizures ceased. Six months later, motor coordination, as well as muscle strength and mass had continued to improve. MRIs showed no change in tumor size during the period.</td>
</tr>
<tr>
<td>Case No. 7: stage IV, nodular and poorly differentiated, lymphocytic lymphoma, B-cell type IGM λ with increased ganglia in the right lung, a bilateral cervical gangliar chain, and para-aortic and intra-abdominal ganglia. After a 4-month remission, subsequent chemotherapy (Chlorambucil) caused alterations in hepatic and hematological functions and thrombocytopenia; treatment response was poor.</td>
<td>(PR) At 3 months, an increase &lt;25% in the volume of intra-abdominal and posterior para-aortal ganglia was found. At 7 months, ganglia became normal in size, at 8 months liver and bone marrow biopsies were reported as normal. By the end of the trial, he had been asymptomatic for 22 months, but MRIs still showed slightly enlarged ganglia at the level of the right lung.</td>
</tr>
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</table>

° (SD), stable disease ≥12 months; (CR), complete response; (PR), partial response; (PD), progressive disease.

of the antitumor response of group 1 patients and their 10-year follow-up after the trial.

DISCUSSION

The results of this trial demonstrate that the long-term use of the IPLD at a daily radiant exposure of $4.5 \times 10^3$ J/m² or its cumulative effect does not produce dose-limiting toxicity in patients with advanced neoplasias. This fact appears well supported by studies on the effects of low-energy infrared lasers (23, 28), pulsed weak EMFs (1, 2), and ultrasound signals within the range of the IPLD carrier wave (30). The findings narrated in the “Pain” and “Ocular Toxicity” sections should, nevertheless, be commented at this point. First, the occasional mild headaches of decreasing intensity described appeared to be of vascular origin and may be attributed to an increased blood flow caused by a higher release of nitric oxide in vessel walls as described by Maegawa et al. (31) using near-infrared low-level laser irradiation in animal experiments. Nonetheless, patients were observed to develop tolerance to this effect and generally did not require medication. Second, the mild local pain referred appears consistent with reports that low-energy infrared laser irradiation applied to skin over the course of a peripheral nerve significantly affects latencies in that nerve (32). Yet, this symptom was also reversible and disappeared when the IPLD point of application was relocated. Finally, the reported evolution of the preexisting cataracts of 2 patients could be related to the natural history of the opacities. However, considering the potentially reparative effects reported in this and other studies (12, 18, 19), the changes observed in the size and density of one of the cataracts (meningioma transitional) suggest the need to investigate possible long-distance IPLD-induced deterministic effects related to the initial metabolic or biochemical state of lens opacities. In this sense, the lack of modifi-
cations observed in the other preexisting cataract (breast cancer) may have been caused by the high tumor/host relationship of the patient as would be suggested by the second law of thermodynamics, which indicates that energy is most likely to flow toward areas with the lowest energy state. Tumor cells have a high level of entropy and a low energy state; this translates into injury potentials of as much as 1.5 V with regards to peripheral non-neoplastic cells (29). Consequently, differences in electrochemical potentials would have favored the absorption of the IPLD signal by tumor cells before an effect could be induced in areas with smaller redox potentials such as the cataract of the latter patient. In any case, the result of the ophthalmologic monitoring tests and the preservation of the transparency of the contralateral lenses of the 2 patients mentioned as well as those of the other patients (OU) in the trial appear to discard any ocular

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Fig. 1 Results of the Wilcoxon matched-pairs signed-rank test on KPS and Spitzer QLI data for group 1 (patients with advanced neoplasias treated with IPLD who were still alive by the end of the study). The number of patients evaluated at each interval is recorded inside the column (white number). The significance level of the observation at each assessment compared with the pretreatment score is shown above each column. PRE, pretreatment; NS, not significant; Follow-up Intervals (months): First: 0–3; Second: 4–6; Third: 7–9; Fourth: 10–12; Fifth: 13–15; Sixth: 16–18; and Seventh: 19–39.

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Fig. 2 Results of the Wilcoxon matched-pairs signed-rank test on KPS and Spitzer QLI data for group 2 (patients with advanced neoplasias treated with IPLD who died during the course of the study). The number of patients evaluated at each interval is recorded inside the column (white number). The significance level of the observation at each assessment compared with the pretreatment score is shown above each column. PRE, pretreatment; NS, not significant; Follow-up Intervals (months): First: 0–3; Second: 4–6; Third: 7–9; Fourth: 10–12; Fifth: 13–15; Sixth: 16–18; and Seventh: 19–39.
toxicity caused by the IPLD. In conclusion, the toxicity results of this study suggest that the regimen of IPLD irradiation studied is safe for clinical use in the treatment of advanced neoplasias (1, 2, 11, 18).

The above statement on the safety of the regimen studied appears substantiated by the positive KPS and Spitzer QLI data here reported. These results seem specially promising given that the side effects of many cancer treatments often cause suffering and profoundly affect these variables. In particular QOL has become increasingly important in technology assessments and cancer treatment guidelines. This variable is so important that, in the case of metastatic cancer, the American Society of Clinical Oncology has proposed that a treatment can be recommended even without an improvement in survival if it improves QOL (33). However, information on the impact of Phase I trials on the QOL of cancer patients is still limited (34). Numerous instruments have and continue to be developed to measure health-related QOL in cancer patients. We selected the Spitzer QLI among other potentially useful QOL indicators available at the time this trial was performed because of its history of proven validity, applicability to patients with different types of neoplasias, simplicity of use, and ease of reproducibility by others (25).

Although the Spitzer QLI is now used less frequently, the validity of the QOL results of this study is supported by their high correlation with KPS data ($P < 0.0001$). Moreover, whereas it is possible that a placebo effect could have contributed to the QOL results of the study, this appears unlikely because placebos primarily affect variables linked to suffering (35). Conversely, objective responses were observed during this trial.

One of the central findings observed in neoplastic cells during this trial was a highly significant increase in cytomorphicologic changes associated with programmed cellular death (19). In contrast, no apparent changes were noted in non-neoplastic cells. These results together with those here presented indicate a possible selective effect of the IPLD irradiation. Yet, it is important to note that no significant variations in the rate of mitosis of neoplastic cells were found in the previously referred study (19). This lack of mitotic changes may be explained as follows. It has been reported that low-energy laser irradiation can induce an apparent adaptive response in Indian muntjac fibroblast in the form of a reduction in the frequency of chromosome aberrations induced by radiation but not in cell survival (36). In addition, as described previously, the radiant exposure of near-infrared laser irradiation studied was between values, which had been reported to produce stimulating/proliferating biological effects and those reported to produce inhibitory effects (27, 28). Therefore, it appears reasonable to presume that the regimen of IPLD irradiation studied may progressively affect the viability of tumor cells without initially interfering with their reproduction.

In light of the above, it is not surprising that the tumor/host relationship before the start of treatment was essential to the response achieved by the patients of this trial. In this sense, it is interesting to note that an initial stimulation of CD25 cells was measured in all of the patients under study (18). However, a decrease in TNF-α and sIL-2R together with an increase in CD4+ and CD4+CD45RA cells was detected only in the group of living patients. These results suggest that, although an initial immune stimulation was generally achieved, the high tumor/host relationship existing before the IPLD treatment permitted enough time for only some patients to modulate the reparative response induced. The patient age and the possibility to extirpate

### Table 3

<table>
<thead>
<tr>
<th>Case no.</th>
<th>10-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ADC colon: 1 month after the end of the trial the patient presented ictericia and 1 month later the liver metastasis compressed the inferior vena cava. The patient died a few weeks later after receiving 19 months of IPLD treatment.</td>
</tr>
<tr>
<td>2</td>
<td>Malignant meningioma (R). By the end of the study the patient was and continued to be in good physical and mental condition and without surgical deformations which would have impeded normal feeding and adversely affected his social/professional life. The patient died 22 months after the end of the trial of a myocardial infarct before the scheduled removal of the recurrent left cheek mass.</td>
</tr>
<tr>
<td>3</td>
<td>Chondrosarcoma: Although the remaining mass in the posterior fossa could not be removed because of its location, the patient is currently alive and has been asymptomatic for over 10 years.</td>
</tr>
<tr>
<td>4</td>
<td>Osteoblastoma (R): More than 9 years after the end of the trial, the patient walks with a cane, leads a normal professional life, and has fathered 2 children. The patient only complains of premature ejaculation.</td>
</tr>
<tr>
<td>5</td>
<td>ADC parotid (R): Five years after treatment, control images showed no apparent sign of disease. The patient was under considerable and sustained emotional stress during the 5 succeeding years, and in 2001, CAT scans and MRIs showed a possible recurrence of parotid lesion with metastasis in the right leg and lungs. Biopsy report: metastatic acinic cell carcinoma. Immunohistochemical tests were negative for mutant p53, MDM2, CA 125, CA15-3, CA, CA242, CAE, and THY-1; and slightly positive for BCL2 and 53BP. Cytokines in plasma IL-2R, IL-2, and TNF-α or chemokinas were also negative. There were few cells stained with CD45, CD3, and CD4; and none were stained with CD8, CD16, CD19/20, CD45RA, CD45RO, CD27, CD25, HLA-DR, and CD38. After five cycles of chemotherapy (Kitril, Taxol, Decadron, and Carboplatino) with poor results, the patient was allowed to initiate adjuvant treatment with the IPLD.</td>
</tr>
<tr>
<td>6</td>
<td>Meningioma T. (R): The patient withdrew from the study after 15 months because the distance from her place of residence (~500 Km) and her socioeconomic condition made it impossible for her to attend control evaluations. The patient’s current state is unknown.</td>
</tr>
<tr>
<td>7</td>
<td>NHL (R): After the end of the study the patient voluntarily discontinued the treatment and died 7 months later because of a recurrence.</td>
</tr>
</tbody>
</table>

* (R): recurrent.

1 Pathology reports submitted by the MD Anderson Cancer Center on 06 August 2001, and by Servicio de Anatomía Patológica, Centro Médico de Caracas, on 16 August 2001.

1 Immunohistochemical report submitted by the Unité d’Immuno-hematologie et d’immunopathologie, Institut Pasteur, on September 12.
tumor masses without sectioning them were also observed to positively influence outcome.

Concurrently with the above cytromorphologic and immune results, MRI monitoring tests showed noticeable changes in the heterogeneity of the neoplasias as indicated by their ADCs of water. ADC measurements are sensitive to the biophysical characteristics of tissues, including the fraction of water in the extracellular space. Because radiation therapy (37) and chemotherapy (38) significantly increase the fraction of extracellular water, Zhao et al. (39) have argued and shown that modifications in tumor ADC may reflect treatment response before decrease in volume is measured. In addition, pre- and posttreatment MRI data from two patients (malignant meningioma and non-Hodgkin’s lymphoma were analyzed by Martin and Martin-Landrove (40) as part of a study using an algorithm for tumor characterization. The results of their measurements suggest, in agreement with Zhao’s conclusions, that the changes in tumor ADCs measured in this trial may have been predictors of anticancer activity. In our opinion, tumor ADC evaluations may be useful in future investigations to better understand the seemingly intricate action mechanisms of the modulated IPLD irradiation studied. An upcoming manuscript will additionally present results of microdensitometry assessments performed on tumor images to analyze the pathophysiology of tumor heterogeneities shown by T2-weighted MRI in this trial.

Several mechanisms for the biological effects of different types of low-energy near-infrared lasers have been documented. On one hand, low-power lasers have been shown to produce singlet oxygen (41). At low radiation doses, singlet oxygen modulates biochemical processes in the cell by energy transfer from porphyrin. Antibodies can also convert molecular oxygen into hydrogen peroxide; potentially aligning recognition and killing within the same molecules (42). On the other hand, low-level lasers in the near infrared have been shown to cause a marked increase in blood flow mediated initially by NO and subsequently by Ca2+ (31). It should be noted that NO is one of the main factors in the intra- and intercellular regulation of the organism (43, 44), and that stimulation of the NO/cyclic GMP/protein kinase G pathway has shown promise in the treatment of melanomas (45) and other types of cancers (46, 47). Interestingly, besides exerting effects on NO, low-energy near-infrared lasers have been shown to photoactivate Ca2+-ATPase (48) and cyclic GMP (49). Significant effects on the activity of enzymes have also been documented in studies using both low-energy lasers (12, 13, 50) and weak EMFs (51). Yet, to the best of our knowledge, no studies other than those of our group have explored the possibility of inducing physiologically reative bioeffects through the activation and modulation of complex nonlinear chaotic dynamics.

To aim at such modulation, each component of the modulated laser beam is critical. As described previously, the laser beam used in this study is made of two superposed waves, which, according to the superposition principle, can pass through each other without being destroyed or even altered. The IPLD beam consists of a near-infrared drive-force wave (904 nm, 3.31 × 1014 Hz, 0.27 eV) transported by a carrier wave in the ultrasound range (100 m, 3MHz, 10−8 eV). The IPLD peak power, 35 mW, is adjusted to the values of the membrane potential (dielectric band; Ref. 51). The sum of these attributes originates an external field, signal intensity, and a periodicity of the modulated wave that enters in vibrational and/or stochastic resonance through the drive force wave in the near infrared primarily with H2O and CO2 molecules (52). Meanwhile, the IPLD carrier wave furthers the penetration of the modulated beam and produces EMFs that exceed the voltage detectable above thermal noise (53). Recent calculations also reveal that the timescale range for resonant intermolecular transfer of vibrational energy in liquid water (54) and the activation energy for the reaction of OH with H (55) match the duration of the cycle of the electric field (3.02 × 10−15 s, or 3.02 femtoseconds) and the energy of the drive force wave (0.27 eV). This may be particularly important because old and recent data suggest a deep role of the inositol phosphate group (and, in general, for energy transfer via water dynamics) in ion-channel physiology, membrane dynamics, and nuclear signaling (56, 57). In addition, the energy of IPLD drive force is within the range of the strength of hydrogen bonds (58), and its carrier wave oscillates at a frequency (3 × 1016 Hz) that enters in vibrational resonance with the rate of electron transfer through the DNA double helix (59). These characteristics, which set the IPLD apart from other low energy lasers, may allow its modulated photon beam to modulate important biochemical, biophysical, and biomechanical processes through the activation of complex chaotic dynamical systems in molecular structures (12).

Chaotic dynamics are deeply engrained in nature. It is well known that chaos is vital in everything from chemical reaction rates to the stability of the solar system (60). Indeed, cells are immersed in a typically chaotic environment dominated by thermal and quantum fluctuations. Nevertheless, cells are able to pump ions, ferry materials, and create proteins all with almost 100% efficiency. One of the keys to the functioning of the molecular pumps and motors responsible for these activities consists in rectifying directionless environmental energy to produce nonrandom effects, an idea that has been described as the Brownian ratchet principle (61). Astumian (62) has shown that pulsed EMFs can cause nonequilibrium fluctuations that can bias Brownian motion. Astumian and others (1, 63, 64) have also reported biologically important phenomena with pulsed EMFs. In the case of the IPLD, the drive-force wave component transfers (within a physiological range) and magnifies the energy available within the system. Meanwhile, the carrier wave induces pulsed EMFs that rectify and modulate the vibrational effects induced (53, 65, 66).

The resulting effect of the modulated IPLD irradiation is akin to that of a transistor; a semiconductor device used for amplification, switching, and detection where the current of one of its pairs of terminals controls the current between the other pair. Recently, Hummer et al. (67) concluded from molecular dynamics simulations that nonpolar carbon nanotubes might be one day used as molecular channels for water and protons, where channel occupancy and conductivity might be tunable by changes in local polarity and solvent condition. Indeed, many biological structures such as aquaporin-1 (68) and cytochrome c oxidase, a photoacceptor of near-infrared irradiation (13), contain channels with hydrophobic linings that function as conduits for water through proteins. Although additional research is necessary to fully elucidate the potential intra- and intermolecular chaotic dynamics effects induced, our H nuclear magnetic
resonance data suggest that chaotic dynamics induced by the IPLD in water molecules may result in complex effects on the internal motions of biopolymers (12).

In contemporary physics, the “control” of matter using light has been a prominent theme in recent years (6). Still, many questions remain to ascertain the possibility of weak EM control of biochemical processes in complex biological systems (69). Nonetheless, pioneers in the field such as Basset (1) long recognized that “the surface of bioelectromagnetics has only been scratched, but beneath it there appears to be considerable treasure to be discovered” and that “bioelectromagnetics may hold a unique promise for modifying the malignant behavior of certain types of experimental cancers, athermally.” Whereas additional research and development is needed, the findings obtained in this clinical trial suggest that, indeed, modulated low-energy laser beams may be able to achieve this goal.

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