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Editorial / Editorial

Evolution of Lung Cancer Management

Evolución del manejo del cáncer de pulmón

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Lung cancer is the malignant neoplasm with the highest incidence worldwide according to the 2022 Globocan [1]. Of all malignant neoplasms, in men, it ranks first with 15.2%; in women, second with 9.4%, thus becoming a public health problem. Unfortunately, most of the patients are diagnosed at advanced and metastatic stages. The traditional view divided it into two major groups: Non-Small Cell Lung Cancer and Small Cell Lung Cancer. The first included squamous type, adenocarcinoma, and large cells. In this context, the treatment was based on systemic chemotherapy with platinum salts around 1978, and then other drugs such as taxanes, Gemcitabine, and Vinorelbine were added. By the year 2000, the median survival had increased from 4 to 10 months, and the overall survival rate reached only 5% at 5 years [2]. Later, better understanding of molecular biology allowed the discovery of certain genetic anomalies at the cellular level of adenocarcinoma-type tumors, such as mutations, rearrangements, and amplifications, which conferred specific characteristics to their biological behavior and enabled the use of targeted therapies according to the alterations presented.

It is known that there are various receptors at the cell membrane, like tyrosine kinase receptors: a family of enzymes that catalyze the transfer of a phosphate group to a tyrosine amino acid of a protein. This process is called phosphorylation and is involved in intracellular signal transduction, that is, the transmission of information from the outside of the cell to the inside. It triggers various cellular processes such as proliferation, differentiation, maturation, and cell survival.

Recent advances have implicated the role of tyrosine kinases in the pathophysiology of cancer. Although its activity is tightly regulated in normal cells, it can acquire transforming functions due to mutations, overexpressions, autocrine and paracrine stimulation leading to malignancy. The most well-studied mutations are those of the Epidermal Growth Factor Receptor (EGFR), the most frequent being in exon 19. The incidence of the mutation is variable according to different geographical regions, ranging from 16% to 60%. Based on these concepts, drugs that could block all these activities called Tyrosine Kinase Inhibitors (TKI) emerged.

The first generation were Gefitinib and Erlotinib [3-4], whose various randomized clinical trials compared them with first-line chemotherapy. The results in objective response rates (ORR) ranged from 58% to 83% for TKIs and from 15% to 47.3% for chemotherapy. Similarly, progression-free survival (PFS) ranged from 9.2 to 13.7 months vs 4.6 to 6.4 months. There were no differences in overall survival in any of the trials, probably due to the crossover of patients to TKI. It is important to remember that these high rates of objective responses and significant progression-free survival were observed in patients who had mutations, especially those located in exon 19.

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The second generation of TKIs appears with Afatinib [5] in randomized studies versus chemotherapy, results were: ORR ranged from 56% to 67% vs. 23% for TKIs and chemotherapy, and PFS from 13.1 to 6.9 months, respectively. For overall survival, TKI ranged from 31.4 to 33.3 months and chemotherapy from 18.4 to 21.1 months. Likewise, all these positive and significant results were observed in patients with exon 19 mutations. The other TKI is Dacomitinib, whose results regarding ORR and PFS have been similar without impacting overall survival.

The problem with the use of TKIs is Acquired Resistance [6] through various mechanisms, the main one being the T790M mutation in 50 to 70% of cases, and others in small percentages such as MET amplification, HER2: Human Epidermal Growth Factor Receptor 2, small cell lung cancer, and combinations between them.

The third generation is Osimertinib [7] used in patients with this mutation whose results showed a similar ORR, with prolonged PFS and significant improvement in overall survival, especially in the exon 19 subgroup, which reached up to 45.7 months compared to the overall 38.6 months. These results are significantly better than with chemotherapy, achieving PFS of 9 to 14 months, median survivals of 18.6 to 30.5 months, and around 15% at 5 years.

Another important mutation is the ALK rearrangement (Anaplastic Lymphoma Kinase) described in 2007 [8]. EML4 (Echinoderm Microtubule-Associated Protein-Like 4) is the most common fusion gene in this neoplasm, allowing the tumor expression of the oncogenic fusion protein EML4–ALK.

The first-generation TKI inhibitor, Crizotinib, was evaluated in a clinical trial vs. chemotherapy, achieving ORR of 60 to 65%, PFS of 10.9 vs. 7 months, and a 54% survival rate at 2 years. Ceritinib achieves similar ORR and a PFS of 61% at 12 months, and Alectinib achieves an ORR of 93.5%, with a PFS of 27.7 months and a 2-year survival rate of 79%, both second-generation inhibitors.

Immunotherapy has significantly changed the approach to lung cancer treatment. First, because it generates a response that lasts over time due to the generation of immunological memory, allowing for very prolonged responses not achieved with cytotoxic therapies; second, because of its safety profile and relatively fewer side effects.

The immune system has the ability to prevent any damage to the normal cells of our body, for this purpose, it uses checkpoints, which are proteins in immune cells that function as switches that need to be turned on or off to initiate an immune response. Tumor cells use these checkpoints to avoid being destroyed.

In 1992, Tasuku Honjo [9] discovered PD1 (programmed cell death protein 1), a protein expressed on the surface of T cells that usually prevents normal cells from being destroyed, but when blocked, it enhances the immune response against tumor cells.

In 1994, James Allison [9] studied a protein of T lymphocytes, CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), which helps the body keep immune responses under control. CTLA-4 binds to another protein called B7, preventing T cells from destroying other cells, such as cancerous ones.

These discoveries allowed the development of drugs targeting these checkpoints, causing a blockade of their functions, called Checkpoint Inhibitors, which have been divided into two groups: PD1 Inhibitors (Pembrolizumab and Nivolumab) and PD-L1 inhibitors (Atezolizumab and Durvalumab). The other group corresponds to CTLA-4 Inhibitor (Ipilimumab).

Different clinical trials initially used in the second line [10], and then in the first one, have shown promising results when combined [11] and with others such as chemotherapy [12]. This yielded longer long-term survival with 5-year rates of 20%, lower risk of progression compared to chemotherapy, especially in patients with high tumor mutational burden, and significant benefits in patients with specific mutations. These results are even better when the expression of the PD-L1 marker is increased. Consider that the time to response may take several months to assess the efficacy of the therapy. Possible side effects such as fatigue, diarrhea, and skin rashes are manageable, and in some cases, autoimmune reactions can occur.

Recent research is looking for new implicated genes that are useful as biomarkers; for instance, the expression of the ERO1A gene (Endoplasmic Reticulum Oxidoreductase 1 Alpha) [13] identified as a poor prognostic indicator in EGFR gene mutations, and the expression of the non-coding RNA LNX1-AS2 as a poor prognostic indicator for pulmonary adenocarcinoma [14].

Some advances in artificial intelligence (AI) [15] are transforming diagnosis and treatment primarily through the analysis of genomic data and pathological images. DeepGEM, an AI model, predicts genetic mutations quickly and accurately using thousands of tissue sample images, generating mutation maps that improve diagnostic efficiency to guide personalized treatments.

The HPL System [16] histomorphological phenotype learning, classifies tumor phenotypes and associates them with clinical outcomes, achieving 99% accuracy in subtype differentiation, helping to predict recurrences and tumor aggressiveness, and allowing for optimal treatment for patients.

Conclusion: The evolution of lung cancer management has progressed from conventional chemotherapy to targeted therapies based on genetic alterations such as EGFR and ALK. The emergence of tyrosine kinase inhibitors and immunotherapy has significantly improved survival rates. Artificial intelligence emerges as a key tool for personalizing diagnosis and treatment.

1. Abbreviations

EGFR: Epidermal growth factor receptor.

TKI: Tyrosine kinase inhibitor.

ORR: Objective response rate.

PFS: Progression-free survival.

ALK: Anaplastic lymphoma kinase.

CTLA-4: Cytotoxic t-lymphocyte-associated protein 4.

2. Administrative information

2.1 Additional files

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2.3 Author contributions

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2.5 Availability of data and materials

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3. Statements

3.1 Approval of the ethics committee

Not applicable.

3.2 Consent for publication

Does not apply, as the manuscript does not contain personal data or identifiable patient information.

3.3 Conflict of interest

The author declares no conflict of interest related to the content of this editorial.

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