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Epidermal growth factor receptor (EGFR) positive non-small-cell lung carcinoma (NSCLC) patients in the Gulf region: current status, challenges, and call for action

Abstract

Background: Baseline epidemiology information specific to the region is important to guide disease management. However, data and publication with focus on in-patient populations with advanced stage epidermal growth factor receptor (EGFR) positive non-small-cell lung carcinoma (NSCLC) across the Gulf is limited.

Methods: Epidemiology data of various hospital centers from four Gulf nations (United Arab Emirates, Kuwait, Oman and Qatar) were provided by the esteemed panel of experts. Data related to prevalence of newly diagnosed cases, EGFR mutation rates, demographics associated with the mutations, type of mutation testing administered, and management with anti-EGFR therapy agent were collected and analyzed.

Results: From 2014 to 2016, a total of 17,026 newly diagnosed cancer cases were reported in the region, with lung cancer present in 5.7% of the confirmed cases. Advanced stage lung cancer cases were diagnosed in 76% of these patients. The EFGR mutation prevalence in the region was at 36.9%. Among the EGFR positive cases that progressed on anti-EGFR therapy, only 46% of the cases were tested for T790M mutations. The substantial lack of testing data, highlights either a potential need for routine mutation testing or identification of a standard of care for NSCLC cases harboring a T790M mutation.

Conclusion: Results showed a high prevalence of EGFR positive lung cases in the region despite the low incidence rate of subsequent molecular testing. Recommendations from the expert panel include the implementation of prospective observation trial and use of novel agents, such as osimertinib, as standard anti-EGFR therapy when biomarker testing is challenged.

Keywords: epidemiology, epidermal growth factor receptor mutations, gulf, non-small cell lung cancer, T7

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Introduction

Non-small cell lung cancer (NSCLC) represents a heterogeneous group of pulmonary malignancies comprising around 85% of all lung cancers cases.[1] Epidermal growth factor receptor (EGFR) mutations are commonly observed in NSCLC patients with adenocarcinoma histology with increased prevalence in non-smokers, females and Asians.[2–4]

EGFR mutations commonly occur in exon 19 or 21 (approximately 45 and 40% of patients, respectively) in NSCLC patients that activate the tyrosine kinase domain in epidermal growth factor receptors.[5] As EGFR mutational status is critical in the management of advanced stage lung cancer, early EGFR testing has gained importance over time so as to provide timely and personalized treatment therapies to such patients.[6] National Comprehensive Cancer Network (NCCN) guidelines recommend the use of EGFR tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib, afatinib, osimertinib and dacomitinib) as the first line agents for the treatments of EGFR positive NSCLC patients.[7] TKIs have demonstrated improved progression-free survival (PFS), higher response rates, better overall quality of life, and fewer side effects in comparison to standard platinum-based chemotherapy.[8–10] However, disease progression secondary to acquired resistance to TKI treatment (after a median of 10-14 months), occurred in up to 60% of patients due to acquired T790M mutations[11] while primary T790M mutations are very rare.[12]

In the Gulf region, substantial data on the prevalence, burden, diagnosis and management of advanced stage NSCLC is still limited. In addition, challenges in mutation testing faced by clinician's further impact disease management. This article aims to provide information on the current status of diagnosis and management of patients with advanced stage EGFR positive NSCLC in the Gulf region, as well as identify potential solutions to improve patient care.

Methods

The article focuses on the gaps and challenges faced in the diagnosis and management of EGFR positive NSCLC in the four Gulf nations–UAE, Kuwait, Oman and Qatar, based on the expert consensus achieved in the year 2018. Epidemiology data from various

major hospital centers were provided by the esteemed panel of experts, and representative of 70 to 100% of each country wide reported cases. Data related to prevalence of newly diagnosed cases, EGFR mutation rates, demographics associated with the mutations, type of mutation testing administered, and management with anti-EGFR therapy agent were collected and analyzed. The median value was calculated to represent the regional epidemiological landscape of EGFR positive NSCLC patients.

Epidemiological landscape of EGFR positive NSCLC in the Gulf

NSCLC in the Gulf region: A retrospective analysis of the epidemiology data from the major centers/hospitals across UAE, Kuwait, Oman and Qatar for past three years (2014-2016) is presented in Table 1. Between 2014 and 2016, a total of 17,026 newly diagnosed cancer cases were reported in the region of which 5.7% (962 cases) comprised of lung cancer cases.

Table 1 Epidemiology of NSCLC in Gulf region

In past 3 years (2014 -2016)	UAE			Kuwait	Qatar	Oman
	Mafraq	Tawam	Total			
New diagnosed cases (No. of cases)						
·Lung Cancer	75	243	318	351	154	139
·Other solid tumors	1846	3796	5642	3900	2980	3542
Newly diagnosed lung cancer cases (No. of cases)						
·Non-small cell lung cancer	65	207	272	298	146	129
.Non-squamous NSCLC	50	165	215	223	140	103
Males	25	116	141	146	NA*	72
Females	25	49	74	77	NA*	31
·Small cell lung cancer	10	36	46	53	8	10
NSCLC cases						
· **Age group (% of cases)**						
o25-35	7%	5%		2%	3%	3%
o35-45	13%	12%		5%	15%	5%
o45-65	44%	70%		57%	55%	41%
oAbove 65	36%	13%		36%	27%	51%
·**Nationality (No. of cases)**						
oLocal	18	61	79	155	24	97
oArab	30	97	127	106	53	4
oAsian	21	44	65	34	59	2
oOthers	6	41	47	3	10	0
· **Staging (% of cases)**						
oStage 1	7%	3%		5%	4%	2%
oStage 2	7%	5%		5%	6%	3%
oStage 3	20%	12%		15%	14%	5%
oStage 4	66%	80%		75%	76%	90%
· **EGFR mutations (No. of cases)**						
EGFR +ve patients (%)	12	46	58			
oSmokers / non-smokers	20/80	25/75		45	42	19
oArabs / non-Arabs				65/35	36/64	80/20
oMale / Females	64/36	65/35		70/30	36/64	90/10
	50/50	56/44		70/30	36/64	40/60
EGFR wild patients	45	124	169	133	70	72
Unknown	3	2	5	45	28	12

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Table Continued...

In past 3 years (2014 -2016)	UAE			Kuwait	Qatar	Oman
	Mafraq	Tawam	Total			
EGFR status (No. of cases)						
·Tested by liquid testing	0	29		26	0	13
·Tested by tissue testing	48	111		135	112	75
· Both	0	8		17	0	4
·Total number tested	48	148		178	112	92

*NA, not available

NSCLC formed majority (845 cases, 88.5%) of these newly diagnosed cases indicating a similar prevalence observed in the global prevalence of 85%.[6] Non-squamous histology accounted 79.5% (681 cases) of these NSCLC cases, with higher prevalence in males. Furthermore, more than half of the NSCLC cases were observed in the age group of 45–65years with majority (76%) of them being diagnosed in advanced stages (mostly stage IV). Of the total NSCLC cases, 76.3% (645 cases) were reported in Arabs and the others in the remaining heterogeneous population.

Advanced EGFR positive NSCLC: Amidst the 698 cases tested for EGFR mutation status across the region, 164 cases tested positive of EGFR mutation. This indicated an EGFR mutation rate of 36.9% (amongst patients who did not fail the test), which was similar to that observed by Jazieh AR et al.[13] in 2015. Tissue testing was commonly used to analyze the EGFR status; however certain centers also used liquid testing or both. The epidemiology data revealed that female gender and non-smoking status were associated with EGFR mutations.

Although there is no data regarding the first line treatment in the patients, it was observed that 93 EGFR positive cases progressed on anti-EGFR therapy (33 in UAE, 42 in Kuwait and 18 in Oman), of which 46% (43 cases; 17 in UAE and 26 in Kuwait) were tested for acquired T790M mutation, 17 of them came positive (39.5%) (Table 2). This indicated that a wide majority of the patients are not even tested for T790M mutations. In Qatar and Oman centers, no data available about number of patients tested for T790M mutation and testing techniques. Majority of the centers in the region used liquid testing techniques to test for T790M status; however, some centers also used tissue testing techniques or both. One of the reasons for the wide use of liquid testing techniques could be related to the range of challenges faced obtaining a tissue biopsy upon progression.

Table 2 Status of EGFR T790m in progressed patients in Gulf region

In past 3 years (2014-2016)	UAE		Kuwait	Qatar	Oman
	Mafraq	Tawam			
Number of patients progressed on anti-EGFR therapy	4	29	42	NA*	18
Number of patients tested for T790M mutation	4	13	26	NA*	0
·Tested by tissue biopsy	All by tissue testing	5	9		
·Tested by liquid testing		7	11		
·Both	4	2	6		
·Total number tested		13	26		
Number of patients tested positive for T790M	2	4	11	None	None

*NA, not available

Testing for EGFR mutations: Historically, the standard for EGFR mutation testing involved direct sequencing of DNA extracted from samples of tumor tissue gathered during biopsy or resection, usually in the form of formalin-fixed paraffin-embedded (FFPE) diagnostic blocks. EGFR mutation testing is recently recommended in all NSCLC with an adenocarcinoma histology or NSCLC-NOS.[14,15] However in cases of squamous histology, EGFR testing can be considered in never smokers or limited tissue samples.[14] The National Comprehensive Cancer Network (NCCN) guidelines recommends the testing of EGFR, ALK, ROS1, BRAF mutations to be conducted as a part of the broad molecular profiling.[7]

NSCLC patients are usually identified in advanced stages and the procedures required to obtain an adequate tumor sample for proper diagnosis may not always be possible due to location, co morbidities, or other reasons.[16] Also, in certain cases the specimens for molecular testing have poor quality and reduced quantity of sample.[17] Blood or liquid testing is a potential substitute in such cases and provides a noninvasive, easily accessible, and repeatedly measurable source of genotypic information.[18] Acquired T790M mutations can be tested using either liquid testing, tissue biopsy, or both.[19]

EGFR mutation testing in the Gulf: The importance of T790M mutation testing is recognized in the Gulf region; however, it is associated with a range of issues.

Challenges in further molecular testing in local centers: Not all cancer centers/hospitals in the Gulf region are fully equipped to conduct T790M mutation testing in-house. Due to which, tissue samples are sent to external laboratories wherein the tissue quality

may be jeopardized due to the quality assurance measures adopted during transportation.

Longer turnaround time: The ideal turnaround time for the receipt of the T790M mutation tests should be usually 10 working days.[19] These turnaround times are further lengthened when samples are sent to external laboratories, thus causing delay in the facilitation treatment decisions in patients.

Use of other sequencing assays: Moreover, the challenges encountered in performing a tissue biopsy upon disease progression encourage the wide use of liquid testing techniques in the region. Although liquid biopsy tests provide potential information about the T790M mutation status; it can have lower sensitivity to detect the low quantity of circulating DNA in the blood. This in effect, increases the chances of a false negative result which further presents the need of repeat biopsies. On the other hand, liquid biopsy cannot confirm the presence of other acquired resistant mutations or small cell transformation.

Owing to these multiple challenges faced covered above, it is acknowledged that there is an unmet need to improve the T790M mutation testing capability in the region.

Discussion

Expert recommendation on EGFR T790M mutation testing

The epidemiology data obtained from the various centers were indicative of a much lower percentage of T790M mutation positive patients in the Gulf region as compared to what is reported globally i.e. up to 60%.[20] The authors suggested several reasons for the low prevalence:patients are not tested for T790M mutations due to the non-accessibility to testing; patients deny any invasive procedure to get a new tissue biopsy; or they have a poor performance status to proceed with any further treatment due to which testing is avoided. Another explanation cited by the experts is the possibility that the low mutation rates reflect the current status of the EFGR mutation incidence in the Gulf region. To further investigate the issues behind low T790 mutation prevalence in the region, the authors recommended a prospective study to be conducted by the centers. Real-world identification of T790M mutation-positive patients by investigation of testing and patient treatment can provide a clear view of the diagnostic challenges and guide selection of appropriate treatment.

Management of EGFR positive NSCLC

European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) have approved EGFR TKIs as the potential first-line treatment for advanced NSCLC patients with EGFR mutations[7,20] due to the improved progression-free survival (PFS) compared to chemotherapy in the first line (from 5 to 12 months).[21–23] The first and second generation of TKIs include gefitinib, erlotinib and afatinib.[10,21,24,25] Osimertinib, a third-generation EGFR TKI was approved for the treatment for T790M mutation developed due to the TKI resistance on the basis of the AURA trials.[26,27]

Expert recommendation on management of EGFR positive NSCLC

At the time of the article development, Osimertinib was not yet approved for first line treatment but has been available in the Gulf market.Osimertinib, with its proven benefits was indicated for the treatment for T790M mutation as second line. However, the results of the phase III FLAURA trial indicated the first line oral osimertinib significantly in such patients prolonged PFS [18.9months vs 10.2months] and doubled the duration of response (17.2 versus 8.5) as compared to standard of care (TKIs) with the well-tolerated safety profile.[28] Furthermore, the clinical practice in the region revealed that the median PFS survival for EGFR positive patients on first generation TKIs is 10.2 months[28] and data from clinical trials for first generation TKIs also indicated that approximately 2 out of 3 EGFR positive patients do not receive second line treatment[19,29,30] signifying that these patients miss out on the opportunity to benefit from T790M inhibitors. Thus, the experts were of the opinion that the use of osimertinib in the first line could be beneficial for such patients.

Detection of the EGFR T790M mutation in patients is necessary before initiating osimertinib in the second line. In asymptomatic patients, the proposed testing pathway is liquid testing to analyze the presence of T790M mutation and possible use of osimertinib. In case of a negative result, re-testing should be performed using tissue sample to test for T790M mutation and other actionable driver mutations such as KRAS, MET, HER2 and RET. If acquired T790m mutation was detected, osimertinib is the standard. If other driver mutation(s) was detected, individualized treatment options could be used. In case of negative results, either continue on anti-EGFR therapy ± local therapy, re-tested for mutations using blood/tissue sample or opt for chemotherapy. However, the later would have its own implications and re-testing for mutations would be a challenge.

On the other hand, in case of symptomatic progression, both liquid and tissue testing should be conducted alongside to test for T790M mutation and use osimertinib if tested positive. If T790M mutation isn't detected, other driver mutation tests can be conducted, and respective treatment options should be used. If the patients test came negative for the other driver mutations, chemotherapy +/- immunotherapy should be used as the treatment option.

Conclusion

In the Gulf region, there is a lower incidence of T790M mutation as compared to that observed globally. This may be indicative of the fact that many EGFR NSCLC patients are unable to carry through their molecular targeted journey due to the reasons relating to T790M mutation not detected timely and accurately. Subsequently, this impacts anti-EGFR treatment and patient outcomes when patients fail to benefit from tailored therapy.

Compared to first generation TKIs, the use of osimertinib could offer a reasonable solution for advanced EGFR positive NSCLC cases by providing optimal treatment benefit early on. Otherwise, there is a need to devise strict guidelines to improve the T790M mutation testing scenarios in order to tackle the existing diagnostic challenges. Furthermore, the authors also recommended a prospective study to be conducted by the centers to provide a clear understanding on the reasons for low T790M mutation prevalence in the Gulf region.

There was special emphasis on the need to homogenize the clinical practice for mutation testing as well as develop novel and better testing techniques across the region. Aside from this, the authors recommended the development of standard guidelines for identifying treatment options used in various lines, including considerations in performing re biopsies in these patients. Additionally, collection of updated epidemiology data can be limited by the heterogeneity of the patients consisting mostly of expats and moving populations across the Gulf region.

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