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Using recombinant endostatin and platinum-based radiotherapy for non-small cell lung cancer

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Abstract

Non-small Cell Lung Cancer (NCLC) is the predominant form of lung cancer, representing the primary cause of cancer-related mortality on a global scale. In recent decades, significant research has been conducted on tumor angiogenesis in treating NCLC, owing to its pivotal role in advancing cancer. Numerous anti-angiogenic pharmaceuticals, including Recombinant Endostatin (RE), have undergone extensive assessment in preclinical and clinical settings, yielding varied outcomes that frequently fall short of expectations. Nevertheless, there is a growing fascination with RE owing to its capacity to induce a circulatory normalizing window, thereby potentially enhancing the therapeutic effectiveness of the conventional treatment for NCLC. This work aimed to assess the potential benefits of RE in enhancing the effectiveness and safety of Platinum-based Radiotherapy (PRT) when administered through intravenous and pulmonary infusions for patients with stage IIIA/B-NCLC. This paper presents a comprehensive review of both experimental and clinical investigations that have examined the combined administration of RE-PRT as a therapeutic approach for NCLC treatment. Out of the total sample size of 14 individuals who were assessed, the treatment's combined effectiveness is 77.6%. This percentage indicates a substantial proportion of positive results about the therapeutic intervention. The disease control rate, encompassing patients who display complete or partial responses, exhibits a noteworthy rise of 89.6%. The results underscores the effectiveness of RE-PRT in successfully arresting or reversing the advancement of the NCLC

Key Words: recombinant endostatin, platinum-based radiotherapy, non-small cell lung cancer, therapeutic approach, immunotherapy.

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INTRODUCTION TO TUMOR TREATMENT

NCLC is a highly prevalent and lethal form of malignancy that has a substantial impact on healthcare systems globally and is a primary contributor to cancer-related deaths [1]. NCLC constitutes approximately 85% of all cases of lung cancer, and it is frequently diagnosed at an advanced stage, leading to restricted treatment choices and compromised patient outcomes. In recent years, there has been a notable transformation in the therapeutic strategies employed for NCLC, encompassing a diverse range of approaches, including surgical interventions, chemotherapy, targeted therapies, and immunotherapies.

Nevertheless, attaining long-lasting responses and enhancing overall survival rates in advanced NCLC presents a formidable obstacle [2]. Implementing anti-angiogenic treatments, such as RE, has presented novel opportunities in the treatment of NCLC by specifically targeting the tumor's vascular network. Similarly, platinum-based radiotherapy has garnered attention as a potentially productive strategy due to its capacity to induce DNA damage and impede cellular proliferation. The introductory section establishes the context for investigating the possible synergistic outcomes resulting from the combination of RE-PRT. It elucidates the reasoning, mechanisms, and potential advantages of this innovative therapeutic strategy for NCLC [3].

Platinum-based chemotherapy is the initial treatment option extensively employed for managing advanced NCLC. Nevertheless, in the context of advanced NCLC, the efficacy of chemotherapy is observed to be constrained by significant toxicities, resulting in a median survival rate that does not surpass 7.9 months [4]. The emergence of agents that selectively target natural molecules has presented a novel approach to managing NCLC.

In the initial or quiescent stages of cancer progression, tumors can persist without vascularization for prolonged durations, ranging from months to years. Nevertheless, the lack of tumor vasculature plays a crucial role in tumor advancement. A sufficient

supply of nutrients and oxygen is crucial to fulfill the metabolic requirements of an expanding tumor [5]. Furthermore, as the neoplasm increases, it gives rise to areas characterized by apoptosis and necrosis. The occurrence of hypoxia within the developing tumor mass serves as a crucial initial trigger for tumor vascularization and the onset of angiogenesis. Angiogenesis is a highly regulated biological process in normal physiological conditions. However, in the context of tumor angiogenesis, the resulting vascular network is characterized by significant abnormality and disorder, leading to heightened permeability of the vascular system [6].

With the progression of knowledge regarding the molecular and cellular mechanisms that underlie NCLC, there has been an increasing recognition of the significance of angiogenesis and tumor vasculature in advancing the disease [7]. RE, an effective inhibitor of vascular development, has demonstrated significant potential in preclinical and clinical investigations due to its capacity to suppress the growth of endothelial cells, induce death in tumor blood vessels, and augment the effectiveness of traditional cancer therapies. Simultaneously, PRT, frequently employed as simultaneous chemoradiotherapy, administers radiation to malignant cells, inducing DNA damage and impeding cell division [8].

The justification for the combination of RE-PRT is rooted in the potential synergistic interaction between their anti-angiogenic and cytotoxic properties, respectively. The combined strategy seeks to advance the therapeutic response, reduce the likelihood of resistance, and increase survival rates for patients with NCLC by interrupting the tumor vasculature using RE and administering radiotherapy. Implementing this novel treatment approach presents the possibility of enhanced therapeutic effectiveness, a more substantial decrease in tumor size, and a more favorable long-term outlook for patients confronting the complexities associated with advanced NCLC. The subsequent sections delve into a two-pronged approach that shows the potential to revolutionize the field of therapy for NCLC. This strategy highlights the urgent requirement for ongoing studies and clinical trials to comprehend its potential advantages and validate it as a widely accepted treatment for this hostile and frequently challenging disease.

RELATED WORKS

NCLC is often diagnosed late, has a high incidence rate, and has few treatment options, making it a major oncology challenge. NCLC treatment has advanced over time, including a variety of methods for this aggressive cancer. Among the options considered, RE-PRT is innovative and promising. This literature review examines the causes, methods, and results of studies on the potential benefits of combining radiation therapy with precision radiation therapy for NCLC. Combining anti-angiogenic drugs with radiation may improve treatment outcomes and disease progression.

Qin et al. (2022) tested RE in NCLC patients via continuous intravenous infusion. This method used chemotherapy and an infusion pump. During implementation, regular chemotherapy and RE are administered via an infusion pump [9]. The output includes treatment responsiveness and survival estimates. Continuous RE infusion may increase therapeutic efficacy and tumor suppression. However, administering a continuous infusion is complicated and may cause side effects.

The technique described in reference [10] evaluated the efficacy and safety of endostatin and chemotherapy for NCLC patients. Endostatin is given with chemotherapy during implementation, and results are assessed. These include therapy efficacy and patient well-being evaluations. This approach may improve treatment results but may have side effects or experimental limitations.

In a meta-analysis, Feng et al. (2021) examined the effects of RE and chemotherapy on advanced squamous cell lung carcinoma patients [11]. Implementation involves data collection and statistical analysis. A comprehensive synthesis of previous research is the result. A study's advantages include a thorough data summary, but its limitations may result from study design changes and patient group characteristics.

Endostar consolidation treatment after sequential chemoradiotherapy is suggested for stage III lung adenocarcinoma patients with genetic alterations [12]. Implementation involves endostar

consolidation treatment and patient response monitoring. The results evaluate therapy efficacy within a genetic framework. This approach may allow patient-specific treatment. Due to the case report's uniqueness and limited generalizability, this method's findings may not be applicable.

Zhang et al. (2022) used a systematic assessment meta-analysis to assess the efficacy of RE, gemcitabine, and cisplatin in NCLC treatment [13]. Implementation involves data collection, meta-analysis, and interpretation. Methodical evaluation of several studies is the result. The comprehensive integration of many pieces of information benefits this approach, but the studies may vary. Reference [14] examined how RE affects NCLC treatment outcomes, angiogenesis, tumor cell proliferation, and migration. Implementation involves endostatin injection and endpoint data collection. The output evaluates treatment results and biological reactions. Detailed therapy evaluation is one of the main benefits of this approach. This method has limitations, such as patient heterogeneity.

Zhang et al. (2020) examined the efficacy and safety of RE with radiation or chemoradiotherapy in locally advanced NCLC [15]. The implementation phase includes endostatin and radiation delivery and data analysis. The output evaluates therapy efficacy and safety. Benefits of this approach include synergistic effects, but drawbacks include increased toxicity and complex treatment regimens. The reference [16] explores using RE as a radiosensitizer for NCLC management. Radiosensitizing effects are assessed through preclinical and possibly clinical trials during implementation. RE may improve radiotherapy, according to the findings. This method may help develop a new treatment. This approach requires more research and clinical validation, which may have drawbacks.

The literature review on the application of RE-PRT for NSCLC demonstrates a dynamic and promising landscape in the ongoing battle against this debilitating illness. This technique presents a unique way to increase the treatment response and improve patient outcomes by targeting tumor angiogenesis and administering intense radiation simultaneously. Nevertheless, it is important to acknowledge the existence of hurdles and limits in this field. These problems include patient heterogeneity, possible toxicities, and more clinical validation requirements. As a result, it is imperative to continue researching to address these issues.

RE-PRT FOR NCLC

The combination of RE and PRT represents a potentially effective and novel strategy for managing NCLC. Using RE as an anti-angiogenic agent specifically targets the tumor's vasculature, disrupts its blood supply, and inhibits tumor growth. The potential for a synergistic effect arises when PRT, a cytotoxic treatment that causes damage to tumor DNA and hinders cell proliferation, is combined. Utilizing this combined strategy can augment the comprehensive therapeutic response, as it restricts the tumor's vascularization and facilitates the targeted delivery of potent radiation to malignant cells. The proposed methodology has the potential to yield enhanced results for patients with NCLC, effectively addressing a pressing requirement in the ongoing fight against this formidable malignancy. Nevertheless, conducting comprehensive clinical trials and continuing research endeavors to evaluate this intervention's effectiveness and safety is imperative. This could potentially lead to the development of a more efficient treatment approach in the management of NCLC.

Radiotherapy and Anti-Angiogenic Therapy

The coexistence of radiotherapy and anti-angiogenic therapy within the domain of cancer treatment poses a multifaceted and captivating quandary. Radiotherapy is pivotal in treating diverse malignancies due to its established capacity to target and induce harm to malignant cells selectively. The treatment modality presents a promising opportunity for achieving localized tumor control, frequently resulting in notable therapeutic responses among individuals. In contrast, anti-angiogenic therapy, exemplified by bevacizumab and recombinant endostatin, aims to disrupt the vascularization of tumors, thereby inducing a state of nutrient deprivation by inhibiting neovascularization. This methodology has demonstrated potential in mitigating the proliferation of tumors and prolonging the duration of progression-free survival in particular forms of cancer, particularly when

utilized in conjunction with other therapeutic interventions.

Nevertheless, a difficulty emerges when contemplating the concurrent utilization of these therapeutic approaches. The efficacy of radiotherapy is contingent upon the proper functioning of the vascular system, as it facilitates the delivery of oxygen to tumor cells. This phenomenon, known as oxygen-enhanced radiation sensitivity, can significantly enhance radiotherapy's therapeutic effectiveness. The intended purpose of anti-angiogenic agents is to mitigate this phenomenon by decreasing the vascularity of tumors. Hence, the simultaneous administration of radiotherapy and anti-angiogenic therapy can compromise oxygen-dependent radiosensitivity, potentially constraining radiation's therapeutic advantages. Achieving an optimal equilibrium between maximizing the efficacy of radiotherapy and harnessing the advantages of anti-angiogenic therapies continues to pose a significant obstacle. The successful management of this intricate dilemma in the field of cancer care requires a comprehensive comprehension of the intricate relationship between these two methodologies. Additionally, it demands careful consideration of patient selection, innovative treatment scheduling, and the implementation of a personalized medicine approach.

RE and its mode of response

RE is a synthetic variant of the endogenous anti-angiogenic protein produced by expressing a recombinant gene that encodes endostatin's precise amino acid sequence. The chemical composition of the substance indicates the fundamental arrangement of endostatin, which is comprised of a sequence of endostatin domains encompassing distinct amino acid sequences. The RKTS (Arg-Lys-Thr-Ser) sequence is a widely recognized motif in recombinant endostatin, and it serves as a crucial element in its anti-angiogenic function. The mechanism of action of recombinant endostatin involves the selective targeting of endothelial cells, which are the fundamental constituents of blood vessels. It exerts inhibitory effects on angiogenesis, a crucial biological process involved in the progression of tumors, by employing various mechanisms. Through its interaction with cell surface receptors, such as integrins, it exerts regulatory control over intracellular signaling pathways, suppressing endothelial cell proliferation, migration, and angiogenesis. Moreover, the administration of RE leads to the initiation of programmed cell death in endothelial cells, thereby playing a role in diminishing the vascularization of the tumor. The multifaceted mechanism of action effectively interferes with tumor angiogenesis and restricts the provision of nutrients to the tumor, thereby impeding its growth and potential for metastasis.

The potential of recombinant endostatin as an effective anti-cancer therapy is attributed to its chemical structure and mechanism of action. Its efficacy is further enhanced with other treatment modalities, such as chemotherapy and radiotherapy. The capacity of this intervention to selectively target the tumor's vascular supply establishes its significance as a valuable modality for inhibiting the growth and spread of tumors. Current research endeavors are focused on enhancing the clinical utilization of RE to fully exploit its therapeutic capabilities and optimize its chemical characteristics to enhance the efficacy of NCLC treatment.

PRT and its action mechanism

PRT involves the administration of platinum-containing compounds, such as cisplatin or carboplatin, in conjunction with radiation therapy as a therapeutic modality for cancer. The action of these platinum compounds is exerted through a complex mechanism characterized by their chemical structure consisting of a central platinum atom coordinated with chloride and ammonia ligands. Upon intravenous administration, these compounds undergo dissociation, resulting in the formation of active species that engage in interactions with DNA within cancer cells. Purine bases are known to engage in covalent bonding with platinum, creating platinum-DNA adducts. The presence of these adducts hampers the process of DNA replication and transcription, resulting in DNA damage and impeding cellular proliferation. The combination of radiation therapy with enhanced DNA damage and inhibition of DNA repair mechanisms yields a robust cytotoxic effect, ultimately culminating in the demise of cancer cells. The chemical composition of platinum-based agents, in

conjunction with their mode of operation, underscores their pivotal function in enhancing the effectiveness of radiotherapy in the treatment of NCLC.

PRT has been widely recognized as a highly effective strategy for treating different types of malignancies, particularly in situations where the concurrent administration of chemotherapy and radiation therapy is advantageous. The chemical composition and mechanism of action of platinum compounds highlight their importance in enhancing the susceptibility of tumor cells to the harmful impacts of radiation. Despite the potential drawbacks and difficulties encountered in their clinical application, platinum-based agents are essential components of comprehensive NCLC treatment approaches due to their chemotherapeutic and radiosensitizing capabilities. These properties play a crucial role in enhancing patient outcomes and driving the continuous advancement of lung cancer care.

Combined administration of RE-PRT as a therapeutic approach for NCLC treatment

The combination of RE and PRT is motivated by the urgent requirement to augment the effectiveness of treatment for NCLC. Although effective when considered separately, both approaches possess distinct and complementary mechanisms of action. The utilization of RE as an anti-angiogenic agent effectively restricts tumor angiogenesis by targeting endothelial cells and disrupting the tumor's blood supply. In contrast, PRT induces DNA damage and suppresses the proliferation of cancer cells via radiation. The integration of these strategies presents the possibility of achieving synergy.

The utilization of RE can potentially enhance tumor cells' sensitivity toward radiation, thereby increasing their vulnerability to the cytotoxic impacts of radiotherapy. Additionally, it can effectively suppress the process of angiogenesis, thereby reducing the likelihood of tumor regrowth. This integrated approach presents the potential for enhanced local tumor control, delayed disease progression, and improved patient survival. The incorporation of RE-PRT has emerged as a compelling approach to confront the aggressive characteristics of NCLC and the difficulties presented by its advanced stages. This highlights the necessity of leveraging the synergistic advantages offered by these therapeutic methods in the battle against this formidable malignant condition.

Fig. 1 shows the combined administration of RE-PRT as a therapeutic approach for NCLC treatment. The upper section of the diagram depicts the primary strategy, in which anti-angiogenic therapy impedes blood vessel development and intensifies tumor oxygenation. This is achieved by reducing the number of blood vessels, leading to heightened resistance to radiation therapy during PRT. A circulatory normalization window will manifest at a particular time when RE is administered at a specific dose. The timing of this window may vary depending on factors such as tumor type, mode of handling, and dosage. In this particular scenario, the potential benefit for the PRT lies in the process of vascular standardization.

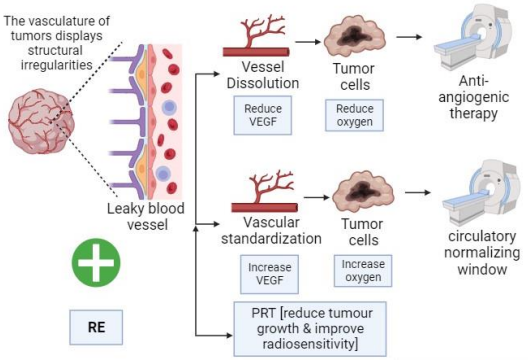

Fig.1. Combined administration of RE-PRT as a therapeutic approach for NCLC treatment.

This process involves transforming a disordered vascular network within the tumor into a more orderly and typical configuration. Consequently, this transformation leads to improved tumor oxygenation and an increased sensitivity to PRT. This phenomenon has been observed to enhance tumor control and induce cell death in experimental RE-PRT investigations.

RESULTS AND DISCUSSION

Patient's profile

This study's commencement occurred in October 2019 and its conclusion occurred in December 2021, per the defined protocol. Specifically, the trial was prematurely terminated due to the occurrence of severe

pulmonary toxicity, specifically grade III or higher, in at least six out of the initial ten patients who finished therapy. This outcome prompted the examination to close swiftly, per the predetermined methodology. Table 1 displays the attributes of the 21 patients that can be evaluated.

Tab.1. Patient's profile.

Features		Number of patients
Age (yrs)	Mean	61
	Range	35-70
	< 55 years	11
	>=55 years	10
Sex	Male	17
	Female	4
Smoking habit	>=350	16
	never	5
Cancer stage	III A	6
	III B	15

Table 1 offers a comprehensive summary of the demographic and clinical features of the patient population included in the research investigation. The average age of the patients is 61 years, with a range of 35 to 70 years, indicating the presence of a comparatively older group of patients. Among the cohort of 21 patients, it is observed that 11 individuals fall below the age threshold of 55 years, while the remaining ten patients are aged 55 years or above. This distribution of ages within the cohort demonstrates a notable diversity. The analysis of gender distribution reveals a significant gender disparity among the patients, with a majority of 17 being male and only four being female. The smoking behaviors of the patients demonstrate a noteworthy correlation, as 16 individuals have a documented smoking history, whereas five patients have never engaged in smoking. To the staging of cancer, a significant proportion of the patients in the study (15 individuals) have been identified as having stage III B cancer, with the remaining six individuals being diagnosed with stage IIIA-NCLC. This distribution highlights the prevalence of advanced-stage cancer cases within the population under investigation. The patient profile presented in this study serves as a valuable resource for comprehending the demographic and clinical attributes of the participants, thereby facilitating the interpretation of research findings and the formulation of customized treatment approaches.

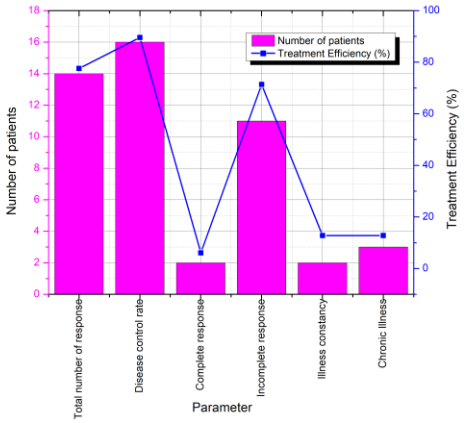

Fig.2. Treatment efficiency (%) using RE-PRT for NCLC based on number of patients.

Fig. 2 depicts the treatment efficiency (%) using RE-PRT for NCLC based on number of patients. Of the 14 patients evaluated, the collective treatment efficacy is 77.6%, signifying a significant proportion of favorable outcomes in response to the therapeutic intervention. The disease control rate, which includes patients exhibiting complete or incomplete responses, demonstrates a significant increase at 89.6%. This highlights the efficacy of RE-PRT in effectively halting or reversing the progression of the disease. Nevertheless, it is crucial to acknowledge that the comprehensive response rate is a relatively modest 6.1%, indicating that only a limited proportion of patients fully recover.

In contrast, the rate of incomplete responses, representing patients experiencing notable treatment advantages, is 71.4%. This figure suggests a considerable proportion of individuals who exhibited favorable disease management. The prevalence rates of illness constancy (12.8%) and chronic illness (12.8%) underscore the persistent disease burden among the patients in the cohort, underscoring the need for ongoing assessment and improvement of treatment strategies. The values mentioned above collectively emphasize the potential of RE-PRT in managing NCLC, specifically in attaining disease control. However, they also bring attention to the necessity for additional strategies to improve complete response rates and diminish the persistence of illness within this specific group of patients.

CONCLUSION

This study aimed to evaluate the potential advantages of RE in improving the efficacy and safety of Platinum-based Radiotherapy (PRT) when delivered via intravenous and pulmonary infusions for individuals diagnosed with stage IIIA/B-NCLC. This manuscript thoroughly examines experimental and clinical studies that have investigated the concurrent use of RE-PRT as a therapeutic strategy for the treatment of non-small cell lung cancer (NCLC). The study evaluated a sample of 14 individuals and found that the treatment demonstrated an overall effectiveness rate of 77.6%. This percentage signifies a significant proportion of favorable outcomes concerning the therapeutic intervention. The disease control rate, which includes patients who demonstrate complete or partial responses, demonstrates a significant increase of 89.6%. This highlights the efficacy of RE-PRT in effectively halting or reversing the progression of the NCLC.

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