Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Esophageal cancer and the importance of epidermal growth factor receptor (EGFR)

Kazem Anvari (MD)[1], Azam Anvari (MD)[2*], Mahdi Silanian Toosi (MD)[1]

[1]*Solid Tumor Treatment Research Center, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Article type
Review article

Article history
Received: 15 Jan 2014
Revised: 2 Feb 2014
Accepted: 16 Feb 2014

Keywords
Epidermal growth factor receptor (EGFR)
Esophageal cancer
Survival

ABSTRACT

Esophageal squamous cell carcinoma (ESCC) is one of the most frequent malignancies, worldwide. It is important to find out what prognostic factors can facilitate diagnosis, optimize therapeutic decisions, and improve the survival of these patients.

Despite improvements in surgical techniques combined with chemotherapy and/or radiotherapy, the novel therapies such as small molecule inhibitors of tyrosine kinases (TKIs) and humanized monoclonal antibodies (mAbs) are very much needed. On the other hand, neoadjuvant chemotherapy which may improve the outcome is accompanied by toxicity by destruction of normal cells. Side effects may be avoided by developing therapies that specifically target molecular characteristics of tumors.

Epidermal growth factor receptor (EGFR) is one of tyrosine kinases receptors widely distributed in human epithelial cell membrane. Genetic polymorphisms in EGFR genes influence cell cycle progression, angiogenesis, apoptosis and metastasis. EGFR mutations are mostly observed in lung tumors; curiously they are more prevalent in Asian women diagnosed with adenocarcinoma. Also, esophageal SCC shows a relatively high incidence of EGFR (33%) and/or HER2 (31%) overexpression. Patients who carry these mutations in EGFR have been founded tending to have a better response to gefitinib, an EGFR-TKI, whereas patients with the wild-type genotype show a better response to conventional chemotherapy. Therefore, finding clinical characteristics and environmental interactions with EGFR can affect on investigations about novel anti-cancer therapies like monoclonal antibodies and gene therapy and studies which identify patients who may benefit from EGFR targeted therapies. Hence, it may be effective on the improvement of prognosis in these patients.

***Corresponding author:** Azam Anvari.
Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
***E-mail:** anvaria891@mums.ac.ir*
***Tel:** 051-38022736*

Please cite this paper as:
Anvari K, Anvari A, Silanian Toosi M. Esophageal cancer and the importance of epidermal growth factor receptor (EGFR). Rev Clin Med. 2014;1(2):44-50.

Introduction

Esophageal cancer is one of the most common worldwide malignancies with the annual incidence of almost 4.4 per 100000 individuals each year. In 2000, the mortality rate was estimated to be more than 300000 patients (1). Esophageal squamous cell carcinoma (ESCC) has high prevalence in Asian countries which accounts for over 95% of the esophageal cancers. The poor prognosis of this disease can be due to the detection of patients not in the early-stages of the cancer, and also the high possibility of lymph nodes involvement even in the localized disease (2).

Esophageal carcinoma is among the 10 most common cancers in the world and it is one of the exceptional gastrointestinal malignancies which encompass two specific histopathologic types including Adenocarcinoma and Squamous cell carcinoma (3).

In developing countries such as China and Iran, ESCC is considered to be the most prevalent esophageal cancer (almost 90% of esophageal cancers), but recent studies in Iran have shown that ESCC incidence decreased in the past 20 years while the adenocarcinoma occurrence increased (4). Various issues such as life style, social, economic, and environmental factors influence on the type of esophageal cancer in every individual or its dominance in a specific geographic area.

Epidemiology

According to the studies back to 35 years ago in the city of Rasht-south western of Caspian Sea- and the surrounding area, the ESCC age-standardized incidence rates (ASRs) were 20 and 10 per 100000 men and women respectively. In contrast, in southeast of the Caspian Sea, around the city of Gonbad toward the East, it had an equal prevalence between men and women which had the highest ASRs in comparison with other parts of the world (more than 100 per 100000 cases). The unusual age-standardized incidence rate and the greatly higher incidence raise the possibility of the presence of a noticeable risk factor for this disease. Addition to the north parts of Iran, esophageal cancer has been reported in East and Central Asia such as Turkmenistan, Uzbekistan, and Kazakhstan. Recent studies of the province of Golestan showed a male/female ratio of about one and the higher rate of squamous cancer. This substantial decline can be probably due to the improvements of socio-economic conditions in the city of Gonbad and the other area of Golestan province. This decline is in concordance to the esophageal statistics in developed countries which occurs in ESCC, a main subtype of esophageal cancer in Iran (5).

According to studies conducted in Iran, the risk of ESCC in first degree relatives of patients is twice the risk of disease in individuals without family history of the disease. Hot tea and other beverages, opium, polycyclic aromatic hydrocarbons, nitrate concentrations in drinking water, Human papilloma virus type 16, inadequate nutrition, are the possible risk factors for the high prevalence of the esophageal cancer in Iran (5,6).

A recent study in Golestan province showed that mutation of BRCA2 will significantly increase the risk of ESCC. Almost 50% of the esophageal tumors have somatic mutations in TP53 mainly in men.

Transition of C>T in CPG and mutation of T: A pair are the most common mutations in both sexes. High frequency of C>T mutations in CPG part indicate the possibility of inflammatory process involved in ESCC in Iran. High incidence of T:A mutations in Iran may propose the drug usage effects and other masculine behavior. Gene polymorphism related to ESSC is also evaluated and it considered the enzymatic polymorphism as a possible change in the incidence of cancer. The prevalence of polymorphism of 10 theoretically effectual genes in esophageal cancer has been compared among the following three Iranian ethnic groups, high risk Turkamans form Golestan province, medium risk Azeri's from Ardabil, and low risk resident Zoroastrians of Tehran. Compared to Zoroastrians, Turkamans has contained high frequency of 4 alleles including ADH2*1, CYP2A6, CYPLAM2, and CYPLAM1, which was considered to have more carcinogen effects. Results were compatible with the effects of the mentioned alleles on population with high possibility of ESCC (5,7).

Epidermal growth factor receptor (EGFR) is one of the tyrosine kinases receptors with high expression in esophageal cancer cells. EGFR as a transmembrane protein contains an extracellular receptor, a transmembrane component, and an intercellular part. The activation of the EGFR components leads to proliferation, cell differentiation, angiogenesis, metastasis, and anti-apoptotic effects (8).

The high expression of EGFR has been detected in various malignancies such as head and neck, colorectal, breast, lung, and bladder tumors and almost in 40-70% of ESCC. Some studies reported a negative correlation between high expression of EGFR in tumor cells and the patients' survival rate, chemotherapy resistance, and lymphatic metastasis. Conversely, high expression of EGFR is suggested to be associated with high chemotherapy response in other studies (9).

Epidermal growth factor receptor

Tumors are almost the consequences of the alternation in expression of responsible proteins for regulation, proliferation, and vital activities of cells such as growth factors and their receptors which are important for normal tissues growth and also development and progression of neoplasms (10). Epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) which is indentified in more than 50% of malignancies are transmembrane proteins with tyrosine kinase activity and participate in various functions including cell growth, proliferation, and differentiation (11).

According to previous studies, mutations of EGFR gene activates the cellular receptor and leads to the cell survival via inhibiting the apoptosis pathways and affects the response rate to its EGFR antagonists such as Gefitinib in non-small cell lung cancer, so an association has been detected between EGFR polymorphism and advanced stages of tumors (12-15).

EGFR is an oncogene contains 28 exons and spans approximately 188 kb. EGFR oncogenic function leads to the alternation of the cellular processes such as increase in cell proliferation, angiogenesis, invasion and metastasis (16). It is involved in pathphysiology of several malignancies with epithelial origin such as esophagus, lung, colon, and breast cancers (17).

It is also important in the prognosis and progression assessments of the clinical stages of the disease. It has been reported that different forms of EGFR alleles are Influential in lung cancer however these mutations are rare in gastric cancer (18,19).

EGFR polymorphism rate is dependent

on the patient's race and is different in every population, for instance the amount of polymorphism is 2% in united state and 26% in Japan. This polymorphism is important in cancer progression, metastasis and response to receptor antagonist drugs and is known as a diagnostic and therapeutic marker and a landmark in increasing the patient's lifespan (20).

In EGFR-family, EGFR (HER1) and HER2 are the founding members which are mostly involved in human malignancies. The over expression of mRNA and protein along with gene amplification are the major changes in EGFR which are observed in most of the head and neck cancers (70-90%) (21).

The entire gene sequencing has specific priority in genetic disorder detection of cancers and it is the only suggested method. For instance, exon content of EGFR gene should be analyzed while assessing the relation of EGFR gene mutations with ESCC. Mutations in EGFR were firstly reported in lung cancers that had better response to tyrosine kinase inhibitors. These mutations mainly occurred in 18-21 exons of the EGFR gene of none smoker women with adenocarcinoma and also were detected in 25% of breast cancers and 15-25% of gastric tumors. In 1986, these changes were reported in SCC cell line (22).

According to the previous studies considered the changes of EGF and EGFR mRNA in ESCC patients, the over expression of EGFR and PYGO2 mRNAs were observed in ESCC correlated with the tumor progression. The over expression of EGFR and PYGO2 as two biomarkers of invasive tumors that have oncogenic function was significantly dependent on each other (23).

Fluorescence in situ hybridization (FISH)-positive was significantly correlated with the over expression of EGFR and the depth of invasion and lymph node metastasis. Based on the prior investigations, the over expression and the increased gene copy number of EGFR were common in ESCC and EGFR has been proposed as an appropriate target for the ESCC therapeutic approaches (24). Amplification of C-erbB-2 from EGFR-family introduced this gene as a prognosis biomarker in ESCC (25).

Besides the recent improvements in radiotherapeutic techniques there is still low treatment response and survival rate. Therefore, there is a strong need to invent new methods for treating the ESCC patients (26). Because of the expression of EGFR as a therapeutic target in normal cells, its overexpression in tumor cells may be considered to distinguish between normal and malignant cells. Evidences on the EGFR role in different types of cancers have been resulted in designing agents that selectively target this receptor such as anti-EGFR monoclonal antibodies that inhibit the proliferation of overexpressed EGFR cells in both in vivo and in vitro conditions (27).

Other gene mutations activated by this receptor play a role in carcinogenic procedures and also no proper response to the EGFR inhibitors. For instance, in colorectal cancers with KRAS and BRAF gene mutations, patients do not response to Panitumum ab monotherapy as an anti-EGFR monoclonal antibody recently approved by FDA (28).

The large size and the long serum half life full-length antibodies are the barriers of tumor penetration and distribution of antibodies and are the limitating factor in their usage in the therapeutic and prognostic purposes. This clarifies the importance of single chain monoclonal antibodies in diagnostic and therapeutic methods as the most common types of recombinant antibodies easily produced in different expressional systems. These antibodies

possess antigen binding sites that include variable domains of heavy and light chains (VH and VL domains) in which the two domains are connected by a flexible linker segment. Pentadeca linker is one of the most common linkers which are the polypeptides with 10 to 25 hydrophilic amino acids in length. These antibodies are mainly derived from genes separated from mouse hybrid cells and their antigen attachment ability is similar to the monoclonal antibody which they are derived from. The first monoclonal antibody was produced by Huston and colleagues based on the recombinant DNA and protein engineering, derived from monoclonal anti-digoxin antibody expressed in E. coli bacteria. These antibodies are the basis of investigations on therapeutic approaches of several malignancies such as esophageal and breast cancers. Trastuzuamb and Gefitinib are anti-EGFR antibodies mainly used in the studies on the esophageal cancer. According to previous studies the combination of anti-EGFR drugs and radiation can be effective in prognosis of this disease (29).

Several studies have suggested the requirement of future investigations on drugs which act through EGFR for the treatment of esophageal cancer cells. Kono in 2006 resulted that these drugs had anti-proliferative and cell cytotoxicity antibody-dependent effects against cancer cells (30,31).

Partial response to Gefitinib has been observed in patients with EGFR overexpression and SCC pathology which showed the over activity of the mentioned drug in treatment of ESCC cell line (1). Gotoh mentioned that although this biomarker may be effective in predicting the SCC response to chemoradiotherapy, future studies are needed for the definite conclusion (32).

Gene therapy is in progress as a potential therapeutic method in controlling the genetic process of cancer cells and treatment of metabolic diseases. There are wide varieties of approaches in the field of gene therapy which are varied from a substitution of single mutated or deleted tumor suppressor gene to the stimulation of the immune system against cancer cells (33).

Conclusion

Compared Genetic examinations on EGFR gene have contributed to the development of gene therapy methods. Several studies have been conducted on the EGFR mutations in different cancers with limited cell line. Future researches on EGFR and its prevalence in esophageal cancer can be effective in improving the anti-cancer therapeutic methods such as monoclonal antibodies, gene therapy, and also the prognosis of the disease.

Acknowledgement

We would like to thank Clinical Research Development Center of Ghaem Hospital for their assistant in this manuscript. This study was supported by a grant from the Vice Chancellor for Research of the Mashhad University of Medical Sciences for the research project as a medical student thesis with approval number of 900895.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Gotoh M, Takiuchi H, Kawabe S, et al. Epidermal growth factor receptor is a possible predictor of sensitivity to chemoradiotherapy in the primary lesion of esophageal squamous cell carcinoma. Jpn J Clin Oncol. 2007;37:652-657.
2. Kuwano H, Sadanaga N, Watanabe M, et al. Oesophageal cancer composed of mixed histological types. Eur J Surg Oncol. 1996;22:225-231.
3. DeVita VT, Hellman S, Rosenberg SA. Cancer: principles and practice of oncology. Philadelphia: JB; 2001.
4. Kamangar F, Malekzadeh R, Dawsey SM, et al. Esophageal cancer in Northeastern Iran: a review. Arch Iran Med. 2007;10:70-82.

5. Malekzadeh R, Semnani S, Sajjadi A. Esophageal cancer in Northeastern Iran. Govaresh. 2008;13:25-34.
6. Lavergne D, de Villiers EM. Papillomavirus in esophageal papillomas and carcinomas. Journal international du cancer. 1999;80:681-684.
7. Buttar NS, Wang KK, Leontovich O, et al. Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. Gastroenterology. 2002;122:1101-1112.
8. Koshy M, Esiashvilli N, Landry JC, et al. Multiple management modalities in esophageal cancer: epidemiology, presentation and progression, work-up, and surgical approaches. The oncologist. 2004;9:137-46.
9. Sirotnak FM, Zakowski MF, Miller VA, et al. Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. Clin Cancer Res. 2000;6:4885-4892.
10. Abbaszadegan M, Afsharnezhad S, Raziee H, et al. P16/INK4a promoter hypermethylation in serum, blood and tumor of patients with esophageal squamous cell carcinoma. Iran J Basic Med Sci. 2004;6:4-6.
11. Mu XL, Li LY, Zhang XT, et al. Gefitinib-sensitive mutations of the epidermal growth factor receptor tyrosine kinase domain in Chinese patients with non–small cell lung cancer. Clin Cancer Res. 2005;11:4289-4294.
12. Liang Z, Zeng X, Gao J, et al. Analysis of EGFR, HER2, and TOP2A gene status and chromosomal polysomy in gastric adenocarcinoma from Chinese patients. BMC cancer. 2008;8:363.
13. Lee JW, Soung YH, Kim SY, et al. ERBB2 kinase domain mutation in a gastric cancer metastasis. APMIS. 2005;113:683-687.
14. Yokoyama T, Kondo M, Goto Y, et al. EGFR point mutation in non-small cell lung cancer is occasionally accompanied by a second mutation or amplification. Cancer science. 2006;97:753-759.
15. Mammano E, Belluco C, Sciro M, et al. Epidermal growth factor receptor (EGFR): mutational and protein expression analysis in gastric cancer. Anticancer Res. 2006;26:3547-3550.
16. Marchetti A, Martella C, Felicioni L, et al. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. J Clin Oncol. 2005;23:857-865.
17. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. The New England journal of medicine. 2004;350:2129-2139.
18. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. PNAS. 2004;10:13306-13311.
19. Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma: review and considerations for future directions. Ann Surg. 2005;241:27-39.
20. Liakakos T, Xeropotamos N, Ziogas D, et al. EGFR as a Prognostic Marker for Gastric Cancer. World J Surg. 2008;32:1225-1226.
21. Morgan S, Grandis JR. ErbB receptors in the biology and pathology of the aerodigestive tract. Exp Cell Res. 2009;315:572-582.
22. Press MF, Sauter G, Bernstein L, et al. Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res. 2005;11:6598-6607.
23. Moghbeli M, Abbaszadegan MR, Farshchian M, et al. Association of PYGO2 and EGFR in esophageal squamous cell carcinoma. Med Oncol. 2013;30:516.
24. Yang YL, Xu KL, Zhou Y, et al. Correlation of epidermal growth factor receptor overexpression with increased epidermal growth factor receptor gene copy number in esophageal squamous cell carcinomas. Chin Med J. 2012;125:450-454.
25. Zhang G, Zhang Q, Yin L, et al. Expression of nucleostemin, epidermal growth factor and epidermal growth factor receptor in human esophageal squamous cell carcinoma tissues. J Cancer Res Clin Oncol. 2010;136:587-594.
26. Lerut T, Coosemans W, De Leyn P, et al. Treatment of esophageal carcinoma. Chest. 1999;116:463S-465S.
27. Lorenzen S, Lordick F. How will human epidermal growth factor receptor 2-neu data impact clinical management of gastric cancer? Curr Opin Oncol. 2011;23:396-402.
28. Sequist LV, Joshi VA, Janne PA, et al. Epidermal growth factor receptor mutation testing in the care of lung cancer patients. Clin Cancer Res. 2006;12:4403s-4408s.
29. Jimeno A, Rubio-Viqueira B, Amador ML, et al. Epidermal growth factor receptor dynamics influences response to epidermal growth factor receptor targeted agents. Cancer Res. 2005;65:3003-3010.

30. Hanawa M, Suzuki S, Dobashi Y, et al. EGFR protein overexpression and gene amplification in squamous cell carcinomas of the esophagus. Int J Cancer. 2006;118:1173-1180.
31. Mimura K, Kono K, Maruyama T, et al. Lapatinib inhibits receptor phosphorylation and cell growth and enhances antibody-dependent cellular cytotoxicity of EGFR- and HER2-overexpressing esophageal cancer cell lines. Int J Cancer. 2011;129:2408-2416.
32. Janmaat ML, Gallegos-Ruiz MI, Rodriguez JA, et al. Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. J Clin Oncol. 2006;24:1612-1619.
33. Huston JS, McCartney J, Tai MS, et al. Medical applications of single-chain antibodies. International reviews of immunology. 1993;10:195-217.