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Running title: Neuroimmune treatment of advanced solid tumors

Neuroimmune treatment of advanced solid tumors: 3-year survival after angiotensin 1-7, pineal indoles, and cannabinoids

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In a recent study, the exogenous administration of angiotensin 1-7 (Ang 1,7) together with melatonin, 5-methoxytryptamine, and cannabidiol increased 1-year survival in advanced cancer patients, underlining the utility of neuromodulation in oncology. We now report a single-arm interventional study to evaluate the effectiveness of introducing Ang 1-7 in the neuroimmune regime, including pineal indoles and cannabinoids. Two cohorts of patients with advanced solid tumors refractory to standard oncologic treatments and with an estimated life expectancy of less than six months were studied. The full neuroimmune regimen cohort consisted of 100 consecutive patients treated over the last three years with Ang 1-7, pineal indoles, and cannabinoids, while the comparator cohort included 212 consecutive patients treated between 2015 and 2019 with pineal indoles and cannabinoids alone. Gastroprotected capsules of Ang 1-7 coupled with cyclodextrin were administered at 0.5 mg p.o. twice/day. Melatonin (100 mg) and 5-methoxytryptamine (20 mg) were given p.o. at bedtime and in the early afternoon, respectively. Cannabidiol or cannabigerol (in the case of glioblastoma) was given at 20 mg p.o. twice/day. Clinical response, disease control, and overall survival, along with the lymphocyte-to-monocyte ratio, were evaluated. In the full regimen cohort, disease control was achieved in 67 of 100 patients, with objective tumor regression observed in 23%. In the comparator cohort, disease control was obtained in 111 of 212 patients, with objective regression in 8%. Three-year overall survival was significantly higher in the full regimen cohort (37%) compared with the comparator cohort (19%). Both treatments were associated with a significant increase in the lymphocyte-to-monocyte ratio, suggesting an improvement in systemic immune status. The addition of Ang 1-7 to a neuroimmune regimen combining pineal indoles and cannabinoids was associated with improved disease control and long-term survival in patients with end-stage solid tumors lacking effective therapeutic options.

Key words: angiotensin 1-7; cancer; cannabinoids; melatonin; 5-methoxytryptamine; supportive care

Angiotensin 1-7 (Ang 1-7) is a heptapeptide produced by the angiotensin converting enzyme (ACE) 2 as an essential component of the renin–angiotensin system [1-4]. While the ACE1 product

angiotensin II, acting via the angiotensin type 1 receptor, promotes vasoconstriction, inflammation, cell proliferation, and angiogenesis (all factors that enhance tumor development), Ang 1-7 largely counteracts these effects via the Mas receptor [1, 2, 5, 6]. In essence, Ang 1-7 works as a natural brake for angiotensin II: it leads to vasodilation, dampens inflammatory signals, and, critically, exerts anti-proliferative and anti-angiogenic influences that may interfere with tumor growth and progression.

At the cellular level, Ang 1-7 inhibits key processes in cancer biology [2, 3, 7, 8]. For example, tumors require the formation of new blood vessels (angiogenesis) to secure nutrients, and Ang 1-7 has been observed to downregulate proangiogenic factors like vascular endothelial growth factor [9] This reduction in neovascularization not only limits the tumor's blood supply but also disrupts the microenvironment that otherwise favors cancer cell survival and metastasis. In certain animal models, such as those of lung and prostate cancers, administration of Ang 1-7 correlated with a noticeable decrease in tumor size and spread, suggesting a direct anti-tumor effect [10-12].

Beyond its direct influence on tumor cells, Ang 1-7 also appears to modulate the tumor microenvironment [2, 3]. In many cancers, the interplay between inflammatory mediators, stromal cells, and immune cells creates a niche that supports tumor development. By reducing local inflammation and influencing extracellular matrix remodeling, Ang 1-7 helps shift this balance [13, 14]. The peptide's actions can render the tumor's surroundings less amenable to growth and dissemination, opening the possibility of using it in combination with conventional therapies (like chemotherapy or radiotherapy) to potentially enhance treatment outcomes.

In a recent study the exogenous administration of Ang 1-7 together with two main components of the endogenous anticancer network, i.e. pineal indoles (melatonin and 5-methoxytryptamine) and endocannabinoids, prolonged the 1-year survival in advanced cancer patients [15]. To assess the importance of Ang 1-7 in this neuroimmune regimen we now report the 3-year survival in 100 patients receiving the full regimen of Ang 1-7, pineal indoles and cannabinoids as compared to that of 212 patients who received the pineal indoles / cannabinoids comparator regimen or to a historical control receiving Best Supportive Care (BSC) alone. All groups included advanced solid tumor patients, who failed to respond to the standard antitumor treatments and with life expectancy less than 6 months.

Patients and methods

Study design. This was an interventional, non-randomized, controlled clinical study designed to evaluate whether the addition of Ang 1-7 to a neuroimmune regimen combining pineal indoles and cannabinoids was associated with improved clinical outcomes in patients with advanced solid

tumors. Given the absence of effective standard oncologic options in the study population, the analysis was explicitly framed as exploratory and associative.

Three patient groups were evaluated: A) a cohort treated with the full neuroimmune regimen including Ang 1-7, pineal indoles, and cannabinoids; B) a comparator cohort treated with pineal indoles and cannabinoids alone; and C) a historical control group treated with best supportive care (BSC) only.

Patients. Eligible patients had histologically confirmed solid tumors with measurable disease according to WHO criteria and had progressed after standard oncologic therapies or were deemed unsuitable for further antitumor treatment. All patients had an estimated life expectancy of less than six months at study entry.

Eligibility criteria included: 1) measurable disease documented by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET); 2) lack of response or progression after standard treatments, including chemotherapy, endocrine therapy, anti-angiogenic agents, targeted therapies, or immunotherapies; 3) no concomitant use of other complementary or alternative anticancer therapies.

Patients were considered untreatable according to conventional oncologic strategies after at least three lines of chemotherapy for breast, colorectal, and ovarian cancers, or at least two lines for other tumor types, including lung, gastric, pancreatic, biliary tract, bladder, and brain tumors. Progression under immunotherapy or targeted therapy was also required where applicable.

Patients receiving chronic treatment with pregabalin were excluded due to its inhibitory effect on Ang 1-7 activity. Patients requiring opioid therapy for pain management were excluded if treated with fentanyl or other major immunosuppressive opioids. When opioid analgesia was required, only agents with minimal immunosuppressive effects, such as oxycodone or hydromorphone, were permitted.

Treatment regimes. All treatments were administered orally and supplied by the same manufacturer (San Ruffino Laboratory, Smerillo, Italy). In Group A (full neuroimmune regimen), patients received Ang 1-7 at a dose of 0.5 mg twice daily. To enhance oral bioavailability and protect the peptide from gastric degradation, Ang 1-7 was administered as a supramolecular inclusion complex with β-cyclodextrin.

Melatonin was administered at a target dose of 100 mg/day at bedtime. To minimize initial adverse effects, treatment was initiated at 20 mg/day and escalated to the target dose within the first week. Five-methoxytryptamine was administered orally at a dose of 20 mg/day in the early afternoon. Cannabidiol was administered at a dose of 20 mg twice daily. In patients with glioblastoma, cannabigerol was used instead of cannabidiol at the same dosage.

Group B patients received the same regimen of pineal indoles and cannabinoids without Ang 1-7. Group C patients received best supportive care alone. Treatment was continued without interruption until radiological or clinical evidence of disease progression.

Clinical evaluation and response assessment. Baseline clinical and radiological assessments were performed prior to treatment initiation. Tumor response was evaluated every three months using CT, MRI, or PET, depending on tumor type and disease localization.

Clinical responses were classified according to WHO criteria as complete response, partial response, stable disease, or progressive disease. Disease control was defined as the achievement of complete response, partial response, or stable disease.

Immune biomarker assessment. Peripheral blood lymphocyte-to-monocyte ratio (LMR) was evaluated as a predefined biomarker of systemic immune status. LMR was calculated from routine blood counts obtained at baseline and during follow-up. Based on laboratory reference values, low baseline LMR was defined a priori as a value below 2.1. Associations between baseline LMR, LMR normalization during treatment, and clinical outcomes were explored.

Statistical analysis. Continuous variables were summarized as medians and ranges, while categorical variables were reported as absolute numbers and percentages. Comparisons between groups for categorical outcomes, including disease control and objective response rates, were performed using the Chi-square test or Fisher's exact test, as appropriate.

Overall survival (OS) was defined as the time from initiation of the neuroimmune treatment to death from any cause or last follow-up. Survival curves were compared between treatment groups using the log-rank test.

Given the non-randomized design and the use of historical comparator cohorts, exploratory Cox proportional hazards regression models were constructed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival. Treatment group (Ang 1-7-containing regimen vs. pineal indoles plus cannabinoids regimen) was included as the primary covariate. Multivariable models were adjusted, where data completeness allowed, for clinically relevant baseline factors, including age, sex, tumor type (glioblastoma vs. non-glioblastoma), disease extension (locally advanced vs. metastatic), and baseline LMR.

The proportional hazards assumption was assessed graphically by Schoenfeld residuals. Owing to the exploratory nature of the study, regression models were intentionally parsimonious and aimed at identifying clinically meaningful associations rather than establishing causality.

LMR was analyzed as a predefined prognostic biomarker based on its established relevance in advanced cancer. Low LMR was defined a priori as values below the lower limit of normal observed in our laboratory (< 2.1). Associations between baseline LMR and clinical outcome

(disease control vs progression) were assessed using contingency-table analysis, odds ratios, and Chi-square testing.

Exploratory analyses evaluated whether normalization of LMR during treatment was associated with improved clinical outcome. Interaction analyses between treatment group and baseline LMR were considered hypothesis-generating.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software.

Institutional review board statement. Study was approved by the local Ethical Committee of the Institute of Biological Medicine: acta no. 01/10, dated February 1, 2020, for the full regimen; acta no. 4, dated January 10, 2015 for the comparator group. The clinical protocol was explained to each patient and his/her relatives, and a written consent was obtained. All procedures were conducted in accordance with the Declaration of Helsinki.

Results

Clinical response and disease control. Clinical responses according to WHO criteria are summarized in Table 1. In the group treated with the full neuroimmune regimen including Ang 1-7 (Group A), complete response was achieved in 5 patients (5%), while partial response was observed in 18 patients, resulting in an objective tumor regression rate of 23%. Stable disease was documented in 44 patients, yielding an overall disease control rate of 67%. The median duration of disease control in this group was 18 months (range 6-36 months).

In the comparator group treated with pineal indoles and cannabinoids alone (Group B), complete response occurred in 2 patients (1%) and partial response in 14 patients, for an objective tumor regression rate of 8%. Stable disease was observed in 95 patients, resulting in an overall disease control rate of 52%. The median duration of disease control was 13 months (range 4-35 months).

The disease control rate achieved with the Ang 1-7-containing regimen was significantly higher than that observed in the comparator group (67% vs. 52%, $p < 0.02$, Chi-square test).

Overall survival. At a median follow-up of 36 months, overall survival differed significantly among treatment groups. Three-year overall survival was achieved in 37% of patients treated with the full neuroimmune regimen including Ang 1-7, compared with 19% of patients treated with pineal indoles and cannabinoids alone. Survival outcomes in both treated groups were superior to those observed in the historical control group receiving best supportive care only. Percent overall survival at predefined time points analysis demonstrated a significant separation of survival curves in favor of the Ang 1-7–containing regimen (log-rank test, $p < 0.01$) (Figure 1).

In exploratory Cox proportional hazards regression analysis, treatment with Ang 1-7 was associated with a clinically meaningful reduction in the risk of death compared with the comparator regimen. This association remained consistent after adjustment for age, sex, tumor type, disease extension, and baseline LMR, supporting the robustness of the observed survival signal despite the non-randomized study design (Table 2).

Lymphocyte-to-monocyte ratio and clinical outcome. Baseline LMR showed a strong prognostic association with clinical outcome in both treatment groups (Table 3). Patients with low pretreatment LMR values exhibited significantly higher odds of disease progression compared with those with normal LMR, both in the Ang 1-7-containing regimen and in the comparator regimen.

In exploratory analyses, normalization of LMR during treatment was associated with improved disease control. This association reached statistical significance in the comparator group and showed a favorable trend in the Ang 1-7 group, although the latter did not reach statistical significance, likely due to limited sample size.

These findings support the role of LMR as a clinically relevant biomarker of immune competence in patients undergoing neuroimmune modulation and suggest that baseline immune status significantly influences treatment outcomes.

Safety and tolerability. The neuroimmune treatments were well tolerated in all patients. No clinically relevant biological toxicity was observed, and no significant reductions in blood pressure were recorded following Ang 1-7 administration. Transient headache occurred in approximately 6% of patients during initiation of melatonin therapy.

Most patients reported subjective improvement in general well-being, including reduced pain, anxiety, and asthenia, along with improved mood and sleep quality.

Discussion

The present study provides clinically relevant evidence that the addition of Ang 1-7 to a neuroimmune regimen combining pineal indoles and cannabinoids is associated with a substantial improvement in long-term survival and disease control in patients with advanced solid tumors who have exhausted standard oncologic options. In this heavily pretreated population, characterized by an expected survival of less than six months, the achievement of a 37% three-year overall survival represents a striking and clinically meaningful signal.

Recent discoveries in Psycho-Neuroendocrine-Immunology have identified both anti-inflammatory and pro-inflammatory networks in the human body [16, 17] Major anti-inflammatory / anticancer molecules include Ang 1-7 [2, 3, 7, 8], the pineal indoles melatonin and 5-methoxytryptamine (produced during the night and the light period of the day respectively) [18, 19] and

endocannabinoids [20, 21] These molecules exert anticancer action through several mechanisms, including direct cytotoxic activity, stimulation of the anticancer immunity, and anti-angiogenic activity. The stimulation of the anticancer immunity is due to stimulation of interleukin (IL)-2 production from TH1 lymphocytes by melatonin [22] inhibition of IL-17 secretion by endocannabinoids [23] and inhibition of tumor growth factor-beta production from regulatory T lymphocytes by Ang 1-7 [24] Moreover, these molecules are interconnected by interactive mechanisms, as indicated by the melatonin inhibition of ACE1 and stimulation of ACE2 expression with the consequent enhanced production of Ang 1-7 instead of angiotensin II [25] and the endocannabinoid-mediated stimulation of melatonin secretion from the pineal gland [26].

A key observation of this study is the dissociation between systemic immune activation and long-term survival outcomes. Both the Ang 1-7-containing regimen and the comparator regimen were associated with comparable improvements in the LMR, indicating enhancement of systemic immune competence. However, only the group receiving Ang 1-7 demonstrated a marked and durable survival advantage. This finding suggests that Ang 1-7 may exert antitumor effects that extend beyond generalized immune modulation.

Mechanistically, Ang 1-7 is known to counterbalance the pro-tumoral effects of angiotensin II through activation of the Mas receptor, leading to inhibition of angiogenesis, attenuation of inflammatory signaling, and suppression of TGF-β-mediated immune tolerance. These actions may directly influence the tumor microenvironment, rendering it less permissive to tumor growth and dissemination. Within the context of a neuroimmune framework that already enhances anticancer immunity through pineal indoles and cannabinoids, Ang 1-7 may therefore represent a critical final regulatory component capable of converting immune activation into durable tumor control.

The prognostic role of baseline immune status was further supported by the strong association between low pretreatment LMR and disease progression across both treatment regimens. This observation aligns with previous evidence identifying LMR as a robust marker of host immune competence in advanced malignancies [27]. Although normalization of LMR during treatment was associated with improved clinical outcomes, the survival benefit conferred by Ang 1-7 appeared to be only partially explained by changes in systemic immunity, reinforcing the hypothesis of additional tumor-specific mechanisms of action.

From a clinical perspective, the oral administration of Ang 1-7 using a cyclodextrin-based formulation represents a pragmatic and well-tolerated strategy to overcome the peptide's inherent pharmacokinetic limitations. The absence of relevant toxicity, together with the reported improvements in quality of life, underscores the feasibility of integrating this approach into supportive and integrative oncology settings.

In many clinical trials, a 3-year overall survival endpoint is used to assess the long-term benefit of treatment. For instance, in studies evaluating therapies for advanced esophageal squamous cell carcinoma, researchers compared the long-term outcomes of patients receiving immunotherapies such as nivolumab; they reported differences in overall survival at the 3-year mark, which provided insights into the durability of the treatment effect [28]. Similarly, in the context of adjuvant therapy for high-risk gastrointestinal stromal tumors, comparing 3-year survival outcomes helped demonstrate that a longer duration of treatment (3 years vs. 1 year) was associated with improved overall survival [29].

Moreover, for certain malignancies like metastatic melanoma treated with immuno- oncology agents, survival curves often display a plateau around 3 to 4 years [30]. This pattern suggests that patients who remain progression-free at 3 years may experience a prolonged period of disease control or even potential functional cure. The 3-year mark thus serves as an important landmark, not just statistically but also clinically, to indicate that the treatment has conferred a durable clinical benefit and may predict long-term remission.

Taken together, these findings support a conceptual shift in advanced cancer management, emphasizing restoration and modulation of endogenous regulatory networks rather than exclusive reliance on cytotoxic or molecularly targeted strategies. While the present results do not establish causality, they provide compelling proof-of-concept evidence that targeting the ACE2/Ang 1-7 axis within a neuroimmune framework may meaningfully alter the natural history of end-stage solid tumors.

This study has several limitations inherent to its non-randomized design and the use of historical comparator cohorts, which introduce the possibility of selection bias, residual confounding, and temporal effects related to changes in supportive care. Consequently, the statistical analyses should be interpreted as exploratory and associative rather than causal.

Nevertheless, the magnitude and consistency of the observed survival benefit, its persistence after adjustment for key clinical covariates, and its strong biological plausibility collectively support the robustness of the findings. These results justify prospective randomized clinical trials to formally assess the therapeutic role of Ang 1-7 within neuroimmune oncology strategies.

As a conclusion, the integration of Ang 1-7 into a neuroimmune regimen comprising pineal indoles and cannabinoids is associated with a marked improvement in disease control and long-term survival in patients with advanced solid tumors lacking effective therapeutic options. The observed survival advantage, together with favorable immune modulation and excellent tolerability, identifies Ang 1-7 as a promising oncostatic agent within an integrative neuroimmune framework. Although exploratory in nature, these findings provide clinically meaningful proof-of-concept evidence

supporting further prospective evaluation of Ang 1-7-based strategies aimed at restoring endogenous anticancer regulatory networks and achieving durable clinical benefit in advanced-stage disease.

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Figure Legends

Figure 1. Percent overall survival at predefined time points in patients with advanced solid tumors treated with a neuroimmune regimen including Ang 1 7, pineal indoles and cannabinoids (Group A), compared with patients treated with pineal indoles and cannabinoids alone (Group B), and with a historical control group receiving best supportive care. Patients treated with the Ang 1 7-containing regimen showed a consistently higher long-term survival across follow-up, with a three-year overall survival of 37% compared with 19% in the comparator group.

Table 1. Clinical response according to WHO criteria in untreatable patients with advanced solid tumors treated with a neuroimmune regimen including Ang 1-7 (Group A) or with pineal indoles and cannabinoids alone (Group B).

Treatment/Tumor type	N	CR	PR	CR+PR	SD	DC	PD
Ang 1-7+pineal indoles+cannabinoids	**100**	**5**	**18**	**23**	**44**	**67**	**33**
Glioblastoma	25	1	5	6	9	15	10
Triple-negative breast cancer	8	1	1	2	3	5	3
Breast cancer (non-TN)	3	0	0	0	2	2	1
Non-small cell lung cancer	6	1	1	2	1	3	3
Pancreatic adenocarcinoma	10	0	2	2	4	6	4
Biliary tract carcinoma	12	0	2	2	6	8	4
Gastric cancer	5	1	0	1	2	3	2
Colorectal cancer	5	0	1	1	2	3	2
Renal cell carcinoma	2	0	1	1	1	2	0
Ovarian carcinoma	5	0	1	1	3	4	1
Endometrial carcinoma	2	0	0	0	2	2	0
Bladder carcinoma	4	0	1	1	2	3	1
Neuroendocrine tumors	7	0	1	1	5	6	1
Malignant astrocytoma	4	1	1	2	1	3	1
Malignant melanoma	2	0	1	1	1	2	0
Pineal indoles+cannabinoids	**212**	**2**	**14**	**16**	**95**	**111**	**101**
Glioblastoma	46	0	0	0	21	21	25
Triple-negative breast cancer	6	0	1	1	2	3	3
Lung cancer	36	1	2	3	16	19	17
Hepatocellular carcinoma	6	0	1	1	3	4	2
Pancreatic adenocarcinoma	22	0	1	1	10	11	11
Biliary tract carcinoma	11	0	2	2	2	4	7
Gastric cancer	12	1	0	1	3	4	8
Colorectal cancer	25	0	2	2	13	15	10
Ovarian carcinoma	14	0	2	2	7	9	5
Prostate cancer	4	0	0	0	3	3	1
Bladder carcinoma	5	0	1	1	3	4	1
Soft tissue sarcoma	15	0	0	0	8	8	7
Malignant melanoma	10	0	2	2	4	6	4

Note: Tumor-specific analyses are descriptive and intended to illustrate the distribution of responses across histotypes.

Abbreviations: CR-complete response; PR-partial response; SD-stable disease; DC-disease control (CR+PR+SD); PD- progressive disease

Table 2. Exploratory Cox proportional hazards regression analysis for overall survival in untreatable patients with advanced solid tumors.

Variable	Direction of association	Interpretation
Ang 1-7–containing regimen	↓ Risk	Associated with reduced risk of death
Age (continuous)	≈ Neutral	No strong association
Male sex	≈ Neutral	No strong association
Glioblastoma histology	↑ Risk	Associated with poorer survival
Metastatic disease	↑ Risk	Associated with poorer survival
Low baseline LMR (< 2.1)	↑ Risk	Associated with poorer survival

Note: Cox regression models were exploratory and adjusted for clinically relevant covariates. Hazard ratios are reported directionally to indicate consistency of associations rather than precise effect estimates. Results should be interpreted as associative and hypothesis-generating

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