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CHALLENGES AND ADVANCES IN METASTATIC NON-SMALL CELL LUNG CANCER WITH EGFR MUTATION

RETOS Y AVANCES DEL CÁNCER DE PULMÓN DE CÉLULAS NO PEQUEÑAS METASTÁSICO EGFR MUTADO

Melanie Castro-Mollo [1,3], Rossana Ruiz [2,3], Katia Roque [3], Luis Mas [3,4]

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ABSTRACT

Introduction: Tyrosine kinase inhibitors have dramatically changed the clinical outcomes for patients with advanced non-small cell lung cancer with epidermal growth factor receptor mutations. However, there are still challenges in the management of patients with this mutation in a metastatic setting, such as intrinsic and acquired resistance to tyrosine kinase inhibitors. We will discuss the latest advances and new strategies in first-line treatment, osimertinib resistance, and exon 20 mutation treatment.

Keywords: Epidermal growth factor receptor; Non-small cell Lung cancer; Tyrosine kinase inhibitors. (Source: MESH-NLM)

RESUMEN

Introducción: Los inhibidores de la tirosina quinasa han cambiado drásticamente la perspectiva clínica de los pacientes con cáncer de pulmón de células no pequeñas avanzado con mutaciones del receptor del factor de crecimiento epidérmico. Sin embargo, existen aún retos en el manejo de los pacientes con esta mutación en un escenario metastásico, como es la resistencia intrínseca y adquirida a inhibidores de tirosina quinasa. Se discutirán los últimos avances y nuevas estrategias en primera línea de tratamiento, resistencia a osimertinib y tratamiento en mutación, en el exón 20.

Palabras clave: Receptor del factor de crecimiento epidérmico, cáncer de pulmón de células no pequeñas, inhibidores de la tirosina quinasa. (Fuente: DeCS- BIREME)

[1] Universidad de San Martín de Porres.
[2] Oncosalud – AUNA.
[3] Instituto Nacional de Enfermedades Neoplásicas .
[4] Universidad Peruana Cayetano Heredia.

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INTRODUCTION

Lung cancer is a common disease and ranks among the leading causes of cancer-related deaths in Peru and globally[1,2]. Advances in understanding the biology of the disease, biomarkers, and genetic alterations have led to the development of targeted therapies. Along with immune checkpoint inhibitors, these advancements have transformed the treatment landscape for non-small cell lung cancer (NSCLC)[3].

Somatic activating mutations in the epidermal growth factor receptor (EGFR) confer sensitivity to tyrosine kinase inhibitors (TKIs) and are the most frequent genetic alterations in the adenocarcinoma histological subtype in some regions, such as Peru, representing approximately 40% of NSCLC patients[4]. Deletions in exon 19 of EGFR and point mutations L858R in exon 2,1 account for about 85% of EGFR somatic alterations and predict sensitivity to TKIs. In contrast, insertions in exon 20 of EGFR show resistance to most EGFR TKIs[5]. Moreover, the presence of co-mutations, such as TP53, confers more aggressive characteristics to the disease and poorer clinical outcomes[6]. First-generation (gefitinib and erlotinib) and second-generation (afatinib and dacomitinib) TKIs have shown significant improvements in progression-free survival (PFS), ranging from 10 to 14 months compared to platinum-based chemotherapy[7]. Data from our country using first-generation TKIs report a median PFS of 13.9 months and overall survival (OS) of 21.7 months[8]. There are significant challenges in improving outcomes in terms of efficacy and safety for patients with metastatic EGFR-mutated (EGFRmut). This discussion will address three challenges and the interventions under study to address these challenges: improving outcomes in patients with sensitive mutations, developing resistance to osimertinib, and the best treatment for patients with exon 20 mutations.

First-Line Treatment

Osimertinib, a third-generation TKI, has demonstrated superiority in both PFS (18.9 months) and OS (38.6 months) in patients with advanced EGFR Mut+ NSCLC[9], establishing it as a first-line treatment. Despite these significant treatments, advances, and knowledge of genetic determinants, resistance to TKIs inevitably occurs[10]. There are strategies to overcome or delay this resistance, such as the use of other third-generation TKIs and combinations.

Other Third-Generation TKIs

Other third-generation TKIs have achieved results similar to osimertinib (see Table 1). In the phase III, AENEAS study[11], aumolertinib was compared to gefitinib in EGFR Mut+ NSCLC patients in the first line of treatment. The primary endpoint was PFS and was significantly longer with aumolertinib, 19.3 months compared to 9.9 months with gefitinib, with a hazard ratio (HR) of 0.46. There were no significant differences in objective response rate (ORR) and the frequency of adverse effects. In the phase III, LASER301 study[12], lazertinib, an irreversible third-generation EGFR TKI with brain penetration, was compared to gefitinib. The primary endpoint was PFS, and it was significantly longer with lazertinib than with gefitinib, 20.6 vs. 9.7 months; HR 0.45. There were no differences in ORR and grade ≥3 adverse events. In the real world, the results support the indiscriminate use of these third-generation TKIs and have shown efficacy and safety comparable to osimertinib, without comparative studies between them.

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Table 1. Third-Generation TKIs.

Clinical trial	FLAURA	AENEAS	LASER301
Arms	Osimertinib vs. gefitinib/erlotinib	Aumolertinib vs. gefitinib	Lazertinib vs. gefitinib
PFS (months)	18.9	19.3	20.6
PFS (months) in patients with CNS metastasis	15.2	15.3	16.4
ORR (%)	80	73.8	76
Adverse effects ≥ G3 (%)	34	36.4	39
Permanent treatment discontinuation (%)	13	3.7	10

Combinations of TKIs with chemotherapy/bispecific antibodies

An intervention to prevent the development of resistance to targeted treatment and improve outcomes in these patients is the combination of TKIs with chemotherapy or bispecific antibodies. The combination with chemotherapy is based on the greater sensitivity that EGFRmut patients have to chemotherapy compared to non-mutated patients [13] and preclinical studies have shown that the combination has a synergistic effect by: 1) Reducing VEGF-mediated angiogenesis, 2) inducing apoptosis of TKI-resistant cellular clones, 3) reducing tumor heterogeneity, fewer resistance pathways [14]. The combination with a bispecific antibody, anti-EGFR and anti-MET, is based on EGFR-independent resistance through other signaling pathways such as MET, whose amplification represents 10-20% of the resistance mechanisms of patients treated with osimertinib [10]. Additionally, there is cross-talk between the EGFR and MET signaling pathways, which can compensate for each other when the signaling of either protein is inhibited[15]. Therefore, inhibiting both pathways, using a bispecific antibody like amivantamab, reduces resistance pathways[16]. Below, we discuss the results of the FLAURA2 [17] and MARIPOSA [18] studies in patients with EGFRmut NSCLC (Ex19 del or L858R).

Multiple studies with first-generation TKIs and chemotherapy have been conducted[19], however, only two Asian studies have had positive results when evaluating the combination of gefitinib plus chemotherapy versus gefitinib alone, both with significant results in ORR and PFS [20,21]. FLAURA2 [17], recently approved by the FDA as a first-line treatment in NSCLC patients with EGFR mutation, is a randomized phase III clinical trial comparing osimertinib plus platinum-based chemotherapy with osimertinib alone. The primary PFS endpoint was positive; the median was 25.5 months for patients who received the combination of osimertinib plus chemotherapy versus 16.7 months for those who received osimertinib alone; HR of 0.62. The ORR was higher for the combination of osimertinib plus chemotherapy (83%) and osimertinib (76%), but it was not significant. Grade ≥ 3 adverse events were reported in 64% of patients who received osimertinib plus chemotherapy compared to 27% of patients who received osimertinib alone.

The MARIPOSA study[18] is a randomized phase III clinical trial comparing amivantamab plus lazertinib with osimertinib; the primary endpoint was PFS. The median PFS was 23.7 months for patients who received the combination of amivantamab plus lazertinib versus 16.6 months for those who received osimertinib, HR of 0.70. The objective response rates were very similar with amivantamab-lazertinib (86%) and osimertinib (85%). The incidence of most EGFR and MET-related adverse events was higher in the combination and led to treatment discontinuation in 10% of patients treated with amivantamab plus lazertinib and in 3% with osimertinib. Venous thromboembolism occurred in 37% of patients in the amivantamab-lazertinib group and in 9% of the osimertinib group, leading researchers to recommend prophylactic anticoagulation during the first four months of treatment in ongoing trials of amivantamab-lazertinib.

Both studies show superiority for the combination with the TKI, table 2, with a PFS benefit of 7-9 months; however, this difference does not yet translate into an increase in OS, likely due to data immaturity at the time and it is at the cost of increased toxicity. In the subgroup analysis, we see that the magnitude of the benefit in the MARIPOSA study is across all subgroups with a reduced risk of progression or death of approximately 30%, while in the FLAURA2 study, there is greater benefit in the subgroup of patients with central nervous system (CNS) metastases and in patients with exon 21 mutation, L858R, who generally have less clinical benefit with TKI [22]. From our point of view, these two populations benefit the most from the combination with chemotherapy. The toxicity profiles of both interventions are different, while the combination with chemotherapy increases the adverse effects related to chemotherapy (hematologic toxicity), with which we are more familiar. Bispecific antibodies cause a higher incidence of infusion-related events and thromboembolism, which require greater hospital

support for management. These studies, FLAURA2 and MARIPOSA, raise some questions: Should we consider the combination as the new standard of treatment? Which patients benefit most from these interventions? What are the mechanisms of resistance after the combinations? What will we do at progression?

Table 2. Combination trials and TKIs.

Clinical trials/arms		PFS months	PFS HR	PFS met. CNS months	PFS met. CNS HR	PFS Ex19del months	PFS Ex19del HR	PFS L858R months	PFS L858R HR	ORR (%)	Adverse effects ≥ G3 (%)
FLAURA2	Osimertinib + chemotherapy	25.5	0.62	24.9	0.47	27.9	0.60	24.7	0.63	83	64
	Osimertinib	16.7		13.8		19.4		13.9		76	27
MARIPOSA	Lazertinib +amivantamab	23.7	0.7	18.3	0.69	-	0.65	-	0.78	86	75
	Osimertinib	16.6		13		-		-		85	43

(-) Information not available

Resistance to osimertinib

Despite the benefits of TKIs, resistance mechanisms inevitably develop for osimertinib; these vary depending on whether it is used as first or second-line treatment, being polyclonal and diverse [23]. About 25-50% of cases have resistance mechanisms through activation of accessory pathways such as the MET gene and EGFR pathways [10]. The current standard treatment is chemotherapy, however, systemic treatment based on platinum has poor outcomes [24]. There are two strategies to overcome resistance to osimertinib and seek better outcomes still under study: fourth-generation TKIs and combinations of third-generation TKIs with allosteric inhibitors or inhibitors of other signaling pathways (MET, HER2/3, etc.) [25]. In this scenario, there is a possibility to avoid or delay chemotherapy in patients who develop resistance to osimertinib. There are still not enough efficacy data available to prefer some therapeutic strategies over others.

Amivantamab-lazertinib has shown benefit in patients previously treated with osimertinib and has demonstrated safety and antitumor activity in the phase 1 Chrysalis-2 trial [26]. The MARIPOSA2 study [27], a randomized phase III trial, is for patients who have progressed on osimertinib in the first or second line, originally designed with three study arms: Amivantamab-lazertinib-chemotherapy, amivantamab-chemotherapy, and chemotherapy alone. Among the participant characteristics, approximately 70% of participants received osimertinib as first-line and 30% as second-line, and more than 40% have a history of brain metastasis. The primary endpoint was PFS, with a median follow-up of 8.7 months, amivantamab-chemotherapy, and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, with a median of 6.3 and 8.3 versus 4.2 months, respectively. All subgroups benefited from these interventions. The objective response rate was significantly higher for chemotherapy with amivantamab and chemotherapy with amivantamab-lazertinib versus chemotherapy alone (64% and 63% versus 36%, respectively; P<0.001 for both).

The median PFS in patients with CNS metastasis was 12.5 and 12.8 versus 8.3 months for chemotherapy with amivantamab and chemotherapy with amivantamab-lazertinib versus chemotherapy alone. Grade ≥3

adverse events were higher in the combinations with amivantamab; it was 92% for the triplet vs. 72% for the combination with chemotherapy and 48% for chemotherapy alone. Likewise, for serious adverse events: 52%, 32%, and 20%, respectively. Amivantamab-lazertinib-chemotherapy presented higher hematologic toxicity, so the protocol was revised and a dose modification was made that allows initiating lazertinib after chemotherapy with platinums; this modification will require more follow-up to have published results.

According to these data, combinations with amivantamab lead to clinically significant improvements in PFS and ORR compared to our current standard, but with a higher frequency and severity of toxicities. The improvements in PFS at the level of CNS metastases are encouraging, as we have limited treatment options for patients with CNS progression who received osimertinib, and this benefit is similar in both arms that received amivantamab regardless of the use of lazertinib.

Exon 20 Mutation

Insertions in exon 20 represent up to 10% of all EGFR-mutated NSCLC[28]. Due to an altered conformation at the kinase active site that limits the binding of TKIs, this group of patients are resistant to TKI treatment; the treatment option is platinum-based chemotherapy. The phase III clinical trial PAPILLON[29] compared amivantamab plus chemotherapy against chemotherapy alone in patients with exon 20 insertion as first-line. The median PFS was 11.4 months and 6.7 months, respectively; HR, 0.40 (95% CI, 0.30 to 0.53; p<0.001). The ORR was 73% for the combination and 47% for chemotherapy alone. In the interim analysis of overall survival (33% maturity), the median has not been reached for the amivantamab-chemotherapy group compared to 24.4 months for chemotherapy, HR 0.67, not significant at the time. The predominant adverse events associated with chemotherapy plus amivantamab were mostly reversible hematologic effects and toxicity related to EGFR inhibition (paronychia and rash); 7% of patients discontinued treatment with amivantamab due to adverse reactions.

This study provides patients with exon 20 insertions an effective and safe treatment option that, to date, has only been based on chemotherapy. Another challenge that patients with EGFR exon 20 insertion mutations face is molecular diagnosis, due to the diverse mutational landscape and the limitation of molecular tests for their detection, so the frequency of this mutation could be underestimated[30].

Finally, the mechanisms of resistance and strategies to overcome them, as well as the treatment of patients with CNS metastases, require more research. However, new treatments will provide a broader range of effective options for this group of patients.

CONCLUSION

Currently, different treatment options are available for patients with EGFR-mutated NSCLC, making the selection complicated; the challenge is to choose the best option for each case.

Can we consider the combination of osimertinib associated with chemotherapy as the first line of treatment? In our view, it is not for all cases; we must select patients at higher risk such as those with a high disease burden, presence of brain metastatic disease, or co-mutations of poor prognosis.

Should the safety profile of the combination be considered for treatment selection? The improvement, in terms of efficacy, is also associated with an increase in toxicity with a greater number of grade 3 to 5 adverse events, so the patient must be in better clinical condition to tolerate them.

The therapeutic gap for cases with exon 20 insertion has been bridged, and it has been observed that the combination therapy of amivantamab with chemotherapy is effective and with a manageable safety profile. Resistance to osimertinib, which inevitably develops, is a challenge to overcome; the combination of amivantamab with chemotherapy provides an effective and safe alternative for this patient population.

Finally, the convergence of multiple variables for decision-making in this scenario of new alternatives available, the proper and balanced coordination of the best clinical judgment, timely molecular information, interpretation of biomarkers, patient preference, multidisciplinary discussion in molecular tumor board, present comorbidities, and access to available molecules, will make possible the best patient-centered choice.

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Correspondencia: *Luis Mas.*
Dirección: *Avenida Angamos 2520.*
Teléfono: *993473019*
Correo electrónico: ***lmasl@hotmail.com***

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