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A Review of EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC) in 2024

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Introduction

Twenty years ago, our understanding of non-small cell lung cancer (NSCLC) treatment was revolutionized by the demonstration of a strong relationship between activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) and the response to tyrosine kinase inhibitors such as gefitinib. These experiments, among many others, have paved the way for two decades of exponential therapeutic growth that we have witnessed.

EGFR-mutant lung cancers account for as much as 23% of NSCLC cases diagnosed in Canada,[1] with significant variations based on geography and ethnicity including a higher prevalence in regions where the Asian population is more important. Therefore, the latest data discussed in this article have the potential to improve outcomes for a large number of patients.

Perioperative approach

Adjuvant osimertinib is approved in Canada for completely resected, stage IB to IIIA EGFR-mutant NSCLC. It is administered until the patient experiences either unacceptable toxicity or disease progression, with a maximum duration of up to three years. This approach has demonstrated a clear benefit in the ADAURA trial, first published in 2020.[2] The trial showed that disease-free survival (DFS) was significantly longer with adjuvant osimertinib compared to placebo at 48 months (70% versus 29% respectively, with a hazard ratio [HR] of 0.23).[3] Highlighting the high central nervous system (CNS) activity of osimertinib, 92% in the osimertinib group did not experience a CNS relapse at 48 months versus 81% in the placebo group, with an HR of 0.36. The substantial benefits of osimertinib are even more pronounced in the stage II to IIIA subgroup of NSCLC patients. The 5-year overall survival (OS) was recently published, confirming a clinically and statistically significant benefit (88% survival rate in the osimertinib group at 5 years versus 78% survival rate in the placebo group, with an HR of 0.49).[4] Currently, consideration for adjuvant chemotherapy in NSCLC is not dependent on the genotype and thus can be offered to patients prior to the initiation of osimertinib treatment. However, if there is a contraindication to cytotoxic chemotherapy, adjuvant osimertinib still offers benefits. This was demonstrated in the subgroup of patients who did not receive chemotherapy first (40% of the study population with a similar HR for OS of 0.47). Despite recent advances in perioperative immunotherapy, this approach is not recommended for EGFR-mutant lung cancer. This is because activity in EGFR-mutant lung cancer is typically inferior to that in wild-type counterparts in the metastatic and locally advanced setting.[5] Furthermore, limited data from the AEGEAN trial support the absence of benefit of adding perioperative durvalumab to chemotherapy for the EGFR-mutant subgroup of NSCLC patients.[6] There is also evidence suggesting that toxicity can be exacerbated when patients receive an immediate sequential use of immunotherapy and a tyrosine kinase inhibitor (TKI),[7] with some experts recommending waiting at least 3 months before initiating osimertinib treatment when this is clinically feasible.[7]

The optimal approach for managing relapse after adjuvant osimertinib needs to be investigated. Confirming histological findings and the persistence of an EGFR mutation with a new biopsy, and then retrying a course of osimertinib if the progression did not occur while on adjuvant treatment, can be considered. However, the benefit of this approach has not been clearly evaluated in clinical trials. If the relapse happens during adjuvant osimertinib, the disease should be treated as a metastatic EGFR-mutant lung cancer progressing

on targeted therapy, with some specific strategies described below.

The NeoADAURA (NCT04351555)[8] and LAURA (NCT03521154)[9] trials are currently investigating the potential benefits of neoadjuvant osimertinib before surgery and adjuvant osimertinib after chemoradiation for patients with stage III unresectable EGFR-mutant NSCLC, respectively, and could potentially provide further improvements in outcomes in the curative setting. Furthermore, very interesting data suggest that the detection of circulating tumour DNA (ctDNA) before or after resection is associated with a poorer DFS.[10] In the future, the ability to detect ctDNA could help us identify the patients who are at a high risk of relapse and who would be likely to derive greater benefit from adjuvant treatment.

Metastatic disease

Although tissue biopsies are typically used to detect EGFR mutations, studies also support the use of liquid biopsies at diagnosis. Liquid biopsy techniques usually have high specificity, especially in advanced disease. Since sensitivity is imperfect, if negative, a next generation sequencing panel should be conducted on a tissue biopsy to identify a biomarker positive subset of NSCLC, including EGFR alterations.[11]

Osimertinib, a third-generation EGFR TKI, was specifically developed to overcome the T790M resistance mutation. This mutation is found in approximately 50–60% of tumours after progression on first- and second-generation TKIs. A key benefit of osimertinib is that it improves CNS penetrance and spares wild-type EGFR which contributes to its increased tolerability.[12] Osimertinib is currently the preferred first-line choice for EGFR exon 19 deletions and exon 21 *L858R* mutations, which represent approximately 80% to 90% of all EGFR mutations.[13] The phase 3 FLAURA trial showed a statistically significant improvement in PFS (18.9 months for osimertinib versus 10.2 months for first-generation TKIs, HR 0.46) and updated OS (38.6 months for osimertinib versus 31 months for first-generation TKIs, HR 0.80).[14] Patients in the study had locally advanced or metastatic NSCLC harbouring an EGFR exon 19 deletion or an *L858R* mutation.[15] In patients with known or treated CNS metastases, the trial shows a consistent benefit of PFS in favour of osimertinib (15.2 months versus 9.6 months, HR 0.47), and an objective response rate (ORR) of 76% with a 13.8 month median duration of response.[15] These findings are notable, considering that 25%[16] of patients harbouring an EGFR mutation have CNS metastases at initial diagnosis and up to 70%[17] eventually develop brain metastases during the course of their illness.

More recently, the phase 3 study FLAURA2 evaluated the addition of platinum-pemetrexed chemotherapy to osimertinib in the first-line treatment of metastatic EFGR-mutated NSCLC. According to investigator assessment, median PFS was improved by 8.8 months with osimertinib and chemotherapy compared to osimertinib monotherapy (25.5 months versus 16.7 months, HR 0.62), respectively. The ORR was 83% for osimertinib and chemotherapy versus 76% for osimertinib monotherapy.[18] The subgroup of patients with measurable and non-measurable CNS brain metastases at baseline derived a significant benefit from the combination therapy (PFS 24.9 months versus 13.8 months, HR 0.47). In addition, the trial showed a complete intracranial response of 59% for combination therapy compared to 43% with osimertinib monotherapy. The safety profiles were as expected for each treatment, with the combination therapy arm demonstrating increased toxicity.[18] Identifying which patients require treatment intensification is a matter of ongoing debate in the medical community. Studies such as SHEDDER (NCT04410796) and PACE-LUNG (NCT05281406), might provide more clarity on this issue by evaluating the addition of chemotherapy to first-line osimertinib in patients who demonstrate ctDNA positivity after a few weeks of osimertinib.

Another intensification strategy is found in the MARIPOSA phase III study, which showed an improved PFS (23.7 months versus 16.6 months, HR 0.70) with the combination of amivantamab, an EGFR and MET bispecific receptor antibody, and lazertinib, a third generation TKI, compared to osimertinib monotherapy.[19] Combination therapy demonstrated a consistent benefit in patients with or without brain metastases. The combination therapy had higher rates of grades 1 and 2 EGFR- and MET- related adverse events, such as rash, diarrhea, and peripheral edema, as well as a significant rate of infusion reactions, mostly limited to the first infusion of amivantamab. Notably, there was also an increased signal for venous thromboembolism occurring in 37% of patients in the combination arm.[19] Prophylactic dose anticoagulation is now recommended for the first 4 months of treatment when this combination is used, further increasing the therapeutic burden

compared with a single-agent oral drug such as osimertinib.

Beyond limitations in drug access and coverage, the intensification strategy for patients with metastatic disease in first line treatment should be individualized based on the patient characteristics, preferences, and the toxicity profile of the combination treatment. Until OS data become mature for both trials, the approaches in the FLAURA2 or MARIPOSA trials should not be considered as new, broadly applicable standards of care for EGFR-mutant advanced NSCLC.

For patients harbouring atypical EGFR mutations (such as *S768I*, *L861Q*, *G719X*), updated guidelines from the NCCN recommend first-line use of osimertinib or afatinib. Clinical data for afatinib come in part from the LUX-Lung studies that allowed inclusion of atypical mutations. A post-hoc analysis showed clinical activity, particularly in patients harbouring uncommon EGFR mutations such as *G719X*, *L861Q*, and *S768I*.[21] Similarly, a randomized phase 3 study evaluating afatinib compared to chemotherapy in treatment-naïve patients with sensitizing uncommon mutations showed an ORR of 61.4% with afatinib and a PFS of 10.6 months.[22] The efficacy of osimertinib in uncommon EGFR mutations was demonstrated in UNICORN, a multicenter retrospective case series. The findings showed that osimertinib had a systemic ORR of 60% and a brain ORR of 46% in those with evaluable brain metastases.[23] The final OS data of the prospective phase 2 study KCSG-LU15-09 demonstrated a median OS of 27 months and an ORR of 51% with osimertinib.[24] The heterogeneity of atypical EGFR mutations emphasizes the importance of individualizing treatment for each patient.

Despite high initial response rates and prolonged progression-free survival, disease progression is expected to occur in all patients. Various molecular mechanisms of resistance to osimertinib have been described and can be classified into three categories, which include secondary and tertiary mutations in EGFR, activation of alternative parallel signalling pathways, and histologic transformation in small cell lung carcinoma and squamous cell carcinoma. When feasible, performing a biopsy of a site where the disease is progressing is recommended to determine if a mutation that can be targeted with therapy is present, and to exclude histologic transformation, which can help guide the choice of second-line therapy. Where available, use of liquid biopsies can also help identify resistance mutations, although they cannot rule out histologic transformation.

MET amplification is observed in 10 to 15% of NSCLC patients with EGFR mutations who are progressing on first line osimertinib, and is often considered the most frequent resistance mechanism in this setting.[25] MET amplification leads to the persistent activation of several common downstream pathway effectors, independent of EGFR signalling. These signalling pathways include mitogen-activated protein kinases, signal transducer and activator of transcription (STAT), and phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT).[26] The phase II study INSIGHT 2 (NCT03940703) evaluated tepotinib in combination with osimertinib in patients with EGFR-mutant NSCLC with MET amplification previously treated with osimertinib. The study's findings showed an ORR of 50% when amplification was detected by fluorescent in situ hybridization (FISH) and an ORR of 54.8% when detected by liquid biopsy. The median duration of response for detection by FISH or liquid biopsy was 8.5 months and 5.7 months, respectively.[27] Although found more frequently after second-line use of osimertinib, the exon 20 *C797S* mutation is the most frequent tertiary resistance mechanism to first-line osimertinib. Oncogenic fusions have also been recognized in 1% to 8% of cases of acquired resistance to first-line osimertinib. For example, combining osimertinib with selpercatinib, a RET-TKI, showed a clinical benefit in patients with an acquired RET fusion on first-line osimertinib, and led to a median duration of treatment of 7.4 months (range, 0.6–6.7 months).[28] In addition, acquired cell cycle gene alterations have been reported to occur in 10% of cases.[25]

If no underlying resistance mechanism is identified, a chemotherapy regimen, such as a combination of platinum and pemetrexed, is recommended as the standard next line therapy. The phase 2 study MARIPOSA-2 was the first to report that amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy combinations showed improvement in PFS versus chemotherapy alone for patients with EGFR-mutant advanced NSCLC who had disease progression on osimertinib, with a reduction in the risk of progression or death of 52% for amivantamab-chemotherapy and 56% for amivantamab-lazertinib-chemotherapy.[29] However, in another phase III trial, the addition of pembrolizumab to chemotherapy in the post-TKI setting did not show a clinical benefit.[20]

It is anticipated that future trials will aim to more accurately characterize the optimal sequencing strategies for treating metastatic EGFR-mutant NSCLC.

Exon 20 EGFR mutations

Insertions in exon 20 of EGFR account for approximately 2% to 12% of all EGFR-mutations in NSCLC.[30] These mutations are less sensitive to currently approved EGFR TKIs and the response rates to these therapies are typically quite low.[13,31]Amivantamab is currently approved after chemotherapy for second-line use in tumours harbouring these mutations. However, the recently published phase III PAPILLON study showed a significant PFS benefit in this population with a first-line treatment that included the addition of amivantamab to chemotherapy compared to chemotherapy alone (11.4 months versus 6.7 months with an HR of 0.4).[32] At 18 months, 31% of patients in the amivantamab-chemotherapy group were still progression-free, compared to 3% in the chemotherapy group. The response rate was also significantly higher (73% in the amivantamab-chemotherapy group versus 47% in the chemotherapy group). These are promising results for this subset of patients; however, OS data remains immature. While the current standard of care typically includes a first-line platinum doublet followed by second-line amivantamab, in jurisdictions where it is covered, the significant benefits reported in the PAPILLON study could justify pursuing the combination therapy as a first-line treatment.[33]

Conclusion

In conclusion, recent therapeutic advances in EGFR-mutant NSCLC have significantly improved the prognosis of the subset of patients with these types of tumours. These developments have also raised new questions regarding the optimal sequencing of treatments and the appropriate use of treatment intensification. This represents a major step forward in the field. Ongoing investigations are expected to provide additional insights, and it will be interesting to closely follow these developments.

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