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RESEARCH ARTICLE

NON SURGICAL TREATMENT OF CARCINOID LUNGS TUMORS

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Abstract

Typical carcinoid lungs tumors are neuroendocrine bronchopulmonary tumors with a low-grade malignancy, and an atypical carcinoid is an intermediate form of these tumors. Their systemic treatment is greatly influenced by therapeutic evidence derived from the more frequent gastroenteropancreatic neuroendocrine neoplasms. Currently, systemic therapies for lung carcinoids, aiming at controlling tumor growth include long acting somatostatin analogues (SSAs), peptide receptor radionuclide therapy, chemotherapy and molecular-targeted therapy.

Introduction:-

Neuroendocrine tumors (NETs) encompass a heterogeneous group of neoplasms that are derived from the diffuse endocrine system and most commonly originate from the lungs, small intestine, and rectum [1]

According to the latest WHO classification, lung NETs are categorized into the following four subtypes—typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine lung carcinoma (LCNELC) and small cell lung carcinoma (SCLC) [2].

Typical and atypical carcinoids are rare tumors that represent 1 to 2% of all primary bronchial tumors. Carcinoids are considered neuroendocrine tumors of low grade at one end of the aggressiveness spectrum of bronchial neuroendocrine tumors, the other end being represented by small cell lung carcinoma. These are tumors malignant because of their local aggressiveness and metastatic potential. CTs represent approximately 80% to 90% of all carcinoid tumors in published surgical series [3].

These entities are distinguished by their clinical, radiological and histological presentation, and their prognosis.

Bronchial typical carcinoid tumors are neuroendocrine bronchopulmonary tumors with a low-grade malignancy, and an atypical carcinoid is an intermediate form of these tumors.

Typical carcinoid tumors represent less than 2% of lung tumors. They grow slowly and rarely spread beyond the lungs ; Atypical carcinoids are much rarer than typical lung carcinoids. They represent less than 0.2% of lung

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tumors and tend to grow faster than typical carcinoids. There is a greater chance that they will metastasize beyond the lungs. [4]

One of the features of this group of tumors is its heterogeneity of evolution, with the possibility of long periods of spontaneous tumor stability, sometimes for several years, including in the forms metastatic. This should be kept in mind with every therapeutic decision.

Given the rarity of metastatic carcinoid tumors of bronchial origin, there are no prospective studies of adequate size to offer validated therapeutics with a sufficient level of evidence. We focused on the non surgical treatment of lung carcinoid (LCs) tumor.

Adjuvant setting:
The role of adjuvant therapy in LCs is controversial. There is no prospecitve studies exploring role of adjuvant treatment.

The European Neuroendocrine Tumor Society (ENETS) suggests adjuvant treatment could be considered in only patients with AC with positive lymph nodes, especially if there is a high proliferative index. [5] While the National Comprehensive Cancer Network (NCCN) suggests adjuvant chemotherapy could be considered, with or without radiotherapy, in resectable stage IIIA ACs. [6]

Palliative setting
The medical management must incorporate multidisciplinary meeting review the treatment of metastatic carcinoid tumors must be based on the both hormone-related symptoms and tumor growth.

Somatostatin analogues (SSAs):
SSAs exert dual inhibitory action, against both hormone secretion and proliferation of cells. The most commonly used agents are octreotide and lanreotide.

There are no dedicated trials, available for lung primary. The benefit of SSAs in the advanced stages has not been confirmed in prospective randomized trials and supporting evidence arises only from retrospective studies [7]

The ability of somatostatin analogs to control the growth of well-differentiated metastatic NETs is a matter of debate. There istwo prospective phase 3 randomized trials in patients with digestive NETs;

In PROMID trial, patients with midgut NET were randomly assigned to either placebo or octreotide LAR 30 mg intramuscularly in monthly intervals until tumor progression or death. Octreotide LAR significantly lengthens time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs.[8]

In CLARINET trial, in patients with non-functional enteropancreatic NETs allocated to either lanreotideAutogel (120 mg/28 days) or placebo, lanreotide was associated with significantly prolonged time to progression (TTP). [9]

To date, ongoing clinical trial - SPINET - is testing lanreotide in unresectable LCs. SPINET is a phase 3, prospective, double-blind, multi-center, randomized, study of efficacy and safety of Lanreotideautogel/Depot 120mg versus placebo for tumor control in subjects with well differentiated, metastatic and/or unresectable typical or atypical lung neuroendocrine tumors.

Taregeted therapy (Everolimus)
Mammalian target of Rapamycin (mtor) has been identified as a kinase activated in the PI3K signaling pathway of lung NETs. A significant progress in the management of progressive advanced LCs has been made with the introduction of everolimus—a mammalian target of rapamycin (mTOR) inhibitor—in clinical practice. It can be used with or without somatostatin drugs, such as octreotide. [10]

The randomized phase III RADIANT 2 trial assessed everolimus 10 mg + octreotide LAR versus placebo + octreotide LAR in advanced functional well to moderately differentiated NETs of diverse primary sites.The study

demonstrated a clinically significant 5.1 month increase in median progression-free survival . The exploratory subgroup analysis of this study in the 44 patients with LCs favored the addition of everolimus to octreotide LAR (improved PFS), even though not reaching statistical significance because of the limited number of cases. [11,12]

Another phase 2 study (RAMSETE) analyzed the antitumor benefit of everolimus monotherapy. It demonstrated favorable PFS in patients with non-functional, non-pancreatic NETs (including LCs). A progression-free survival of 189 days was reported [13].

In February 2016, everolimus was approved by the US Food and Drug Administration (FDA) for progressive, well-differentiated, nonfunctional neuroendocrine tumors (NETs) of lung origin that are unresectable, locally advanced, or metastatic. Approval was based on the RADIANT-4 trial, in which median progression-free survival was 11 months in the 205 patients allocated to receive everolimus (10 mg/day) and 3.9 months in the 97 patients who received placebo. Everolimus was associated with a 52% reduction in the estimated risk of progression or death.[14] The subsequent subgroup analysis in LCs continued showing improved PFS [9.2 *vs.* 3.6 months (HR, 0.50; 95% CI, 0.28–0.88)], establishing the role of targeted therapy in LCs. [15]Common side effects include diarrhea, fatigue, rash, mouth sores and swelling of the legs or arms.

Combination of everolimus with SSAs is under investigation in LUNA trial. This is a prospective, multicenter, randomized, open-label, 3-arm, phase II study with a single-stage design in each arm. The purpose of this study is to test the effectiveness and safety of Everolimus or Pasireotide LAR alone or in combination in adult patients with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of the lung and thymus. Primary Endpoint is defined as the proportion of patients who are progression-free at 9 months according to RECIST. Preliminary results have already been published, showing promising PFS rates at month 9–39% (for pasireotide LAR), 33.3% (for everolimus) and 58.5% (for the combined arm). [16]

Chemotherapy

Chemotherapy should be considered as an option for palliative treatment in patients with advanced unresectable progressive LCs. Due to the small numbers of patients ;There is a lack of randomized trials, especially placebo-controlled studies. Several chemotherapeutic agents have been investigated, but they were generally associated with discouraging results. [17]

Overall response rate (ORR) below 30% has been described with 5-fluorouracil (5-FU), capecitabine, doxorubicin, dacarbazine, streptozotocin (STZ), cyclophosphamide, platinum derivatives, etoposide and temozolomidewhen administered in various combinations. [18,19]

In a study by Sun et al,patients with advanced carcinoid tumors were randomized to either doxorubicin with fluorouracil or fluorouracil with streptozocin. Responses to this treatment were modest. Fluorouracil with streptozocin improved survival ; but not the response rates and the progression-free survival compared with the doxorubicin-based regimen, [20]

Temozolomide as monotherapy shows activity in metastatic lung carcinoids ina larger retrospective study. 31 patients with progressive metastatic bronchial carcinoid treated with temozolomide as monotherapy ; 14 tumors were classified as typical and 15 as atypical carcinoids. Median progression-free survival was 5.3 months and median overall survival was 23.2 months from the start of temozolomide. [21]

Results from an interim analysis of one Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors, including LCs, revealed thatcapecitabine-temozolomomide (CAPTEM) led to 1 complete response (CR), 4 PR, 7 SD and a greater than 22 months median PFS in the cohort of 12 patients with progressive LCs.[22]

In a study by Chong et al., 13 patients with advanced LCs were treated with etoposide with either cisplatin or carboplatin. One of the three responses was complete and was observed after carboplatin plus etoposide treatment. The clinical benefit of this platinum-based chemotherapy in this study was very high, as additional to responses, nine cases (69%) presented SD. [23]

Peptide receptor radionuclide therapy (PRRT)

Peptide receptor radionuclide therapy (PRRT) for the treatment of neuroendocrine tumours (NET) has been explored for almost two decades, but there are still few trials that have exclusively investigated well-differentiated and moderately differentiated NET arising from the respiratory tree.

PRRT with ^{177}Lu-DOTATATE is a favorable therapeutic option in patients with metastatic bronchial and gastroenteropancreatic NETs that express somatostatin receptors. PRRT with ^{177}Lu-DOTATATE is safe with few side-effects and shows good response rates with PFS of 29 months and OS of 63 months. [24]

In a large cohort of patients with advanced BPC treated in a "real-world" scenario and followed up for a median of 45.1 months (range 2-191 months), PRRT proved to be promising in prolonging survival and delaying disease progression. Despite the potential selection biases, considering the risk-benefit ratio, (177)Lu-DOTATATE monotherapy seems the best option for PRRT. The use of PRRT in earlier stages of the disease could provide a more favorable outcome.[25]

The randomized controlled phase III NETTER-1 trial—comparing 177Lu-DOTATATE *vs.* high-dose octreotide LAR in metastatic progressive (after SSA first-line treatment) midgut NETs—revealed demonstrate that treatment with Lutathera provides significantly longer time to deterioration of quality of life for patients with progressive midgut Neuroendocrine tumors (NETs) compared to octreotide LAR alone. Lutathera is the first Peptide Receptor Radionuclide Therapy (PRRT) to receive regulatory registration, with approval by the European Commission in September 2017 and by the US Food and Drug Administration (FDA) in January 2018. [26]

Conclusions:-

The non surgical treatment for advanced LCs broadens after the recent success of everolimus in improving PFS, it is licensed for non-functioning advanced lung carcinoids. SSAs are recommended for treatment of carcinoid syndrome for functioning tumors while the anti-tumour effect of SSAs for LC sis still pending confirmation in prospective randomised studies. The use of adjuvant therapy is not currently recommended. The benefit of chemotherapy (Temozolomide-Capecitabine) and PRRT is prominsig ; prospective studies required.

Conflict of Interest :

The authors declare that they have no competing interests

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Authors' contributions :

MounaBourhafour: drafted the manuscript.

All authors read and approved the final manuscript.

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