·综 述·

免疫检查点综合治疗策略的研究进展

卫治功[①] 王丽红[①] 综述 李平[②] 审校

摘要 免疫治疗的快速发展打破了手术、放化疗以及靶向治疗构成的肿瘤常规治疗模式。与传统肿瘤治疗相比，免疫治疗的疗效更持久，不良反应更小。免疫检查点抑制剂作为免疫治疗的重要组成部分，在临床前及临床试验中已被证实具有广阔的应用前景。然而截至目前，这一疗法所带来的临床获益仅局限于部分肿瘤类型的少部分患者，因此需要合理的综合治疗策略克服这种局限。基因靶向治疗、放疗、化疗、肿瘤疫苗等都可以通过不同机制对免疫系统产生影响，为综合治疗提供了理论依据。本文就免疫检查点治疗及其与其他肿瘤治疗方式联合的综合治疗策略做一综述。

关键词 免疫治疗 免疫检查点 共刺激分子 综合治疗策略
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Comprehensive therapeutic strategies regarding immune checkpoint

Zhigong WEI[1], Lihong WANG[1], Ping LI[2]
Correspondence to: Ping LI; E-mail: leepingmd68@vip.163.com
[1]West China School of Medicine, Sichuan University, Chengdu 610000, China; [2]No. 1 Department of Oncology, West China Hospital, Sichuan University, Chengdu 610000, China

Abstract The rapid development of immunotherapy has exceeded that of standard treatment modes, which include surgery, radiotherapy, chemotherapy, and targeted therapy. Immunotherapy is more durable and less toxic than traditional cancer therapies. Moreover, immune checkpoint therapy is an important component of immunotherapy and has been evaluated in preclinical and clinical trials and proven to exhibit broad prospects. However, its clinical benefits are limited to a small subset of patients with a subset of tumor types. Therefore, reasonable comprehensive therapeutic strategies are needed to overcome this limitation. Gene targeted therapy, radiotherapy, chemotherapy, and tumor vaccine affect the immune system through different mechanisms, and these could provide theoretical bases for comprehensive treatments. In this review, immune checkpoint therapy and its potential comprehensive therapies with other cancer treatments are introduced.

Keywords: immunotherapy, immune checkpoint, costimulatory molecule, comprehensive therapeutic strategies

免疫细胞表面广泛表达多种共信号分子，包括细胞毒T淋巴细胞相关抗原4（cytotoxic T-lymphocyte-associated protein-4，CTLA-4）、程序性死亡受体1/程序性死亡配体1（programmed cell death protein-1/ligand-1，PD-1/L1）、淋巴细胞活化基因3（lymphocyte-activation gene 3，LAG-3）、T细胞免疫球蛋白黏蛋白3（T cell immunoglobulin domain and mucin domain-3，TIM-3）、B和T淋巴细胞弱化子（B-and T-lymphocyte attenuator，BTLA）、CD160等抑制性免疫检查点分子，以及CD28、糖皮质激素诱导的肿瘤坏死因子受体（glucocorticoid-induced TNFR-related protein，GITR）、OX40、CD27、CD40、4-1BB等共刺激分子[1]，这些分子与肿瘤微环境（tumor microenvironment，TME）中的复杂配体相互作用，调节抗肿瘤免疫应答的最终效应。TME中高表达的免疫检查点分子可导致T细胞失能，是肿瘤免疫逃逸的重要机制之一。与传统抗肿瘤治疗模式不同，免疫检查点抑制剂并不直接作用于肿瘤细胞，也不针对肿瘤表面的某些特定物质，而是通过调节T细胞的活性，系统性增强全身抗肿瘤免疫。这一方法理论上讲普遍有效，然而截至目前的临床试验，单个免疫检查点抑制剂的临床获益仅局限于部分患者。借助于放疗、化疗、靶向治疗等传统治疗方式构建或提高TME的免疫原性，或许可以使检查点阻断治疗的疗效变得更为广泛、持久。随着对抗肿瘤免疫应答机制研究的深入，越来越多的综合治疗策略正在被评估中[2]。为了满足个体化治疗的需要，肿瘤治疗的“鸡尾酒疗法”将会是今后肿瘤免疫治疗研究的新方向[3]。

随着抗CTLA-4、抗PD-1/L1抗体的成功，免疫检查点抑制成为免疫治疗的主要方法。CTLA-4表达

作者单位：①四川大学华西临床医学院（成都市610000）；②四川大学华西医院肿瘤一科
通信作者：李平 leepingmd68@vip.163.com

于活化的$CD4^+$和$CD8^+$T细胞，通过阻断T细胞抗原受体（T cell receptor，TCR）下游信号的传导以及与CD28竞争性结合配体从而负调节T细胞应答。针对CTLA-4的单克隆抗体ipilimumab是第一个被证实可以取得生存获益的免疫检查点抑制剂[4]，Ⅲ期临床试验表明ipilimumab可以显著提高进展期黑色素瘤患者的总生存期。多个关于进展期间皮瘤、胃癌、非小细胞肺癌（non-small cell lung cancer，NSCLC）、膀胱癌等的临床试验正在评估抗CTLA-4抗体ipilimumab以及tremelimumab的疗效[5]。PD-1主要表达在活化的T细胞、B细胞、树突状细胞（dendritic cells，DCs）表面。与CTLA-4类似，PD-1与配体结合后也可抑制TCR信号通路的下传。针对PD-1/L1的阻断性抗体在过去几年也已经进入临床阶段，并且在转移性黑色素瘤、肺癌、肾细胞癌中取得了广泛的临床获益[3]。靶向于LAG-3、TIM-3等检查点分子的抗体也正在研究中[6]。此外，T细胞的激活还需要共刺激分子的参与，靶向于GITR、4-1BB、OX-40以及CD40等共刺激分子的抗体可通过增强免疫细胞活性提高抗肿瘤免疫，在多种肿瘤的前期研究中也取得了不同程度的临床疗效[7-9]。

1 免疫检查点抑制剂联合治疗

CTLA-4以及PD-1可调控不同的抑制性通路，研究证实，阻断CTLA-4可以促进T细胞进入肿瘤组织成为肿瘤浸润淋巴细胞（tumor infiltrating lymphocyte，TIL），TIL产生的细胞因子IFN-γ（interferon gamma）反过来具有诱导TME中PD-L1表达的作用[10]，从而增加患者从抗PD-1/L1治疗中获益的机会。在2015年报道的一项Ⅲ期临床试验中，入组约1 000例不可切除的Ⅲ/Ⅳ期黑色素瘤患者，结果表明ipilimumab联合nivolumab治疗组的中位无进展生存期（median progression free survival，mPFS）为11.5个月，与ipilimumab或nivolumab单药组相比分别提高8.6、4.6个月[11]。基于此研究美国食品药品监督管理局（food and drug administration，FDA）批准ipilimumab联合nivolumab用于进展期黑色素瘤的治疗。该联合方案治疗进展期肾癌以及NSCLC的初期数据也显示出较好的疗效[12-13]。

2016年报道的一项Ⅰ期临床试验评估了抗PD-1抗体MEDI0680联合抗PD-L1抗体durvalumab治疗的安全性及最大耐受剂量，初期数据表明该联合方案耐受良好，在入组的30例不同类型的实体瘤患者中，临床获益率约为35%[14]。此外，动物实验证实，PD-1及LAG-3可通过协同作用调节T细胞，增强肿瘤的免疫耐受。双重阻断治疗可以抑制肿瘤生长，促进抗肿瘤免疫[15]。另一种抑制性受体TIM-3的阻断剂在动物模型中也被证实具有抗肿瘤活性，当与抗PD-L1联合应用时这一作用更为明显[16-17]。

2 免疫检查点抑制联合共刺激分子治疗

免疫系统在肿瘤发展过程中是动态变化的，不同共信号分子的表达调控也比较复杂，免疫检查点及共刺激分子在免疫调节中的作用各有不同，且相互补充，联合治疗或许能增强抗肿瘤的疗效[18]。共刺激分子OX-40具有促进T细胞增殖、延长T细胞生存的作用。抗OX-40的激动性抗体联合抗CTLA-4方案在动物肿瘤模型中被研究证实可以显著提高生存率[19]。在对单一治疗无反应的卵巢癌动物模型中抗PD-1联合抗OX-40可引起病灶消退[20]。另一种共刺激分子4-1BB的特异性抗体相关的临床前研究中，抗4-1BB联合CTLA-4阻断、CD40活化或放射治疗时均展现出一定的抗肿瘤活性[6]。

3 传统抗肿瘤治疗相关的综合治疗策略

3.1 基因靶向治疗

基因靶向药物对于含有特定基因突变的患者疗效显著，但耐药性的产生导致缓解期相对短暂。与此相反，免疫检查点抑制剂通过作用于单一靶点，可潜在地释放针对多种不同肿瘤抗原的T细胞，从而产生持久应答[21]。联合治疗或许能够综合两种疗法的优势，产生更为广泛和持久的临床获益。基因靶向治疗通过杀伤肿瘤细胞，导致肿瘤抗原以及新生抗原的释放，这些抗原随后被抗原提呈细胞（antigen presenting cells，APCs）提呈给肿瘤特异性T细胞，诱导其活化，同时上调CTLA-4、PD-1等表达，增加检查点抑制剂的作用靶点，从而提高免疫治疗疗效。此外靶向治疗释放的肿瘤抗原还可以使检查点抑制剂产生的免疫反应更为集中，从而减轻不良反应[22]。

一项表皮生长因子受体（epidermal growth factor receptor，EGFR）抑制剂erlotinib联合抗PD-1抗体nivolumab治疗晚期NSCLC的研究表明，联合用药是克服靶向耐药的一项选择[23]。治疗黑色素瘤的BRAF抑制剂vemurafenib被证实可以提高肿瘤抗原以及MHC分子的表达，使得肿瘤细胞更易于被免疫系统攻击[24]。然而并非所有研究都取得了期望中的结果，一项关于vemurafenib联合ipilimumab的临床试验由于严重的肝毒性而终止[25]。另一项BRAF抑制剂dabrafenib联合ipilimumab的临床试验则表现出较好的耐受性[26]。类似的情况也出现在酪氨酸激酶抑制剂sunitinib联合不同的检查点抑制剂治疗转移性肾癌的研究中[27-28]。上述结果表明在评估联合治疗方案时，药物种类、剂量和（或）给药周期等均需给予特别关注。

3.2 放疗

放疗对免疫系统同样存在多方面的影响。研究表明，放疗可以诱导或增强所有阶段的T细胞应答，包括T细胞激活、转移以及在肿瘤内的应答等。可能的机制包括：促进肿瘤抗原的释放、摄取以及DCs的交叉提呈，促进诱导T细胞及DCs聚集的促炎因子以及趋化因子的产生等[22]。

在临床前研究中，局部放疗联合系统性CTLA-4或PD-1阻断治疗可抑制肿瘤转移[29-30]。动物模型及部分临床个案证实，在给予系统性抗CTLA-4治疗的基础上，局部放疗不仅可以导致已照射区的肿瘤消退，还可引起远处病灶生长延迟甚至消退[31]。这一方案在治疗去势抵抗型前列腺癌的试验中也表现出抗肿瘤活性[32]。此外，共刺激因子OX40抗体被证实与高剂量局部放疗具有协同作用[33]。大量放疗相关联合方案的临床试验正在开展中，将会对未来的研究提供更多有价值的信息[34]。与放疗类似，冷冻疗法等其他肿瘤局部治疗方式也可诱导抗原释放以及局部免疫应答。在动物模型中对原发肿瘤行冷冻消融术联合系统CTLA-4阻断，同样可以抑制远处病灶的生长[35-36]。

3.3 化疗

大部分化学治疗药物在直接杀伤肿瘤细胞的同时，也将通过骨髓抑制等机制导致免疫细胞的减少，因此化疗联合免疫治疗似乎是违反常理的。然而，多项研究证实，化疗也可对免疫系统产生积极影响。化疗诱导的肿瘤细胞免疫原性死亡可导致肿瘤抗原高表达，随后通过活化DCs产生抗肿瘤应答[37]。此外，化疗药物还可以通过影响共信号分子表达，消耗负性免疫调节蛋白等方式，扰乱肿瘤的免疫逃避机制[38]。上述研究结果为化疗联合免疫检查点治疗提供了可能。大量临床前研究评估了不同化疗药物联合免疫检查点抑制剂的疗效[39-40]。一项ipilimumab联合PC方案（紫杉醇+卡铂）治疗晚期NSCLC的Ⅱ期临床试验结果证实了该方案的可行性[41]。而nivolumab联合铂类为基础的化疗方案则表现出不良反应的增加[42]。其他涉及抗PD-1/L1抗体的联合方案也正在评估当中[37]。在共刺激分子激动剂联合化疗的方案中，抗CD40抗体CP-870、CP-893联合吉西他滨治疗进展期胰腺癌的试验表现出较好的临床反应[43]。同样的抗体联合卡铂以及紫杉醇的研究也被证实具有免疫活化的作用[44]。

3.4 肿瘤疫苗

同免疫检查点治疗类似，抗肿瘤疫苗通过活化适应性免疫应答，诱导机体的抗肿瘤免疫。由于肿瘤的免疫逃逸以及抑制性免疫环境的存在，使得肿瘤疫苗的研究和应用相对困难。免疫检查点抑制剂通过打破免疫抑制微环境，影响肿瘤的免疫耐受，从而使肿瘤疫苗充分发挥作用[45]。另一方面，肿瘤疫苗也可活化外周T细胞，促进其浸润至肿瘤组织，从而诱导抗肿瘤免疫以及增强抗PD-1/L1治疗的疗效。此外，与抗CTLA-4联合抗PD-1/L1相比，疫苗相关的联合方案并未显著增加不良反应[46]。

一项Ⅲ期临床试验评估了多肽疫苗GP100联合ipilimumab用于进展期黑色素瘤的治疗，然而并未观察到额外获益[47]，原因尚不明确。DC疫苗联合抗CTLA-4阻断在不同的动物模型中被证实比单一治疗更为有效[2]。由APCs制备的Sipuleucel-T（Provenge）用于难治性前列腺癌的治疗中，病理学证实经Sipuleucel-T治疗的前列腺癌组织中出现了TIL的增加以及PD-1表达[48]。相关临床试验正在评估此类疫苗联合抗PD-1抗体的疗效（NCT01420965）。此外部分临床前试验还证实了经修饰的同源肿瘤细胞疫苗、病毒载体疫苗与免疫检查点抑制剂具有协同作用[2]。

3.5 溶瘤病毒

经基因修饰的溶瘤病毒可以选择性地在肿瘤细胞内复制，导致细胞溶解及死亡，同时释放肿瘤抗原，刺激机体免疫应答[49]。用于黑色素瘤瘤内注射的Talimogene laherparepvec（T-vec）是转染GM-CSF的基因重组单纯疱疹病毒，T-vec联合抗CTLA-4[50]或抗PD-1[51]的临床试验正在开展，初步数据显示出较好的疗效。enadenotucirev是一种可以系统性给药的溶瘤腺病毒疗法，其联合抗PD-1抗体pembrolizumab的临床试验[52]已被报道。

4 总结与展望

免疫检查点抑制剂在越来越多的肿瘤中被证实具有较好的疗效。同时，也需要合理的综合治疗策略使其适用于更多的患者和更广的肿瘤类型。尽管这种治疗方案前景广阔，但是在其应用潜力发挥和广泛临床推广之前，还有许多难题亟待解决。在已经过验证或正在研究的治疗策略中，有很多不仅是无效的，而且会增加不良反应，综合治疗的药物种类，给药剂量、周期以及次序等均会对临床疗效产生影响。此外在缺乏可靠的预测性生物标记物的情况下，免疫治疗的疗效还受到包括肿瘤的组织学类型、患者之间的变异，甚至是同一患者肿瘤内的异质性等多种因素影响。了解肿瘤、免疫系统以及不同治疗方案之间的相互作用机制，将有助于设计出更多新型、有效、合理的肿瘤综合治疗策略。

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作者简介

卫治功 专业方向为肿瘤放射治疗学。
E-mail：839508967@qq.com