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PD-L1 低表达晚期非小细胞肺癌患者药物治疗进展

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摘要：随着免疫治疗的不断发展，晚期非小细胞肺癌患者的诊疗也逐渐精准和完善。免疫检查点抑制剂在程序性死亡配体 1（PD-L1）高表达的非小细胞肺癌患者中的临床获益明显，但在低表达的患者中的效果仍不确切。本文针对 PD-L1 低表达的晚期非小细胞肺癌患者可选择的治疗方案进行综述，旨在为该人群的治疗提供参考和选择。

关键词：程序性死亡配体 1；非小细胞肺癌，晚期；免疫检查点抑制剂；帕博利珠单抗；阿替利珠单抗；卡瑞利珠单抗；纳武利尤单抗；伊匹木单抗；贝伐珠单抗

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Progression of the related anti-tumor drugs in non-small cell lung cancer patients with negative PD-L1 expression

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Abstract: With the continuous development of immunotherapy, the treatment of patients with advanced non-small cell lung cancer (NSCLC) is gradually becoming more and more precise. The clinical benefit of immune checkpoint inhibitors in patients with NSCLC with positive programmed cell death-ligand 1 (PD-L1) expression is obvious, but the effect in patients with negative expression remains inexact. This article reviews the treatment options available for advanced NSCLC patients with negative PD-L1 expression, aiming at providing references and options for their treatment.

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1　免疫检查点抑制剂在非小细胞肺癌(NSCLC)患者中的应用

近些年,NSCLC 诊疗随着免疫抑制剂的临床应用取得了巨大突破,研究发现,癌细胞在肿瘤微环境的背景下通过调节性 T 细胞改变免疫稳态,抑制先天和获得性免疫系统的激活和效应功能,从而逃避免疫监视[1]。免疫检查点抑制剂通过阻断特定的信号通路来恢复和维持免疫系统对肿瘤细胞的功能,其中,细胞毒性 T 细胞在免疫监测和抗肿瘤反应中起重要作用[2]。目前免疫检查点抑制剂主要包括程序性死亡受体 1(programmed cell death 1, PD-1)/程序性死亡配体 1(programmed cell death-ligand 1, PD-L1)抑制剂和细胞毒性 T 淋巴细胞相关蛋白 4(cytotoxic T lymphocyte-associated protein 4, CTLA-4)抑制剂两种药物,而 PD1/PD-L1 抑制剂是研究和应用最广泛的。已经有大量的随机Ⅲ期临床试验证明,抗 PD-1/PD-L1 药物给先前未经治疗的 NSCLC 患者带来了生存获益。

PD-1 最先在京都大学一家研究所中被发现,当其被敲低时,可导致小鼠自身免疫性疾病和异常激活的免疫细胞[3],证实了其免疫抑制作用。PD-L1 是 PD-1 的配体,最先被命名为 B7-H1,目前 PD-1/PD-L1 抑制剂是应用最广泛的免疫治疗类。帕博丽珠单抗和纳武利尤单抗于 2015 年被美国食品药品监督管理局批准用于治疗晚期 NSCLC,是首个用于治疗 NSCLC 的免疫检查点抑制剂[4-5]。

肿瘤细胞复制 PD-1/PD-L1 的调节机制,以保证正常黏膜免受自身免疫攻击,PD-L1 过表达是为了逃避免疫监测,促进肿瘤生长。多种实体瘤类型通过过表达 PD-L1 来利用这一保护屏障,创造免疫抑制的肿瘤微环境。这意味着 PD-L1 的表达对预测免疫治疗的疗效有重要意义。目前这一机制在临床上的应用体现为,免疫抑制剂在 PD-L1 高表达的晚期 NSCLC 中应用广泛,而 PD-L1 低表达的 NSCLC 患者的治疗方案尚无定论[6]。

2　PD-L1 低表达晚期 NSCLC 患者的治疗选择

2.1　PD-1/PD-L1 抑制剂

2.1.1　帕博丽珠单抗(pembrolizumab)　帕博丽珠单抗是一种针对 PD-1 的人源性单克隆抗体,KEYNOTE-024 研究纳入了 305 名先前未先治疗的表皮生长因子受体/碱性磷酸酶(EGFR/ALK)阴性的晚期 NSCLC 患者,这些患者的 PD-L1 表达至少是 50%,该研究中帕博丽珠单抗组和化疗组的中位无进展生存期(progression free survival, PFS)分别为 10.3 个月(95% *CI* 为 6.7~NR)和 6.0 个月(95% *CI* 为 4.2~6.2),证明帕博丽珠单抗较化疗显著延长 PFS 和总生存期(overall survival, OS),且不良事件更少[4],最新 5 年随访数据也支持了这一结论[7]。虽然 KEYNOTE-024 研究证实了帕博丽珠单抗在晚期 NSCLC 中的临床获益,但是数据仅限于 PD-L1 高表达的患者。KEYNOTE-042 将纳入人群范围扩大到了 PD-L1 肿瘤细胞比例评分(tumor cell proportion score, TPS)≥1%的患者,研究证明帕博丽珠单抗单药治疗可作为一线治疗扩展到局部晚期或转移性 NSCLC 患者中,但是亚组分析主要获益人群仍是 PD-L1 高表达(≥50%)的人群[8]。至此,帕博丽珠单抗的受众人群集中于 PD-L1 高表达的患者。随后,KEYNOTE-189 纳入了转移性非鳞状 NSCLC 患者,结果显示无论 PD-L1 表达如何,一线帕博丽珠单抗联合化疗都可显著改善 OS 和 PFS,安全性和耐受性可控[9]。在 KEYNOTE-407 研究纳入的转移性鳞状 NSCLC 患者中,帕博丽珠单抗联合化疗在 OS 显著优于安慰剂联合化疗,两组中位 OS 分别为 17.1 个月(95% *CI* 为 14.4~19.6)和 11.6 个月(95% *CI* 为 10.1~13.7),且无论 PD-L1 表达状态如何,免疫联合化疗均具有显著的生存获益[10]。最新的 5 年随访数据也支持了这一结论[11]。至此,帕博丽珠单抗的获益人群从 PD-L1 高表达患者扩展到所有 PD-L1 表达的患者,尽管帕博丽珠单抗联合化疗适用于 PD-L1 阴性、低表达的患者,PD-L1 低表达的 NSCLC 患者也有了从免疫治疗中获益的可能性,但是亚组分析主要受益者仍然是 PD-L1≥50%的患者。

2.1.2　阿替利珠单抗(atezolizumab)　IMpower 110 研究中,阿替利珠单抗组的中位 OS 在 PD-L1 高表达的 EGFR 和 ALK 野生型的 NSCLC 中比化疗组长 7.1 个月(20.2 个月 *vs* 13.1 个月),证实无论组织学类型如何,阿替利珠单抗在 PD-L1 表达高的患者中的 OS 均显著长于铂类化疗[12]。IMpower 150 研究将纳入的患者随机分成三组,分别是阿替利珠单抗联合卡铂和紫杉醇(ACP),贝伐珠单抗(bevacizumab)联合卡铂

和紫杉醇(BCP)和阿替利珠单抗联合贝伐珠单抗联合卡铂和紫杉醇(ABCP),结果显示 ABCP 组的中位 PFS 比 BCP 长(8.3 个月 *vs* 6.8 个月),在整个意向治疗人群(包括 EGFR 或 ALK 基因改变的患者)以及 PD-L1 表达低或阴性的患者中,ABCP 组的 PFS 也比 BCP 长。这是首个在 PD-L1 低表达的患者中,将免疫联合化疗和抗血管生成联合化疗两种方案进行疗效对比,但亚组分析中 TC0/IC0 患者使用 ACP 方案或 BCP 方案,OS 没有显著差异[13-14]。阿替利珠单抗、贝伐珠单抗、卡铂和紫杉醇的四药联用方案虽然可能对 PD-L1 低表达患者提供获益,但是仍需要更多更大的临床试验去验证。

2.1.3　新兴的国产免疫抑制剂　我国自主研发的 PD-1/PD-L1 单抗也在免疫治疗时代大放异彩。CameL 是一项对比卡瑞利珠单抗(camrelizumab)联合化疗和单纯化疗一线治疗晚期或转移性非鳞状 NSCLC 的Ⅲ期临床研究,接受卡瑞利珠单抗联合化疗的患者 PFS 显著延长(9.6 个月 *vs* 0.9 个月)[15],CameL-sq 则是在鳞状 NSCLC 患者中开展的研究,不仅证实 PFS 和 OS 的获益,还刷新了死亡风险的下降纪录,为晚期鳞癌的患者带来了曙光[16]。ORIENT 11 和 RATIONALE 304 研究分别表明信迪利单抗(sintilimab)联合化疗组和替雷利珠单抗(tislelizumab)联合化疗组相较于单纯化疗,显著延长 PFS 且安全性可控[17-18]。舒格利单抗(sugemalimab)是一种 PD-L1 抑制剂,GEMSTONE 302 研究评估舒格利单抗联合化疗治疗转移性鳞状或非鳞状 NSCLC 患者的疗效和安全性,发现舒格利单抗组的 PFS 明显更长(6.9 个月 *vs* 7.5 个月),该研究证实无论 PD-L1 表达如何,舒格利单抗联合化疗在未经治疗的转移性 NSCLC 患者中均显示出对 PFS 的改善,这为 PD-L1 低表达的患者增加了新的治疗选择[19]。

2.2　*双免治疗*　PD-1/PD-L1 抑制剂已经在肺癌免疫治疗中成为标准治疗,而 CTLA4 作为一个更上游的免疫检查点,其在临床应用尚在进一步探索。Checkmate 9LA 是一项探索纳武利尤单抗(nivolumab)联合伊匹木单抗(ipilimumab)联合化疗和单纯化疗在晚期 NSCLC 患者中疗效的Ⅲ期研究,其在亚洲人群中的亚组分析显示,纳武利尤单抗加伊匹木单抗联合化疗提高了亚洲人群的疗效,并且安全性可控[20],且该研究表明无论 PD-L1 表达如何,患者均可获益。Checkmate 227 的最新生存数据公布,显示在转移性 NSCLC 患者中,纳武利尤单抗和伊匹木单抗的联合治疗与化疗相比有更高的 5 年生存率,且无论 PD-L1 表达如何,都能获得长期且持久的临床获益。以上两个临床研究均表明双免治疗有成为晚期 NSCLC 患者标准治疗的可能,且均无论 PD-L1 表达情况,因此其在 PD-L1 低表达的晚期 NSCLC 患者中的应用值得进一步探索。

2.3　*抗血管生成联合化疗方案*　贝伐珠单抗是一种针对血管内皮生长因子的单克隆抗体,在免疫治疗兴起之前,贝伐珠单抗联合化疗广泛应用于晚期或转移性 NSCLC 患者。BEYOND 是一项研究一线贝伐珠单抗联合铂类双药在晚期或者转移性 NSCLC 患者的临床意义的多中心的Ⅲ期研究,结果显示贝伐珠单抗联合化疗的 PFS 长于单纯化疗组(9.2 个月 *vs* 6.5 个月)[21],在卡铂/紫杉醇的基础上联用贝伐珠单抗耐受性良好,对中国晚期非鳞状 NSCLC 患者产生了具有临床意义的治疗益处。目前,ECOG 4599[22] 和 BEYOND[21] 均表明贝伐珠单抗联合化疗治疗初治的驱动基因阴性晚期非鳞状 NSCLC 患者的 OS 较单独化疗显著改善。因既往对 PD-1/PD-L1 的认识不深入,因此大部分患者的 PD-L1 表达情况不明,结合其临床数据,贝伐珠单抗联合化疗是否对 PD-L1 低表达的患者具有临床获益,尚需要研究。

3　总　结

目前关于 PD-L1 低表达的晚期 NSCLC 患者的标准治疗方案尚无定论,也无大规模Ⅲ期临床研究证实免疫治疗或抗血管生成药物联合治疗或其他治疗方案对 PD-L1 低表达和驱动基因阴性 NSCLC 患者的疗效。仅有少部分荟萃分析将大型研究中的 PD-L1 低表达的亚组之间进行不同治疗方案的疗效对比[23-25],其中一项荟萃分析发现免疫联合化疗和抗血管生成联合化疗方案对 PD-L1 低表达患者的疗效相当,因此对于有免疫治疗禁忌证的患者,贝伐珠单抗联合化疗可作为替代选择。结合目前的大型临床研究的结果公布,PD-L1 低表达的 NSCLC 患者可考虑免疫联合化疗,双免和抗血管生成联合化疗等多种方案,但是否存在最优选择以及一线标准方案的选择未来值得开展头对头的研究去探索。

利益冲突　无

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Anti-tumor drug in the treatment of non-small cell lung cancer with negative PD-L1 expression

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1 Application of checkpoint inhibitors in NSCLC patients

With the clinical application of checkpoint inhibitors, great breakthroughs have been made in the diagnosis and treatment in recent years. It has been found that tumor cells can change the immune homeostasis through regulatory T cells in the tumor microenvironment (TME), inhibit the activation and effector functions of innate and acquired immune systems, and thus evade immune surveillance [1]. Checkpoint inhibitors can restore and maintain the immune system's function against tumor cells by blocking specific signaling pathways, in which cytotoxic T lymphocyte play an important role in immune monitoring and anti-tumor response [2]. For now, the checkpoint inhibitors mainly include programmed death 1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibitors and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and PD-1/PD-L1 inhibitors are the most popular in recent research and clinical application. Numerous randomized phase III clinical trials have proved that anti PD-1/PD-L1 drug can bring survival benefits to previously untreated NSCLC patients.

PD-l was identified in 1992 by Honjo and colleagues at Kyoto University. They found that the knock-down of PD-1 can led to autoimmune diseases and abnormally activated immune cells in mice [3], which confirmed the immunosuppression effect of PD-1. PD-L1 is the ligand of PD-1, which was named as B7-H1 at first. PD-1/PD-L1 inhibitors are the most widely used immunosuppressant. pabolizumab and navurizumab were approved by the US Food and Drug Administration (FDA) in 2015 for the treatment of advanced NSCLC, making them the first immune checkpoint inhibitors to be used for the treatment of NSCLC [4-5].

The regulatory mechanism of PD-1/PD-L1, which is in order to ensure the normal mucosa is protected from autoimmune attacks, can be replicated by tumor cells. Overexpression of PD-L1 can evade immune monitoring and promote tumor growth. Many solid tumors use overexpression of PD-L1 to create an immunosuppressive TME.

Which means the expression of PD-L1 has a great significance in the predicting the clinical efficacy of immunotherapy. The clinical application of this mechanism is reflected in the widespread use of immunosuppressants in advanced NSCLC with high PD-L1 expression, while the treatment plan for NSCLC patients with low PD-L1 expression is still uncertain [6].

2 Treatment options for patients with low expression of PD-L1 in advanced NSCLC

2.1 PD-1/PD-L1 inhibitors

2.1.1 Pembrolizumab

Pembrolizumab is a humanized monoclonal anti-PD1 antibody that has been extensively investigated in numerous malignancies. KEYNOTE-024 included 305 patients with advanced NSCLC who were previously untreated and had negative epidermal growth factor receptor (EGFR)/alkaline phosphatase (ALK) expression, the expression of PD-L1 in these patients were at least 50%. The median progression free survival (PFS) was 10.3 months (95%CI:6.7-NR) and 6.0 months (95%*CI*: 4.2-6.2) in the Pembrolizumab group and chemotherapy group, respectively. The results proved that Pembrolizumab can significantly prolong PFS and overall survival (OS) compared to chemotherapy, with fewer adverse events [4], and the latest 5-year follow-up data also supports this conclusion [7]. Although the KEYNOTE-024 confirmed the clinical benefits of Pembrolizumab in advanced NSCLC, the data is limited to patients with high PD-L1 expression. KEYNOTE-042 expanded the inclusion population to patients with a PD-L1 tumor cell proportion score (TPS) of ≥ 1%, and the results showed that Pembrolizumab monotherapy can be extended as a first-line treatment to locally advanced or metastatic NSCLC patients, but the main beneficiaries of subgroup analysis are still those with PD-L1 high-expression (≥ 50%) [8]. Thus, the target audience of Pembrolizumab is concentrated in patients with high expression of PD-L1. Then, KEYNOTE-189 was included in patients with metastatic non-squamous NSCLC, and the results showed that regardless of PD-L1 expression, first-line Pembrolizumab combined with chemotherapy significantly improved OS and PFS, with controllable safety and tolerance [9]. Among patients with metastatic squamous cell carcinoma NSCLC included in the KEYNOTE-407, the combination of Pembrolizumab and chemotherapy was significantly superior to placebo combination chemotherapy in OS [17.1 months (95%*CI*:14.4-19.6) *vs* 11.6 months (95%*CI* 10.1-13.7)]. The results also showed that immunotherapy combined with chemotherapy has significant survival benefits regardless of PD-L1 expression status [10]. The latest 5-year follow-up data also supports this conclusion [11]. Thus, the beneficiary population of Pembrolizumab has expanded from patients with high-expression PD-L1 to all patients with PD-L1 expression. Although Pembrolizumab combined with chemotherapy is suitable for patients with negative and low PD-L1 expression, and NSCLC patients with low PD-L1 expression also have the possibility of benefiting from immunotherapy, the main beneficiaries of subgroup analysis are still patients with PD-L1 ≥ 50%.

2.1.2 Atezolizumab

IMPower 110 showed that, in the patients with PD-L1 overexpressing EGFR and ALK wild-type NSCLC, the median OS of the atelizumab group was longer in compared to chemotherapy (20.2 months vs 13.1 months), confirming that regardless of histological type, the OS of atelizumab in PD-L1 overexpressing patients was significantly longer than that of platinum chemotherapy [12]. The patients included in the IMpower 150 were randomly divided into three groups: artelizumab combined with carboplatin and paclitaxel (ACP), bevacizumab combined with carboplatin and paclitaxel (BCP), and artelizumab combined with bevacizumab combined with carboplatin and paclitaxel (ABCP), the results showed that the median PFS of the ABCP group was longer than that of BCP (8.3 months vs 6.8 months), and the ABCP group also had longer PFS than BCP in the entire intended treatment population (including patients

with EGFR or ALK gene mutation) and patients with low or negative PD-L1 expression. It is worth noting that this is the first time that immune combination chemotherapy and anti-angiogenic combination chemotherapy are compared for efficacy in patients with low PD-L1 expression. However, there was no significant difference in OS between TC0/IC0 patients using ACP or BCP regimens in subgroup analysis [13, 14]. Although the combination of atelizumab, bevacizumab, carboplatin and paclitaxel may benefit patients with low PD-L1 expression, more and larger clinical trials are still needed to verify it.

2.1.3 Emerging Chinese made immunosuppressants

The independently developed PD-1/PD-L1 monoclonal antibody in China also play an important role in the era of immunotherapy. CameL is a phase III clinical trial to compare camrelizumab combined with chemotherapy and chemotherapy alone in the first-line treatment of advanced or metastatic non-squamous NSCLC. Patients received camrelizumab combined with chemotherapy had a significant prolongation of PFS (9.6 months vs 0.9 months) [15]. While CameL-sq was a study conducted in patients with squamous NSCLC, which not only confirmed the benefits of PFS and OS, but also set a new record for a decrease in mortality risk, which brought the dawn to patients with advanced squamous cell carcinoma [16].

ORIENT 11 and RADIONALE 304 studies showed that both the combination chemotherapy with sintilimab or with tislizumab can significantly prolong PFS and have controllable safety compared to chemotherapy alone [17,18].

Sugemalimab is a PD L1 inhibitor. The GEMSTONE 302 evaluated the efficacy and safety of Sugemalimab combined with chemotherapy in the treatment of patients with metastatic squamous or non-squamous NSCLC, and found that the PFS of the Sugemalimab group was significantly longer (6.9 months vs 7.5 months). This study confirmed that regardless of PD-L1 expression, Shuglizumab combined with chemotherapy showed significant improvement in PFS in untreated patients with metastatic NSCLC, adding new treatment options for patients with low PD-L1 expression [19].

2.2 Dual immunotherapy

PD-1/PD-L1 inhibitors have become the standard treatment in lung cancer immunotherapy, while CTLA4, as a more upstream immune checkpoint, its clinical application is still being further explored.

Checkmate 9LA is a phase III study exploring the efficacy of nivolumab combined with ipilimumab combined with chemotherapy and chemotherapy alone in advanced NSCLC patients. Its subgroup analysis in the Asian population showed that the combination of nivolumab+ipilimumab and chemotherapy improved the efficacy of the Asian population and the safety was controllable [20], and this study showed that patients can benefit from it regardless of PD-L1 expression.

The latest survival data from Checkmate 227 has been released. It showed that, in patients with metastatic NSCLC, the combination therapy of navulizumab and ipilimumab had a higher 5-year survival compared to chemotherapy, and achieved long-term and long-lasting clinical benefits regardless of PD-L1 expression.

The above two clinical studies indicate that dual immunotherapy has the potential to become the standard treatment for advanced NSCLC patients, regardless of PD-L1 expression. Therefore, its application in advanced NSCLC patients with low PD-L1 expression deserves further exploration.

2.3 Antiangiogenic combined chemotherapy

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor. Before the rise of immunotherapy, bevacizumab combined with chemotherapy was widely used in patients with advanced or metastatic NSCLC.

BEYOND is a multicenter phase III trial to study the clinical significance of first-line bevacizumab combined with platinum in patients with advanced or metastatic NSCLC. The results showed that the PFS of bevacizumab combined with chemotherapy was longer than that of chemotherapy alone (9.2 months vs 6.5 months) [21], and the combination of bevacizumab on the basis of carboplatin/paclitaxel is well tolerated, there have been clinically significant therapeutic benefits for Chinese patients with advanced non-squamous NSCLC.

At present, both ECOG 4599 and BEYOND [22] show that, in advanced non-squamous NSCLC patients with negative driver gene, bevacizumab combined with chemotherapy had a higher OS than chemotherapy alone. Due to a lack of in-depth understanding of PD-1/PD-L1 in the past, the expression of PD-L1 in most patients is unknown. Therefore, whether bevacizumab combined with chemotherapy has clinical benefits for patients with low PD-L1 expression still needs to be studied.

3 Summary

At present, there is no consensus on the standard treatment regimen for advanced NSCLC patients with low PD-L1 expression, and there are no large-scale Phase III clinical trial confirming the efficacy of immunotherapy or combination therapy with antiangiogenic drugs or other treatment regimens in patients with low PD-L1 expression and negative driver genes in NSCLC. Only a few meta-analyses have compared the efficacy of different treatment regimens between subgroups with low PD-L1 expression in large clinical trials [23-25]. One of the meta-analyses found that the efficacy of combined immune-chemotherapy and anti-angiogenesis combined with chemotherapy for patients with low expression of PD-L1 was similar, so bevacizumab combined chemotherapy could be an alternative for patients with contraindications to immunotherapy.

Based on the results of current large-scale clinical studies, NSCLC patients with low expression of PD-L1 can consider multiple regimens such as immune-chemotherapy, dual immunotherapy, and anti-angiogenic combination chemotherapy. However, whether there is an optimal choice and the selection of frontline standard regimens is worth exploring through head-to-head research in the future.