doi: 10.13241/j.cnki.pmb.2017.10.045

非小细胞肺癌的免疫治疗进展 *

盛宏旭 王世敏 王吉平 李广华 徐广全△

（哈尔滨医科大学附属第二医院胸外科 黑龙江 哈尔滨 150086）

摘要：肺癌是最致命的恶性肿瘤之一，也是男性肿瘤患者致死率最高的，5 年生存率低于 18%。尽管非小细胞肺癌（non-small cell lung cancer, NSCLC）在手术治疗、化疗、放疗以及靶向治疗方面均取得了一定的成果，但晚期 NSCLC 的预后依然很差。免疫治疗为 NSCLC 患者提供了一个新的治疗方向。免疫治疗目前主要研究方向在免疫检查点抑制剂（Ipilimumab、Nivolumab、MK-3475）和肿瘤疫苗（MAGE-A3, L-BLP25, TG4010, Belagenpumatucel-L）等。免疫治疗具有针对性强、副作用少、效率高的特点，并在Ⅱ、Ⅲ期临床试验中取得了较好的疗效，成为在手术、化疗、放疗以及靶向治疗后一种新的重要治疗手段。本文就当前非小细胞肺癌免疫治疗原理、临床试验及待解决问题作一综述。

关键词：非小细胞肺癌；免疫治疗；肿瘤疫苗；检查点抑制剂

中图分类号：R734.2 **文献标识码**：A **文章编号**：1673-6273（2017）10-1968-03

Advances on Immunotherapy Research in Non-small Cell Lung Cancer*

SHENG Hong-xu, WANG Shi-min, WANG Ji-ping, LI Guang-hua, XU Guang-quan△

(Department of Thoracic Surgery, The 2nd Affiliated Hospital of Harbin Medical University, Heilongjiang, Harbin, 150086, China)

ABSTRACT: Lung cancer is one of the most fatal malignant tumors and male lung cancer patients have the highest mortality rate. Its survival rate in five years is less than 18%. Although certain outcomes have been achieved in surgical treatment, chemotherapy, radiotherapy and targeted therapy of non-small cell lung cancer (NSCLC), the prognosis of advanced NSCLC is still unsatisfying. However, immunotherapy has provided a new direction for the treatment of NSCLC, the currently main research direction of which is immune checkpoint inhibitors (Ipilimumab, Nivolumab, MK-3475) and tumor vaccine (MAGE-A3, L-BLP25, TG4010, Belagenpumatucel-L), etc. Immunotherapy is featured with high pertinence, less side effects and high efficiency with better curative effects achieved in clinical trials of phase II and phase III, for which it has become a new treatment of significant importance after surgery, chemotherapy and radiotherapy and targeted therapy. This paper summarizes the principles, clinical trials and problems to be solved of current non-small cell lung cancer immunotherapy.

Key words: Non-small cell lung cancer; Immunotherapy; Tumor vaccine; Checkpoint inhibition

Chinese Library Classification(CLC): R734.2 Document code: A

Article ID: 1673-6273(2017)10-1968-03

前言

肺癌是最致命的恶性肿瘤之一，其致死率超过了其他三种常见肿瘤（结肠癌、乳腺癌和胰腺癌）的总和[1]，也是男性肿瘤患者致死率最高的，5 年生存率低于 18%[2]。其中非小细胞肺癌（non-small cell lung cancer, NSCLC）占总人数的 85%[3]。随着手术、化疗、放疗以及靶向治疗等治疗方法的不断进步，NSCLC 的治疗取得了很大的进展，但晚期患者预后依然很差。免疫治疗是肿瘤学领域的一项突破性治疗方法，通过机体免疫系统来控制和清除肿瘤细胞。现阶段的研究方向主要包括肿瘤疫苗如 MAGE-A3, L-BLP25, TG4010, Belagenpumatucel-L 等和免疫检查点（CTLA-4、PD-1、PD-L1）抑制剂如 Ipilimumab, nivolumab, MK-3475 等[4]。免疫治疗的疗效在Ⅱ、Ⅲ期临床试验上已经得到了初步的证实。本文就目前免疫治疗的临床试验以及有待解决的问题展开综述。

1 Melanoma-associated antigen-A3(MAGE-A3)

MAGE-A3 普遍表达于肿瘤细胞上（NSCLC 约 35%），但是在除睾丸生殖细胞和胎盘滋养层外的正常细胞中不表达[5]。MAGE-A3 的过表达常常预示着疾病的进展和不良预后[6]。MAGE-A3 作为 NSCLC 的抗原特异性肿瘤疫苗，Ⅱ期临床试验入组 182 名 MAGE-A3 阳性的术后患者。随机接受 MAGE-A3 或安慰剂治疗，前期每三周进行一次治疗，共 5 次；后期每三个月进行一次治疗，共 8 次，以无病期为第一试验终点。经过 28 个月的中位随访时间，无病期（HR=0.73,95% CI：0.45-1.16）和总生存期（HR=0.66，CI：0.36-1.20），无统计学差异[7]。Ⅲ期临床试验 MAGRIT (MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy)正在进行中，计划入组 2270

* 基金项目：黑龙江省自然科学基金面上项目（H2015004）

作者简介：盛宏旭（1992-），男，硕士研究生，主要研究方向：肺癌及食管癌的基础学研究，E-mail: 878559132@qq.com

△ 通讯作者：徐广全，男，硕士研究生导师，教授，主要研究方向：肺癌及食管癌的基础学研究，E-mail: 13904503643@163.com

（收稿日期：2016-10-14 接受日期：2016-10-30）

名ⅠB、Ⅱ、ⅢA 期肺癌术后病人,以进一步评估 MAGE-A3 在 NSCLC 病人中的治疗效果[8]。

2 L-BLP25

L-BLP25 是一种以肽类抗原为基础的疫苗，主要针对 MUC1(mucinous glycoprotein-1)暴露的肽核心[9]。MUC1 是普遍表达于呼吸、泌尿及消化系统粘膜上皮细胞的一种跨膜蛋白。当 MUC1 异常糖基化后,其免疫学特性与正常细胞上表达的 MUC1 不同。而过表达的 MUC1 与接近 60%的肺癌相关,并且常常提示着不良的预后,因此可能成为一个潜在的治疗靶点[10]。Ⅱ期临床试验共入组 171 名ⅢB 和Ⅳ期 NSCLC 患者,其中 88 名接受 L-BLP25 加最优支持治疗（best supportive care, BSC),83 名患者接受单独 BSC 治疗。结果对比发现,L-BLP25 联合 BSC 组病人的中位生存期比单独 BSC 组长 4.4 个月[11];3 年生存率分别为 31%和 17%[12]。Ⅲ期临床试验 START 入组未经手术切除的化疗后稳定的Ⅲ期 NSCLC 患者 1513 名,随机接受 L-BLP25 或安慰剂治疗。尽管没有达到预期结果,但治疗组患者对比对照组有明显的生存期优势[13]。

3 表皮生长因子(epidermal growth factor, EGF)

表皮生长因子(epidermal growth factor, EGF)疫苗目前已经研制成功,并且在古巴、秘鲁和委内瑞拉等国家用于治疗化疗稳定后的进展期ⅢB 期和Ⅳ期 NSCLC。Ⅱ期临床试验入组 80 名ⅢB 或Ⅳ期经过一线化疗结束后的患者，随机接受 EGF 疫苗或 BSC 治疗[14]。结果表明,在接种疫苗后抗体反应良好的病人中,总生存期中位数为 11.7 个月;而抗体反应差的患者中位生存期中位数仅为 3.6 个月。此外,在接种疫苗后血清 EGF 低于 168 pg/mL 的患者总生存期(overall survival, OS)中位数为 13 个月,而 EGF 水平高于 168 pg/mL 的病人 OS 中位数为 5.6 个月。Ⅱ期临床试验证实 EGF 疫苗能够延长病人 OS,在年龄小于 60 岁的病人中更为明显。

4 Belagenpumatucel-L

Belagenpumatucel-L 是一种用含转化生长因子 -β2(TGF-β2)的反义 mRNA 质粒转染的肿瘤细胞疫苗[15],包括 4 种辐射后不同的 NSCLC 细胞系(2 个腺癌,1 个鳞癌,1 个大细胞癌)[16]。研究证实体内高水平的 TGF-β2 能够抑制免疫系统,而 Belagenpumatucel-L 可以通过其表达的反义 RNA 抑制肿瘤的生长[17]。Ⅲ期临床试验入组 532 名 NSCLC 患者在结束一线化疗后随机接受 Belagenpumatucel-L 和安慰剂治疗（270 疫苗和 262 安慰剂),其中 57%为腺癌,27%为鳞癌。从一线化疗结束后开始治疗,直到疾病进展或消失,治疗周期为 4-17.4 周。第一试验终点为总生存期,其他观察项包括无进展生存期、反应率和安全性。结果治疗组的病人总生存期较对照组提升了 7.3 个月。中期总生存期在 Belagenpumatucel-L 组为 20.7 个月,对比安慰剂组为 13.7 个月[18]。此外,在预先接受过放射治疗的病人中,中位生存期也得到了显著改善。

5 TG4010

TG4010 是一种以修改后的 Ankara 或 MVA 病毒为载体的重组病毒疫苗，与 L-BLP25 同样针对肿瘤细胞上 MUC1 暴露的肽核心[19]。Ⅱ期临床试验中,入组 148 例 MUC1 阳性的 II-IB 期及 IV 期患者随机接受 6 周期一线化疗联合(n=74)或不联合 TG4010(n=74)治疗。试验的第一终点是 6 个月无疾病进展时间(progression-free survival,PFS)。TG4010 治疗组 6 个月 PFS 为 43.2%对比对照组 PFS 为 35.1%；总生存期中位数 TG4010 治疗组为 10.7 个月对比对照组 10.3 个月[20]。TG4010 在 NSCLC 治疗效果有待于Ⅲ期临床试验进一步研究。

6 Ipilimumab

细胞毒 T 淋巴细胞抗原 4（cytotoxic T-lymphocyte antigen 4, CTLA-4)是一种表达在 T 细胞表面的跨膜蛋白,能够下调 T 细胞活性,从而导致肿瘤细胞的免疫耐受[21]。前期临床试验证实 Ipilimumab 能够显著提高转移性黑色素瘤患者的总生存期,在 NSCLC 患者中的作用也被证实有效[22]。Ⅲ期临床试验证实在 Ipilimumab 治疗组,1 年生存率为 46.6%;接受传统化疗组的 1 年生存率为 21.6%-38%[23]。Ⅱ期临床试验入组 204 名ⅢB、Ⅳ期 NSCLC 患者,以 1:1:1 随机接受对照组(CP 方案联合安慰剂 6 周期)、同步组(前 4 周期为 Ipilimumab 联合 CP,后 2 周期给予安慰剂联合 CP 方案)和序贯组(前 2 周期给予安慰剂联合 CP 方案,后 4 周期给予 Ipilimumab 联合 CP 方案)。以患者的 PFS 为第一试验终点,结果显示序贯组和对照组的 PFS 分别为 5.1 个月和 4.2 个月,序贯组的 PFS 较对照组有明显的改善[24]。

7 Nivolumab

PD-1 能够通过下调免疫系统来防止 T 细胞的激活，从而诱导肿瘤细胞的免疫耐受及免疫逃逸[25]。多中心、国际性的临床试验(CheckMate 063)入组 117 名ⅢB、Ⅳ期局部进展或转移的肺鳞癌患者应用 nivolumab,客观缓解率(objective response rate, ORR)为 14.5%,主要的不良反应主要包括肺炎、腹泻、骨骼肌疼痛等[26]。Ⅲ期临床试验(CheckMate017)对进展期肺鳞癌患者给予 nivolumab 或多西他赛治疗，对比发现 nivolumab 组比多西他赛组 OS、PFS 显著改善（OS 为 9.2 个月 vs6.0 个月；PFS 为 3.5 个月 vs2.8 个月)[27]。Borghaei H 等的国际性Ⅲ期临床试验入组 582 名一线化疗后进展的非鳞 NSCLC 患者随机接受 nivolumab 和多西他赛治疗，平均总生存期 nivolumab 组和多西他赛组分别为 12.2 个月和 9.4 个月[28]。基于上述的临床试验,在提高进展期 NSCLC 患者总生存期上,Nivolumab 比多西他赛具有更好的疗效[29]。目前,美国食品与药品监督局(FDA)已经在 2015 年批准 nivolumab 上市，用于治疗进展期的 NSCLC 患者[30]。

8 MK-3475(Pembrolizumab)

MK-3475 是一种针对 PD-1 配体 PD-L1 的人源单克隆抗体,能够解除 T 细胞抑制,达到清除肿瘤细胞的效果[31]。Ⅱ期临床试验入组 84 名先前未经治疗的转移性 NSCLC 病人,其中有 57 名患者的肿瘤组织中表达了 PD-L1[32]。经过筛选,最终 45 名患者接受 MK-3475 治疗。具体方案为 2 mg/kg 每三周一次(n=6),10 mg/kg 每三周一次 (n=23),10 mg/kg 每两周一次(n=26)。该临床试验的总体有效率为 36%。其中 2 mg/kg 每三周

组为 67%；10 mg/kg 每三周组为 27%；10 mg/kg 每两周组为 35%[33]。常见的不良反应包括乏力、皮肤瘙痒、腹泻、呼吸困难和皮炎等。对于表达 PD-L1 的局部进展或转移性 NSCLC 患者，MK-3475 具有较好抗肿瘤效果和耐受性。

9 小结与展望

当前，在减少与肺癌相关职业卫生健康危害方面已经取得了显著的进步，尤其是在控制吸烟上。近几年来，免疫检查点抑制剂和肿瘤疫苗在 NSCLC 治疗上已经取得了显而易见的成绩，使治疗更加有针对性、副作用更少、效率更高，以达到延长生存期的目的。免疫治疗展示出了其通过增强和引导机体自身免疫防御来清除肿瘤细胞的方法，成为在手术、化疗、放疗以及靶向治疗后一种新的重要治疗手段。

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