Clinical Response to Osimertinib Compared to Other Tyrosine Kinase Inhibitors and Chemotherapy in Non-Small Cell Lung Cancer

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Abstract

Osimertinib targets the same activating mutations in the EGFR (exon 19 and L858R of exon 21) as other target therapies but it also has action over the T790M mutation (the most frequently resistance mutation found in these tumors) and has better efficacy than 1st and 2nd generation TKI at the Central Nervous System (CNS) level. In Mexico has a higher incidence alterations of the EGFR gene are higher, being the most frequent molecular alteration in up to forty percent of patients with advanced NSCLC and the mutation resistance in T790M is 50% in this group. Here we present 3 cases of patients who received Osimertinib as a 2nd line therapy for metastatic NSCLC obtaining a complete response in one of them.

Keywords: Osimertinib; Non-small lung cancer; Tyrosine kinase inhibitors; Chemotherapy
1. Introduction

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of death among malignancies in the world and in advanced stages carries a somber prognosis [1]. Around 15 years ago the first therapies targeting alterations in the EGFR gene, like a group of deletions of the exon 19 or the punctual mutation of the exon 21 (L858R) were approved, changing the outlook of this sub-group of patients [2]. Current results of a Phase III multicenter research clinical trial reported that Osimertinib, a 3rd generation inhibitor of the tyrosine kinase (TKI) is superior in terms of survival and toxicity compared to 1st generation TKI therapy as a standard of treatment [3]. In the FLAURA trial, patients with advanced NSCLC who received Osimertinib as the initial treatment lived in average 7 months longer than patients who received Erlotinib or Gefitinib. Moreover the improvement in survival did not have a negative impact on the safety of the treatment, and an increase in the occurrence of significant side effects was not observed in patients treated with Osimertinib [4]. The FDA (Food and Drug Administration in the United States) approved as a first line treatment for people with advanced NSCLC with specific mutations in the EGFR gene [5].

Osimertinib targets the same activating mutations in the EGFR (exon 19 and L858R of exon 21) as other target therapies but it also has action over the T790M mutation (the most frequently resistance mutation found in these tumors) and has better efficacy than 1st and 2nd generation TKI at the Central Nervous System (CNS) level [6].

In Mexico has a higher incidence alterations of the EGFR gene are higher than those in Caucasian populations, being the most frequent molecular alteration in up to forty percent of patients with advanced NSCLC [7]. Here we present 3 cases of patients who received Osimertinib as a 2nd line therapy for metastatic NSCLC obtaining a complete response in one of them.

2. Clinical Cases

| Case # 1 | Case # 2 | Case # 3 |
|----------|----------|----------|
| Demographics and clinical data | | |
| Age at Diagnosis 64 | Age at Diagnosis: 60 | Age at Diagnosis: 79 |
| Male | Female | Female |
| No Smoking history | 40 pack year history | 20 pack year history |
| No other smoke exposure | No other smoke exposure | No other smoke exposure |
| Histopathology: Well differentiated Lung Adenocarcinoma | Histopathology: Large cell, micropapillary non mucinous Lung Adenocarcinoma | Histopathology: Acinar Lung Adenocarcinoma |
| | CK7+ | CK7+ |
| | TTF1+ | TTF1+ |
| | | |
| Date of Initial Diagnosis | April 23rd, 2018 | October 31st, 2016 |
|---------------------------|------------------|-------------------|
| EGFR Mutation             | Exon 19          | Exon 19           |
| Site of Metastasis        | Multiple Pulmonary Lesions | T4aNxM1c, CNS, Bone |
|                           | T4NxM1b, Pleura, Bone |
| Previous Therapy          | First line Gefitinib Second line Paclitaxel + Carboplatin + Gefitinib | Afatinib for 3 months and Brain Radiotherapy, posterior G1 and G3 Toxicity. Starts Gefitinib on October 2nd, 2018. In March 2019 GGO positive, Bronchoalveolar Lavage (BAVL) with biopsy and cultures are obtained due to the suspicion of an Infectious Process. T790M was documented. In July of 2019 progression of the disease in the lungs is observed. Gefitinib for 2 months with dose adjusted due to cutaneous Toxicity G2. September of 2017 due to progression of the disease in the lungs patient is given 4 cycles of chemotherapy. Gefitinib was also given from January 2017 through December 2018. In January of 2019 chemotherapy is started again and signs of progression of the disease are found in September of 2019. |
| Time to Response to First Line of Treatment | 3 months | 6 months (Partial Response 90%) |
| Toxicity to First Line of Treatment | Gefitinib – Rash G1 | Afatinib (Acneiform rash G2, Diarrhea G3-4) Gefitinib (Acneiform Rash G1, Diarrhea G2, Transaminitis G1) Gefitinib Acneiform Rash G3 Diarrhea G3 Mucositis G1 |
| Date of Progression of the Disease | 09.12.2016 | 07.03.2019 (Progression Free Survival 12 months) |
| Progression Site          | Lung and Brain | Contralateral Thoracic Lymph Nodes Bilateral Pulmonary Lesions |
| start date of osimertinib | 9.26.2017 | 07.01.2019 | 10.28.2019 |
|--------------------------|-----------|------------|-------------|
| radiographic response to osimertinib | Partial Response | Complete Response | Partial Response at 80% |
| Time to response to OSIMERTINIB | 3 Months | 1 Month | 1.5 Months |
| ToXICITY OF OSIMERTINIB | None | Acneiform Rash G1 | Fatigue G1 |
| Diarrhea G2 | Diarrhea G3 |
| PROGRESSION FREE SURVIVAL TO junNE 2020 | 21 Months | NA | NA |
| OVERALL SURVIVAL TO junio 2020 | 72 Months | 26 Months | 41 Months |

Figure 1 A and B: Images of Chest CAT Scan with pulmonary and soft tissue windows of patient number 2, both at the start of treatment with Osimertinib. C and D. Images of Chest CAT Scan with pulmonary and soft tissue windows showing complete response to treatment at month 12. Patient remains asymptomatic.

3. Discussion
Osimertinib is an oral 3rd generation irreversible inhibitor of the EGFR receptor with significant activity against T790M and less activity against EGFRwt [11,12]. Osimertinib was first approved for the treatment of metastatic non microcytic lung cancer with T790M positive expression and progression to target therapy with first generation agents, based on the results of the AURA trial and suggesting increased efficacy in the CNS compared to platinum based chemotherapy [13, 14].
In that study, Osimertinib achieved an Objective Response Rate (ORR) of 61% and a Free Survival Progression of 9.6 months and established a standard dose of 80 mgs/day for posterior studies. Phase 2 of the AURA trial confirmed both safety and efficacy of Osimertinib as treatment for progression to TKI agents in patients with a T790M mutation [15, 16].

AURA 3 study compared Osimertinib with Platinum based chemotherapy and Pemetrexed in patients with NSCLC EGFR T790M with progression to first line therapy. Results obtained widely favored Osimertinib, reaching 71% ORR versus 31% for the other therapies and a Progression Free Survival of 10.1 months vs 4.4 (HR= 0.30; CI: 0.23-0.41 p<0.001). Osimertinib also had better tolerance as seen by a lower incidence of untoward effects grade 3 (G3) in comparison to chemotherapy (23% vs 47%) [9]. The joint analysis of the AURA and AURA 2 trials confirmed the efficacy of Osimertinib in patient with the T790M mutation reporting an overall survival of 26.8 months and an overall survival rate during the first year of treatment of 80% [17].

Given the results of previous studies and with the intention to avoid the development of resistance mediated by the T790M mutation, a new trial (FLAURA) was launched comparing Osimertinib versus first generation TKI (Gefitinib, Erlotinib) in 556 patients with NSCLC and EGFR mutations, no previously treated. All patients had deletion of exon 19 or mutation L858R during randomization. The primary objective was Progression Free Survival, which favored Osimertinib (18.9 versus 10.2 months, HR: 0.46, 95% CI: 0.37-0.57; p<0.0001) without difference in the rate of Objective Response (80% vs 76% OR 1.27; 95% CI: 0.85-1.90; p=0.24) and the recently reported benefit of overall survival (38.6 vs 31.8 months, HR 0.799; 95.05% CI; p=0.0462 and Overall survival at years 1, 2 and 3 were 89%, 83% and 74% in the Osimertinib group as compared to 59%, 54% and 44% respectively in the Gefitinib/Erlotinib group [10]. Toxicity profile also was better having less untoward effects grade 3 and 4 (34% vs 45%). With these results Osimertinib was granted an indication as a first line treatment independent of the T790M mutation status and also received approval as a potential option for second line treatment after progression of the disease on first generation TKI treated patients but in this instance only those with a T790M mutation [18].

The FLAURA trial also showed good efficacy of Osimertinib against lesions of the Central Nervous System (CNS). In patients with CSN lesions the Free Survival Progression was not reached vs 13.9 months obtained with Gefitinib/Erlotinib and the appearance of new lesions was also better in the Osimertinib arm (12% vs 30%) supporting the protective role of Osimertinib in regards with the appearance of new lesions [19].

The most common mechanism of resistance to the first generation TKI is the EGFR T790M mutation [20, 21]. In the case of Osimertinib, mechanisms dependent or independent of the EGFR have been identified [22-24]. The heterogeneity of the tumor promotes the coexistence of multiple molecular alterations that influence the possible mechanisms of resistance to Osimertinib. The identified mechanisms of resistance to Osimertinib differ whether this has been used as a first or as a second line of treatment [25].
When there is progression to the first line of treatment, the mutations that include the EGFR receptor are present in 6 to 10% of the cases, with C797, L718, G724S and S768I being the most common. Other mechanisms are independent of the EGFR as the amplification of the MET which is present between 7 and 15% of the cases or the amplification of HER2 in 2% of them. Up to 15% present histologic transformation to squamous cell or small cell carcinoma (the latter through the loss of the function of gene RB and alterations of the p53) while still in 40 to 50% of the cases of resistance to Osimertinib as a first line agent, no specific mechanism has been identified.

4. Conclusion
In the case of progression to subsequent lines of treatment, the resistance to Osimertinib dependent of EGFR is present in 10 to 26% of the cases with the most frequent mutations being those in the C797, L792, G796 and L718 alleles and insertions in the exon 30. Of the mechanisms of resistance independent of the EGFR, the amplification of the MET, HER2 and PI3KCA are present in 15%, 5% and 5% respectively. The appearance of fusion genes including FGFR3, NTRK, RET, ALK and BRAF is present in 3-10% of the cases [25]. We present 3 cases of patients with NSCLC and EGFR mutations which developed progression to therapy with first and second generation TKI and posteriorly received Osimertinib as a subsequent line of systemic treatment with a good clinical and radiological response and progression free survival benefit similar to what has been reported in the literature.

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