

Ⅲ期非小细胞肺癌非手术治疗的现状与研究进展

刘华丽 综述, 胡伟国, 宋启斌 审校

(武汉大学人民医院肿瘤中心, 湖北 武汉 430060)

摘要:肺癌是全球范围内引起肿瘤相关性死亡的主要原因, 而肺癌中约 85% 为非小细胞肺癌(NSCLC)。Ⅲ期 NSCLC 患者是一复杂的人群, 其中部分患者是可以治愈的。NSCLC 的治疗包括手术、放疗、化疗以及靶向药物治疗, 并且绝大多数身体合适患者接受的是化疗和放疗。Ⅲ期 NSCLC 患者的最佳治疗方案仍未统一, 但一些治疗原则已被普遍接受。对身体状态良好、各器官功能正常的患者, 同步放化疗是标准的治疗方案。常与放疗联合应用于肺癌治疗的化疗方案包括顺铂/依托泊苷方案和卡铂/紫杉醇方案。与传统方案相比, 新药联合放疗并未提高治疗疗效。而关于诱导化疗、巩固化疗何种方式与放疗配伍更利于患者生存, 仍然存在争议, 迄今为止, Ⅲ期临床研究并未给出确切的结论。部分研究显示抗血管治疗与放化疗联合疗效不显著或存在危险。在未筛选Ⅲ期患者中, 靶向治疗的疗效欠佳。尽管存在这些困难, 但经选择的患者采用放化疗基础上加用分子靶向药物治疗或者在放化疗后加用免疫巩固治疗方案是可取的。本文将总结关于Ⅲ期 NSCLC 患者现有治疗手段和以表皮生长因子受体(EGFR)、间变性淋巴瘤激酶(ALK)、RAS、程序性死亡分子 1(PD-1)及程序性死亡分子 1 配体(PD-L1)为靶点的药物相关研究。

关键词: 癌, 非小细胞肺; 治疗

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Current Standards and Research Progress in Non-surgical Treatment for NSCLC Stage Ⅲ

LIU Hua-li, HU Wei-guo, SONG Qi-bin

(Centre of Cancer, People's Hospital of Wuhan University, Wuhan 430060, China)

Abstract: Lung cancer is the leading cause of cancer throughout the world, of which non-small cell lung cancer (NSCLC) accounts for 85%. Patients with stage Ⅲ NSCLC is a heterogeneous group and some of them may be curable. Combinations of various therapeutic approaches including surgery, radiotherapy, chemotherapy and molecular targeted therapy are performed to treat this disease, and the majority of fit patients will be treated with chemotherapy and radiation alone. The optimal therapy for all patients remains undefined, but certain principles of care are widely accepted. Concurrent chemoradiation is the standard of care for patients who have a good performance status and adequate end-organ function. The most commonly used chemotherapy regimens given in combination with radiation therapy include cisplatin/etoposide or carboplatin/paclitaxel. Compared to these older regimens, studies incorporating newer agents have not improved outcomes. Whether the induction or consolidation chemotherapy following chemoradiation contribute to the survival or not is controversial, and thus far randomized phase Ⅲ trials have not provided supporting evidence for this strategy. There are some cases suggesting that incorporating antiangiogenics with chemoradiation may be ineffective or unsafe. Targeted agents in unselected patient diagnosed with stage Ⅲ disease have not shown survival favour. Despite these recent setbacks, however, there remains a sound rationale for incorporating molecularly targeted agents into chemoradiation regimens in select patient groups or consolidating chemoradiation with immunotherapy. Current standards and clinical trials that incorporate drugs targeting EGFR, ALK, RAS, programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) into the management of patients with stage Ⅲ NSCLC are reviewed.

Subject words: non-small cell lung cancer; therapy

随着疾病谱改变, 目前肿瘤已成为仅次于心血

管疾病, 严重威胁人类生命健康的第二大疾病。肺癌是引起肿瘤相关性死亡的主要原因, 而肺癌中约 85% 为非小细胞肺癌(NSCLC)。Ⅲ期 NSCLC 患者的预后与患者健康状况、肿瘤生物学行为等多种因素

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通讯作者: 宋启斌, 教授, 主任医师, 博士; 武汉大学人民医院肿瘤中心, 湖北省武汉市武昌区张之洞路 99 号 (430060); E-mail: qibinsong@163.com

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相关,其中部分Ⅲ期 NSCLC 患者是有治愈可能的。患者预后不良与治疗毒性和/或患者健康状态变差、体重显著减轻、淋巴转移站数增多以及 V_{20} 等多种因素有关^[1-3]。目前对高龄(年龄中位数为 70 岁)以及与伴有吸烟相关慢性病(包括心肺功能受损)的Ⅲ期 NSCLC 患者的治疗依然存在很大挑战。晚期 NSCLC 患者的治疗方案选择与肿瘤组织类型及驱动基因状态有关,但尚未应用于Ⅲ期 NSCLC 的治疗。

1 Ⅲ期 NSCLC 的非手术治疗演变与现状

在过去三十年,关于Ⅲ期 NSCLC 的治疗已然取得了一系列进展。外科手术仍是部分Ⅲ期 NSCLC 患者治疗的必需组成部分^[2]。但对于大多数Ⅲ期 NSCLC 患者,放疗是主要治疗方法。20 世纪 80 年代,化疗联合放疗的治疗方案被提出。与单一放疗相比,化疗联合放疗使Ⅲ期 NSCLC 患者生存获益,并提高治愈率^[4]。关于同步放化疗与放化疗序贯疗法治疗Ⅲ期 NSCLC 的临床疗效,研究表明,同步放化疗比序贯疗法更佳^[5]。

对于肺功能良好、无严重合并症、无体重减轻、 $V_{20}<35\%$ 的Ⅲ期不适于手术的 NSCLC 患者,一种普遍接受的治疗方案是同步放化疗^[5]。但关于最佳化疗药物及化疗周期数的标准仍未统一。以铂类为基础的化疗方案为标准方案。目前铂类联合长春花碱或依托泊苷、丝裂霉素+长春地辛、长春瑞滨、紫杉醇、多西他赛等化疗药物在Ⅲ期 NSCLC 中的疗效,已有较多临床研究报道^[5-8]。西日本胸部肿瘤协助组(West Japan Thoracic Oncology Group, WJTOG)开展的一项随机Ⅲ期临床研究表明^[6],Ⅲ期 NSCLC 患者中,二代与三代化疗药物治疗组的总生存时间上并没有显著差异性,但放疗联合 MVP 方案(即丝裂霉素、长春地辛及顺铂联合化疗)毒性更高。另一项Ⅲ期临床研究结果显示^[9],局部晚期非小细胞肺癌(locally advanced non-small cell lung cancer, LA-NSCLC)患者中,接受放疗联合 DP 方案(即顺铂与多西他赛联合化疗)的 2 年生存率优于接受 MVP 方案($P=0.059$),但 3~4 级放射性食管炎的发生率亦更高($P=0.056$)。另一项回顾性研究比较了 PE 方案(即顺铂与氟尿嘧啶联合化疗)与卡铂联合紫杉醇化疗方

案,结果显示两化疗方案在总生存时间上没有差异,但 PE 方案的治疗不良反应更高^[10]。

2 Ⅲ期 NSCLC 的诱导化疗与巩固化疗

Dillman 等^[11]人研究结果显示,与单一放疗相较,放疗前行 2 个周期顺铂和长春花碱诱导化疗可以显著提高Ⅲ期 NSCLC 患者中位生存时间及长期生存率,首次显现诱导化疗在Ⅲ期 NSCLC 中的生存获益。而Ⅲ期 NSCLC 患者中,接受卡铂/紫杉醇联合同步放疗治疗前给予 2 个周期卡铂/紫杉醇诱导化疗在总生存时间上与仅接受同步放化疗患者没有差异^[12]。PE 方案化疗联合同步放疗后加 3 个周期多西他赛巩固化疗治疗Ⅲ期 NSCLC 患者,没有提高总生存时间,反而有更高肺炎和发热性中性粒细胞减少症的风险^[13]。同步放化疗后加用卡铂/紫杉醇巩固化疗治疗效果未显示出生存获益^[14]。总而言之,目前研究显示,同步放化疗前诱导化疗或放化疗后加巩固化疗与单独放化疗相比,在生存时间上无统计学差异,甚至可能有更高的不良反应。

目前关于Ⅲ期 NSCLC 患者的治疗,对于化疗药物、放疗剂量及化疗周期的调整,并未显著延长患者生存时间,3 年生存率仅 15%~25%。患者中位生存时间的提高主要取决于入组患者选择、转移分期、放疗技术、支持治疗的提高,以及临床医生对于此类患者治疗经验的积累^[15]。

3 Ⅲ期 NSCLC 的分子靶向药物治疗

近年来肺癌治疗的进步很大程度得益于驱动基因的发现,尤其是 *EGFR* 基因突变、*ALK* 基因(anaplastic lymphoma kinase)融合等驱动基因及相应靶向药物的成功使用,但目前在放化疗的基础上加用吉非替尼、西妥昔单抗分子靶向药物治疗,并未显示出明显提高患者生存时间^[8,16]。尽管如此,关于靶向药物治疗的理论研究已取得一定成就。

目前以 *EGFR* 为靶点治疗Ⅲ期 NSCLC 的相关研究不断开展。研究表明,放疗可增加 *EGFR* 表达,导致放射抵抗^[17];可能机制为电离辐射可诱导 *EGFR* 自身磷酸化,激活下游 *PI3K/AKT* 信号通路从而促进肿瘤细胞生长增殖、抑制细胞凋亡^[17,18]。此外,

EGFR 基因突变型放射敏感性更高, 这可能与突变型 *EGFR* 不能结合 DNA 修复中的关键酶有关。

棘皮动物微管相关蛋白样 4-间变性淋巴瘤激酶融合基因 (echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase, EML4-ALK) 与 NSCLC 发生密切相关, 特别是无吸烟史的肺腺癌。在 NSCLC 中, EML4-ALK 与 *EGFR* 突变密切相关^[19]。体外细胞实验表明, EML4-ALK 与肿瘤细胞放射敏感性相关^[20]。*Ras* 基因与放射抵抗性的产生亦有着密切联系。体外实验表明, 抑制 *Ras* 下游通路可增加放射敏感性。

此外, 目前关于抗血管生成药物的研究未显示生存获益或不安全性^[17-20]。

4 Ⅲ期 NSCLC 的免疫治疗

目前普遍观点认为肿瘤免疫编辑是一个动态发展的过程, 包括免疫清除、免疫平衡和免疫逃逸三个阶段。免疫治疗主要是通过激活体内的免疫细胞特异性清除癌变细胞, 已被证实可有效治疗 NSCLC。Ⅲ期 NSCLC 患者放化疗后加用免疫巩固治疗的研究已有报道。一项Ⅲ期临床研究^[21], 患者接受同步放化疗或序贯放化疗后加用 Tecemotide (一种 MUC1 抗原特异性癌症免疫治疗药物) 巩固治疗, 两组患者在总生存时间上没有统计学差异。

肿瘤免疫应答的产生需要机体免疫系统有效识别和提呈肿瘤抗原、进而活化特异性 T 细胞。有证据表明, 放疗可引起肿瘤抗原的释放, 进而被免疫系统识别^[22, 23]。因此, 辐射可刺激 T 细胞活化与浸润。B7 家族是不可或缺的 T 细胞活化的共刺激分子, PD-L1 是该家族的第三个成员, PD-L1 与活化 T 细胞表面的受体 PD-1 结合后, 可通过诱导凋亡及阻止细胞周期而抑制 T 细胞的反应, 引起负性调节机体免疫应答过程。Nivolumab 是抗 PD-1 的全人型 IgG4 单克隆抗体, 可阻断 PD-1 与 PD-L1 或 PD-L2 的结合, 从而阻断 PD-1 介导的肿瘤免疫抑制。据文献报道, Nivolumab 治疗肺鳞癌安全有效, 可作为肺鳞癌的二线治疗药物^[24]。最新研究表明, Nivolumab 较多西他赛治疗晚期铂类治疗无效的非鳞癌, 可更好可提高患者总生存期^[25]。

5 结 语

Ⅲ期 NSCLC 的治疗进展尚未取得突破性成就。从过去三十多年的试验研究中显示, 现有的化疗药物在晚期 NSCLC 患者中的作用已达到平台。未来研究的方向, 靶向药物和免疫治疗成为控制肿瘤转移的有效治疗方法, 为Ⅲ期 NSCLC 的治愈提供了希望。

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