Original Research Paper

Volume-9 | Issue-5 | May-2019 | PRINT ISSN No 2249 - 555X

Oncology

COMPLETE RESPONSE OF CEREBRAL METASTASES OF A MUTATED EGFR BRONCHOPULMONARY CANCER TREATED WITH AFATINIB: CLINICAL CASE AND REVIEW OF THE LITERATURE.

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ABSTRACT Afatinib is a second generation EGFR receptor tyrosine kinase inhibitor (ITK-EGFR). It has been shown to be effective in bronchopulmonary cancers with EGFR receptor mutation. a complete tumor response in case of brain metastases is rarely described in the literature. We report the case of a patient with metastatic bronchopulmonary adenocarcinoma at the cerebral level with a double mutatuion of EGFR, having presented a complete and durable response to afatinib. we recall the data of the literature on this subject.

KEYWORDS : bronchopulmonary cancer, adenocarcinoma, EGFR mutation, brain metastases, afatinib

INTRODUCTION

EGFR-ITK have improved the prognosis of metastatic broncho pulmonary adenocarcinomas with EGFR mutation (1,2). We report the case of a patient with bronchopulmonary adenocarcinoma with a double mutation of EGFR, metastatic at the cerebral level, treated with afatinib and who had a prolonged survival and a complete response

Medical observation

Mr B.C, 57 years old, non-smoking, former sandblaster and metal cutter, performed a chest X-ray in June 2015 which revealed fortuirte right para-hilar opacity. the histological diagnosis, made by mediastoscopy, found bronchopulmonary adenocarcinoma. The extension assessment made it possible to classify the timers in stage IIIB (figure 1). The patient was initially treated by concomitant chemoradiotherapy chemotherapy with 3 cures of cisplatin-navelbine and media-pulmonary irradiation (60 Gray in 30 sessions and 40 days) from September to December 2015 with a complete TEP-TDM response.

In March 2016, asymptomatic cerebral recurrence occurred with the presence of at least 9 subtemporal lesions below the centimeter on MRI. the search for molecular abnormalities then carried out on the initial tissue samples, concluded that there are two types of EGFR mutation: a deletion of exon 19 associated with a minority clone with a G719X mutation of exon 18.

Afatinib treatment was started in April 2016 at a dose of 40 mg / day. on cerebral MRI performed 2 months after the start of treatment, there was complete disappearance of brain lesions (Figure 2). the patient was still in complete remission after 14 months of treatment with afatinib with good clinical and biological tolerance.

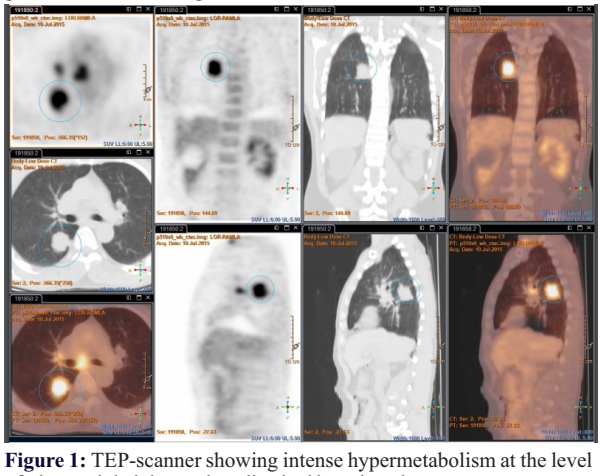

Figure 1: TEP-scanner showing intense hypermetabolism at the level of a lower right lobar and mediastinal lymph node.

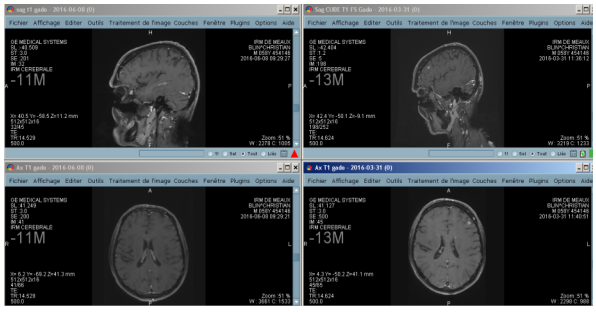

Figure 2: Cerebral MRI showing complete disappearance of brain metastases after three months of treatment with Afatinib.

DISCUSSION

The case that we report here, shows a prolonged survival (14 months) and a complete response in a patient with metastatic mutated bronchopulmonary adenocarcinoma metastatic at the cerebral level, treated with afatinib.

The median survival of patients with untreated metastatic bronchopulmonary cancer does not exceed 6 months (3). it has been improved by pemetrexed to reach almost 12 months (ScagliottI JCO 2008). but it is the advent of the concept of oncogenetic addiction in metastatic bronchopulmonary cancer that has significantly improved the median survival with the arrival of EGFR-TKI in patients with EGFR mutation . (2) There are multiple mutations of EGFR. the most common are the deletion of exon 19 (45%) and the L858R mutation of exon 21 (40%). there are other, much rarer mutations such as the G719X mutation of exon 18 (5%) or the insertion of exon 20 (5%) (11). these different molecular anomalies induce different sensitivity to EGFR-TKIs.

Lafatinib is a second-generation tyrosine kinase inhibitor that irreversibly inhibits ErbB receptors. this family of epidermal growth factor receptors which comprises EGFR, HER3 and HER4 is involved in the interacellular signaling mechanisms controlling crossbrow growth, survival, adhesion, migration and differentiation of the cell (4). afatinib blocks EGFR but also the dimerization of EGFR with HER2, which is an obstacle to downstream signaling, which is an advantage in terms of therapeutic resistance after treatment with a first generation ITK-EGFR. (5)

A few clinical cases reported in the literature have already highlighted the efficacy of afatinib in case of cerebral metastases or carcinomatous meningitis (9,10). however, the authors encouraged further studies on this subject.

In EGFR-mediated metastatic bronchopulmonary adenocarcinoma, afatinib showed in the LUX-lung 3 and LUX-lung 6 (2,6) phase III studies improved overall survival, survival without progression and response rate compared to platinum-salt chemotherapy. a subgroup analysis of patients with brain metastases in these two studies (7) showed a significant benefit in terms of progression-free survival in favor of the afatinib-treated group.

another study, published in 2016, investigating the pharmacodynamics and passage of afatinib across the blood-brain barrier (BHE) in mice with brain tumors, demonstrated the ability of afatinib to cross the BHE in anti-tumor efficiency at the brain level (8)

Our patient had a double mutation of EGFR: a deletion of exon 19 associated with a minority clone with a G719X mutation of exon 18. these 2 mutations confer a sensitivity to the ITK-EGFR but the mitation of the exon 18 seems to bring even greater sensitivity. Yang analyzed the 18 afatinib-treated mutations in the Lux-lung 2,3 and 6 studies, which showed a response rate of 77% (12). good fall in the study ERMETIC found a response rate of 35% in patients with a mutation of exon 18 treated with a first-generation ITK-EGFR (11).

the presence of this double mutation could have contributed to the correct response observed in our patient.

CONCLUSION

the case we report confirms the efficacy of afatinib in terms of survival and response in metastatic broncho-pulmonary adenocarcinomas at the cerebral level in case of mutation of the EGFR and in particular in case of presence of the mutation of the exon 18.

Conflicts of interest

All the authors declare no conflict of interest.

REFERENCES

[1] Keating GM. Afatinib: a review in advanced non-small cell lung cancer. Target Oncol. 2016;11(6):825–35.

[2] Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327–34

[3] Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169–81]

[4] N. Minkovsky et A. Berezov, « BIBW-2992, a dual receptor tyrosine kinase inhibitor for the treatment of solid tumors », Current opinion in investigational drugs, vol. 9, no 12, décembre 2008, p. 1336-1346

[5] Yap TA, Popat S ,Toward precision medicine with next-generation EGFR inhibitors in non-small-cell lung cancer. Pharmgenomics Pers Med. 2014; 7():285-95]

[6] Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213–22

[7] Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, et al.. First-line afatinib versus chemotherapy in patients with non-small-cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016; 11:380-390.

[8] Shi-rong ZHANG and al ; Efficacy of afatinib, an irreversible ErbB family blocker, in the treatment of intracerebral metastases of non-small cell lung cancer in mice, Acta Pharmacologica Sinica (2017) 38: 233–240; doi: 10.1038/aps.2016.107; published online 14 Nov 2016]

[9] Li SH and al ;Afatinib in Treatment-Naive Patients With EGFR-Mutated Lung Adenocarcinoma With Brain Metastasis: A Case Series; Journal List ,Medicine (Baltimore) ,v.94(41); 2015 Oct;PMC4616807

[10] Prashant Mehta1,Response to afatinib, after gefitinib and erlotinib, in a patient with advanced adenocarcinoma of lung with brain metastasis: A case report; International Journal of Molecular & Immuno Oncology ,January-March 2017, Volume 2 ,Issue 1

[11] Scagliotti GV and al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008 Jul 20;26(21):3543-51.

[12] Beau-Faller M and al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. Ann Oncol. 2014 Jan;25(1):126-31.

[13] Yang JC and al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015 Jul;16(7):830-8.