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EGFR 突变与 EML4-ALK 融合共存的非小细胞肺癌的临床病理特征及治疗分析 *

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摘要 目的：探讨表皮生长因子受体(EGFR)基因突变与棘皮动物微管相关样蛋白 4 与间变性淋巴瘤激酶(EML4-ALK)融合基因共存(以下简称双基因异常)的非小细胞肺癌的临床病理特征及治疗策略。**方法：**回顾性收集并分析 2012 年 1 月至 2016 年 12 月我院收治的 EGFR 突变与 EML4-ALK 融合基因共存的非小细胞肺癌患者的临床资料及病理特点。**结果：**11 例双突变非小细胞肺癌占医院同期入院非小细胞肺癌患者的 0.68%(11/1620)；男性 6 例，女性 5 例；年龄 23-70 岁，平均年龄 51.6 岁；11 例患者均不吸烟；腺癌 9 例，肉瘤样癌 2 例；临床分期，IA 期 3 例，IIB 期 1 例，IIIA 期 1 例，IIIB 期 1 例，IV 期 5 例；6 例行手术治疗，4 例使用传统化疗，最好疗效为稳定(SD)，最长无进展生存期(PFS)为 6 月；5 例患者使用表皮生长因子酪氨酸激酶抑制剂(EGFR-TKI)治疗，使用 EGFR-TKI 最好疗效为部分缓解(PR)，PFS 为 3-23 月，中位 PFS 为 9 月；截止 2017 年 12 月，死亡 4 例，11 例患者的生存时间为 1-67 月，中位存活时间为 21 月。**结论：**EGFR 基因突变与 EML4-ALK 融合基因共存型非小细胞肺癌临床少见，多见于不吸烟或少吸烟的肺腺癌患者，双基因异常的非小细胞肺癌的靶向药物的治疗缺乏统一性，有待进一步研究，基于 EGFR 及 EML4-ALK 的磷酸化水平或肿瘤突变负荷选择靶向药物的个体化精准治疗是非常重要的。

关键词：EGFR 突变；EML4-ALK；共存；非小细胞肺癌

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Clinicopathological Features and Therapeutic Analysis of Non-small-cell lung Cancer patients with Concomitant EGFR Mutation and EML4-ALK Fusion*

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ABSTRACT Objective: To investigate the clinicopathological features and therapeutic strategy of non-small-cell lung cancer with concomitant EGFR mutation and EML4-ALK fusion. **Methods:** A retrospective analysis of clinicopathological data of concomitant in Tangdu hospital from May 2012 to December 2016 was performed. **Results:** There were a total of 11 cases with concomitant EGFR mutation and EML4-ALK fusion, accounting for 0.68%(11/1620) of all non-small-cell lung cancer patients diagnosed in our hospital in the same period. There were 6 males and 5 females, the mean age of the patients was 51.9 (23 to 70) years and all of the patients had no smoking history. The histological type of 9 patient was adenocarcinoma and 2 was sarcomatoid carcinoma. Clinical stage: stage IA was in 3 cases, stage IIB was in 1 case, stage IIIA was in 1 case, stage IIIB was in 1 case, stage IV was in 5 cases. 6 patients underwent surgical treatment, 4 patients received traditional chemotherapy and the best response was stable disease, the longest progression-free survival of chemotherapy was 6 months. 5 patient received epidermal growth factor receptor tyrosine kinase inhibitors and the best response was partial response, the progression-free survival of TKIs were 3-23 months (median 9 months). As of December 2017, 4 patients died, and the survival time of the 11 cases was 1-67months (median 21 months). **Conclusions:** Non-small-cell lung cancer patients with concomitant EGFR mutation and EML4-ALK fusion is rare, most of them do not smoke or smoke slightly and are patients with adenocarcinoma. Targeted therapy based on phosphorylated level of EGFR and EML4-ALK or tumor mutational burden is important.

Key words: EGFR mutation; EML4-ALK; Concomitant; NSCLC

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前言

肺癌是全世界范围内发病率及死亡率最高的恶性肿瘤，严重威胁着人类的生命健康[1]。非小细胞肺癌(non-small-cell lung cancer，NSCLC) 是肺癌中最常见的组织学类型，约占肺癌的 80%-85%。传统的治疗方法包括手术、化疗、放疗，治疗效果并不理想，约 70%的患者在确诊时已经发展为晚期，失去了手术根治的机会，化疗方面虽然取得了很大的进步，但是以铂类为

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基础的化疗方案,患者的中位生存期很难超过 10 个月。随着对肺癌发病机制、生物学行为的深入研究以及肺癌个体化治疗大趋势的推动,越来越多的研究者将肺癌的治疗焦点转移到特异性强、毒副作用轻的分子靶向药物上,这些药物与传统的细胞毒类化疗相比显著延长了肺癌患者的无进展生存期(progress-free survival, PFS)和总生存期(overall survival,OS)[2,3]。

当前,表皮生长因子受体(epidermal growth factor receptor, EGFR) 基因突变与棘皮动物微管相关样蛋白 4- 间变性淋巴瘤激酶(echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase,EML4-ALK)融合基因是 NSCLC 最重要的两个驱动基因。既往研究认为 EGFR 基因突变与 EML4-ALK 融合基因是相互排斥不能共存的[4,5],但近年来,国内外学者陆续报道了 EGFR 基因突变与 EML4-ALK 融合基因共存的 NSCLS 病例[6,7]。本研究通过回顾性分析空军军医大学唐都医院 2012 年 5 月至 2017 年 12 月期间收治的 11 例双基因异常的 NSCLC 患者,并复习相关文献,对其临床病理特征、治疗策略及预后进行探讨,以期更好地指导临床实践。

1 材料与方法

1.1 材料

收集 2012 年 1 月至 2016 年 12 月空军军医大学唐都医院收治的并且同时行 EGFR 基因与 EML4-ALK 融合基因检测的非小细胞肺癌患者临床资料。

1.2 方法

分别计算 EGFR 基因与 EML4-ALK 融合基因突变的阳性率,以及 EGFR 基因与 EML4-ALK 融合基因双突变的阳性率;分析 EGFR 基因与 EML4-ALK 融合基因突变检测结果均为阳性的患者临床特点、病理特征、治疗情况及预后。

2 结果

2.1 EGFR 与 EML4-ALK 融合基因突变率

我院 2012 年 1 月至 2016 年 12 月收治并且同时行 EGFR 基因与 EML4-ALK 融合基因检测的非小细胞肺癌患者共 1620 例,检测方法为探针扩增阻滞突变系统(Amplification refractory mutation system, ARMS)PCR 法。结果显示 EGFR 基因突变阳性 352 例 (22%),EML4-ALK 融合基因阳性 103 例 (6.4%),EGFR 基因突变与 EML4-ALK 融合基因共存 11 例 (0.67%);EGFR 突变阳性的患者中双突变发生率为 3.1%(11/352),EML4-ALK 融合基因突变阳性患者中双突变发生率为 10.7%(11/103)。

2.2 EGFR 与 EML4-ALK 融合基因双突变患者临床特点

11 例双突变的患者中,男性 6 例,女性 5 例;年龄 23-70 岁,中位年龄 50 岁,平均年龄 51.6 岁;11 例患者均不吸烟;病理类型分别为腺癌 8 例,肉瘤样癌 2 例,粘液表皮样癌 1 例;临床分期,IA 期 3 例,IIB 期 1 例,IIIA 期 1 例,IIIB 期 1 例,IV 期 5 例;检测标本的类型为手术切除标本 7 例,支气管镜活检标本 3 例,胸腔积液 1 例;EGFR 基因的类型为 19 号外显子缺失突变 5 例,18 号外显子突变 (G719X)2 例,21 号外显子突变 4 例(L858R 3 例,L861Q 1 例)。具体如表 1 所示。

2.3 治疗与预后

11 例双突变 NSCLC 中,6 例行肺癌根治术,1 例行肺叶切除 + 淋巴结采样术;4 例使用传统化疗, 其中 2 例为培美曲塞联合奈达铂,2 例为多西他赛联合顺铂,最好疗效均为稳定(stable disease, SD), 最长无进展生存期 (progression-free survival, PFS)为 6 月;5 例患者使用表皮生长因子酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI)治疗,其中 3 例为吉非替尼,1 例为厄洛替尼,1 例为埃克替尼, 使用靶向药物最好疗效为部分缓解(partial response, PR),PFS 为 3-24 月,中位 PFS 为 9 月。截止 2017 年 12 月,4 例死亡,存活时间为 1-67 月,中位存活时间为 21 月。

表 1 双突变患者的临床情况

Table 1 Clinic information of 11 cases of patients

Patient No	Sex/Age	Smoking	Stage	Histology	EGFR mutation	Surgery	Treatment	Best response	PFS(m)
1	M/50	Never	IV	AC	Exon 18 G719X	N	1.Gefitinib 2. Gefitinib+Pemetrexe+Nidaplatin	1.SD 2.PR	3 11
2	M/57	Never	IV	AC	Exon 19 deletion	N	1.Docetaxel+Cisplatin 2.Gefitinib	1.SD 2.SD	4 23
3	F/47	Never	IV	AC	Exon 18 G719X	N	-	-	-
4	F/66	Never	IV	AC	Exon 19 deletion	N	Gefitinib	PR	6
5	M/67	Never	IV	SC	Exon 21 L861Q	Y	-	-	-
6	M/45	Never	IIB	AC	Exon 19 deletion	Y	1.Docetaxel+Cisplatin 2.Erlotinib	2.SD	9
7	M/23	Never	IA	AC	Exon 21 L858R	Y	-	-	-
8	F/63	Never	IA	AC	Exon 19 deletion	Y	icotinib	SD	11
9	F/42	Never	IA	AC	Exon 21 L858R	Y	-	-	-
10	M/38	Never	IIIB	SC	Exon 19 deletion	Y	-	-	-
11	F/70	Never	IIIA	AC	Exon 21 L858R	Y	Pemetrexe+Nidaplatin	SD	6

Note:M=male; F=female; AC=adenocarcinoma; SC=Sarcomatoid carcinoma; PR=partial response; SD=stable disease; PFS=progression-free survival; N=no; Y=yes.

3 讨论

既往研究认为 EGFR 基因突变与 EML4-ALK 融合基因不能共存,但随着双基因异常的 NSCLC 病例的不断报道,这一特殊类型的 NSCLC 值得我们进行研究。2012 年,韩国学者 Lee[8]等人在对 444 例 NSCLC 患者进行基因突变检测,发现 4 例双基因异常患者,双基因异常发生率为 0.9%(4/444)。2014 年,中国学者杨衿记[9]等人对 977 例 NSCLC 患者同时检测 EGFR 突变和 EML4-ALK 融合,发现 13 例双基因异常患者,双基因异常发生率为 1.3%(13/977)。2016 年,Ulivi P 等人在 380 例 NSCLC 患者中发现 EGFR 和 EML4-ALK 突变的发生率为 1.6%[10]。我们的研究显示我院双基因异常的 NSCLC 的发生率为 0.68%(11/1620),基本与国内外文献报道一致。但 Won[6]等用较高灵敏度的基因突变检测方法,如二代测序(next-generation sequencing, NGS),发现 NSCLC 中双突变共存的发生率约为 4.4-15.4%。双突变共存的现象可以用肿瘤异质性来解释[7,9,11],即不同的基因突变可能出现在肿瘤组织的不同细胞中,也可能出现在肿瘤组织的同一个细胞中,以及原发灶和转移灶之间的肿瘤组织可以出现不同的基因突变。

EGFR 基因突变多见于不吸烟或少吸烟的女性肺腺癌患者中,EGFR 突变阳性率在亚裔及我国约为 50%,在高加索人群中约为 10%[12,13]。文献报道[14,15],西方人群 NSCLC 中 EML4-ALK 融合基因阳性的发生率约为 3%-7%,中国 NSCLC 患者阳性率约为 3-11%,且多见于不吸烟或少吸烟的肺腺癌患者。我们的研究显示 EGFR 突变阳性率为 22%,EML4-ALK 融合基因阳性率为 6.4%,11 例双突变患者均不吸烟,且大部分为腺癌,这些与以往文献报道基本一致。

双突变共存的 NSCLC 的治疗策略是值得我们探讨的,尤其是靶向药物的选择。一些学者认为双突变共存型 NSCLC 对靶向治疗药物反应性差[16],但另外一些学者却报道了靶向药物对双突变型 NSCLC 起到了较好地疗效[17,18]。文献报道在双突变共存型 NSCLC 中,EGFR 基因突变及信号激活是 ALK 抑制剂克唑替尼耐药的一种重要的分子机制[19,20]。中国学者杨衿记[9]等对双突变共存型 NSCLC 对 EGFR-TKI 及 ALK 抑制剂的不同的反应性进行了阐释,他们发现 EGFR 和 ALK 蛋白磷酸化水平与 EGFR-TKI 及 ALK 抑制剂的疗效有相关性,即对 EGFR-TKI 相对敏感的患者,RGFR 磷酸化水平高,ALK 磷酸化水平低,反之,对 ALK 抑制剂有效的患者 ALK 磷酸化水平高,EGFR 磷酸化水平低。我们认为双突变型 NSCLC 对 EGFR-TKI 及 ALK 抑制剂的不同的反应性,可能与肿瘤组织中 EGFR 基因突变负荷和 EML4-ALK 融合基因负荷有关,EGFR 突变负荷相对较大的,即 EGFR 基因突变占优势的患者,对 EGFR-TKI 疗效较好;反之,EML4-ALK 融合基因占优势的患者,对 ALK 抑制剂的疗效较好。我们研究的 11 例双突变共存型患者中,有 5 例患者使用 EGFR-TKI,其中吉非替尼(gefitinb)3 例,厄洛替尼(erlotinib)1 例,埃克替尼(icotinib)1 例,2 例患者最好疗效为部分缓解,PFS 为 3-23 月,中位 PFS 为 9 月。病人 1 在一线使用吉非替尼 250 mg/ 日治疗 3 月后病情进展,更换为吉非替尼 500 mg/ 日联合培美曲塞 + 奈达铂化疗 8 周期后,患者获得 PFS 长达 11 月。文献报道在使用一代 EGFR-TKI 治疗的患者中在药物压力的选择下最终发生耐药,50%以上的获得性耐药与 EGFR T790M 突变有关[21],病人 2 使用吉非替尼在获得长达近 2 年的 PFS 后病情进展,再次行血液基因检测发现 EGFR T790M 突变阳性,病人 6 使用厄洛替尼治疗进展后行血液基因检测同样发现 EGFR T790M 突变阳性。

综上,EGFR 基因突变阳性与 EML4-ALK 融合基因阳性共存型 NSCLC 临床少见,患者多为不吸烟或少吸烟的腺癌。基于磷酸化水平或肿突变负荷选择靶向药物的个体化精准治疗是值得推荐的,同时在治疗过程中获得性耐药发生后,再次行基因检测以便发现新的突变位点,对于治疗策略的调整至关重要。

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