· 研究进展 ·

程序性死亡受体 1 抑制剂联合化疗在晚期胃癌中的研究进展

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摘要：晚期胃癌患者的生存率低，生活质量差。尽管晚期胃癌的化疗方案在不断发展与改善，晚期胃癌患者的生存率仍然较低。目前，晚期胃癌不仅综合治疗手段十分有限，后线治疗手段也十分缺乏，因而亟需针对晚期胃癌的有效治疗方案。近年来，随着对肿瘤免疫学的深入研究，免疫治疗成为人们关注的焦点。程序性死亡受体-1（PD-1）抑制剂作为一种免疫抑制剂，将其与化疗结合起来，不仅能最大限度地发挥免疫抑制剂的临床活性，还可以建立持久的免疫反应。目前，PD-1 抑制剂联合铂类化疗已在晚期胃癌的临床研究中显示出较高的临床应用价值。本文对晚期胃癌的 PD-1 抑制剂联合化疗方案的研究进展进行综述，旨在为其临床应用提供依据。

关键词：晚期胃癌；程序性死亡受体 1 抑制剂；免疫治疗；化疗；信迪利单抗；帕博利珠单抗；纳武利尤单抗；卡瑞利珠单抗；替雷利珠单抗

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Research progress of programmed cell death protein-1 inhibitor combined with chemotherapy in advanced gastric cancer

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Abstract: The survival rate and quality of life of patients with advanced gastric cancer are low. Despite the continuous development and improvement of chemotherapy regimens for advanced gastric cancer, the survival rate of patients with advanced gastric cancer is still low. At present, not only are comprehensive treatment methods very limited for advanced gastric cancer, but there is also a lack of posterior treatment methods. Therefore, there is an urgent need for effective treatment plans for advanced gastric cancer. In recent years, with the in-depth research on tumor immunology, immunotherapy has become a focus of attention. Programmed cell death protein-1 (PD-1) inhibitor, as an immunosuppressive drug, combined with chemotherapy, can not only maximize the clinical activity of immunosuppressive drug, but also establish a lasting immune response. At present, the combination of PD-1 inhibitors and platinum chemotherapy has shown high clinical application value in clinical research of advanced gastric cancer. This article reviews the research progress of PD-1 inhibitors combined with chemotherapy for advanced gastric cancer, aiming to provide a basis for clinical application.

Keywords: Advanced gastric cancer; Programmed cell death protein-1 inhibitor; Immunotherapy; Chemotherapy; Sintilimab; Pembrolizumab; Nivolumab; Camrelizumab; Tislelizumab

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胃癌发病率居全球第五，死亡率居全球第四[1]，根据 2022 年 2 月国家癌症中心最新发表的数据表明，我国胃癌的发病率和死亡率均居所有恶性肿瘤的第三位。晚期胃癌预后更差，中位总生存期（overall survival, OS）仅为 10~12 个月[2]。目前，晚期胃癌的综合治疗手段十分有限，以铂类和氟尿嘧啶类药物为主的一线化疗失败后，二线治疗效果的个体差异大，缺乏有效的后线治疗手段。近年来，随着对肿瘤免疫学的深入研究，免疫治疗成为人们关注的焦点。免疫检查点抑制剂是肿瘤免疫治疗的一种新方法[3]，该疗法通过阻断肿瘤细胞对 T 细胞的抑制作用来降低免疫系统对肿瘤细胞的耐受性，从而提高 T 细胞对肿瘤细胞的有效识别和根除[4]。程序性死亡受体-1（programmed cell death protein-1, PD-1）抑制剂作为一种免疫检查

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点抑制剂,与免疫细胞上的 PD-1 受体特异性结合,阻断免疫细胞上的 PD-1 受体与肿瘤细胞上的程序性死亡蛋白配体(programmed cell death-ligand, PD-L)1 发生特异性结合,减少抑制性 T 细胞凋亡,提高 T 细胞对肿瘤细胞的识别和清除能力,从而抑制肿瘤的免疫逃逸。目前,PD-1 抑制剂单药治疗晚期胃癌患者的疗效已被证实,并得到多个试验的支持。然而,仍然有 30%~60%的患者对 PD-1 抑制剂没有反应,这可能与 T 细胞排斥或衰竭、T 细胞运输不足以及许多免疫抑制因子在肿瘤微环境中积累有关[5]。因此迫切需要可以改善疗效和长期有效的新疗法。将 PD-1 抑制剂与化疗结合,一方面,铂类化疗可以提高肿瘤细胞对 PD-1 抑制剂的敏感性,从而使 PD-1 抑制剂更容易与免疫细胞上的 PD-1 受体结合。另一方面,铂类化疗可能会上调肿瘤组织中 PD-L1 的表达,增加免疫细胞上的 PD-1 受体与肿瘤细胞上的 PD-L1 配体结合的机率,进而促进肿瘤的免疫逃逸,然而这种负性免疫调控可以通过 PD-1 抑制剂的作用途径抵消[6]。目前,PD-1 抑制剂联合铂类化疗已在晚期胃癌的临床研究中显示出较高的临床应用价值。本文对晚期胃癌的 PD-1 抑制剂联合化疗方案的研究进展进行综述,旨在为晚期胃癌的免疫治疗联合化疗提供依据。

1　信迪利单抗联合化疗

信迪利单抗是一种高选择性的单克隆免疫球蛋白 G4(immunoglobulin G4, IgG4)抗体,可抑制 PD-1 与其配体之间的相互作用,具有强烈的抗肿瘤效应[7]。在一项信迪利单抗联合化疗[卡培他滨和奥沙利铂(CapeOX)]一线治疗局部晚期胃/胃食管交界处(gastric/gastroesophageal junction,G/GEJ)腺癌的安全性和有效性研究中[8],对 20 例患者进行了有效性和安全性评估,最终有 17 例(85%)患者达到了部分缓解(partial response, PR),3 例(15%)患者达到疾病稳定(stable disease, SD),疾病控制率(disease control rate, DCR)高达 100%,中位无进展生存期(progression-free survival, PFS)为 7.5 个月,6 个月和 12 个月的总生存率分别为 100%和 68%,使用信迪利单抗联合 CapeOX 方案在治疗晚期不可切除的转移性 G/GEJ 腺癌患者的客观缓解率(objective remission rate, ORR)为 85%。另一项研究中评估了信迪利单抗联合 CapeOX 在晚期可切除 G/GEJ 腺癌患者的安全性和有效性[9],对 36 名 cT3/4NxM0 的晚期可切除 G/GEJ 腺癌患者进行了新辅助治疗,R0 切除率为 97.2%,有 7 例(19.4%)患者的病检结果中找不到恶性肿瘤的组织学依据,即达到病理完全缓解(pathological complete response, PCR),17 名(47.2%)患者病检中残留肿瘤细胞<10%,即达到主要病理反应(major pathological reaction, MPR)。同样有研究将信迪利单抗联合 CapeOX 方案应用于局部晚期胃癌的新辅助治疗中,共纳入 30 例患者,R0 切除率为 100%,PCR 率为 33.3%,MPR 率为 63.3%,ORR 和 DCR 分别为 70%和 100%。22 例(73.3%)患者观察到总 TNM 分期降级[10]。由此可见,信迪利单抗联合化疗方案在 G/GEJ 腺癌的一线治疗中具有良好的抗肿瘤活性。

也有研究表明信迪利单抗联合白蛋白结合型紫杉醇在晚期胃癌或转移性胃癌的二线治疗具有良好的抗肿瘤活性和可接受的安全性[11]。该研究通过回顾性分析,招募了 39 例患者,并进行反应评估。其中没有人达到完全缓解(complete relief, CR),15 例患者达到 PR,16 例患者达到 SD,9 例患者出现了疾病进展(progressive disease, PD)。ORR 和 DCR 分别为 38.5%和 79.5%。中位 PFS 为 5.4 个月(95%*CI*:3.072~7.728)。另一项研究发现在腹腔热疗的基础上,与单独使用紫杉醇相比,信迪利单抗联合紫杉醇静脉化疗方案对存在腹膜转移的胃癌患者来说,是一种可以改善生活和延长生存期的有效替代方案[12]。还有研究表明信迪利单抗联合白蛋白结合型紫杉醇和替吉奥的三联药物方案在晚期胃癌的辅助治疗中将会是一种很有希望的治疗组合[13]。因此,信迪利单抗联合化疗在晚期胃癌的二线或后线治疗中的作用也是非常可观的。

2　帕博利珠单抗联合化疗

帕博利珠单抗是一种人源化、高亲和力的 IgG4-κ 单克隆抗 PD-1 抗体,可与 PD-1 结合,防止 PD-1 与 PD-L1 和 PD-L2 的相互作用[14],并被国家综合癌症网络推荐为高度微卫星不稳定(high microsatellite instability, H-MSI)或错配修复缺陷肿瘤患者的首选二线治疗,并作为 PD-L1 阳性[综合阳性评分(combined positive score, CPS)≥1]肿瘤患者的三线治疗[15]。目前,帕博利珠单抗已在多种恶性肿瘤中展开研究,并被美国食品和药品管理局批准用于治疗晚期黑色素瘤和非小细胞肺癌[16]。帕博利珠单抗在晚期 G/GEJ 腺癌患者中已被证明具有可控的安全性和良好的抗肿瘤活性[17]。已有 25%~65%的胃癌报道,PD-L1 的表达与肿瘤的浸润深度、肿瘤大小、淋巴结转移和中位 OS 较短有关[18-20]。在 KEYNOTE-062[21]试验中,将帕博利珠单抗单药治疗、帕博利珠单抗联合化疗与安慰剂联合化疗在一线进展期胃癌中进行了对比,结果表明,在 CPS≥1 或者更高的组中,帕博利珠单抗单药治疗与安慰剂联合化疗相比,中位 OS 差异不大。帕博利珠单抗联合化疗与安慰剂联合化疗的中位 OS 也相差无几。在 CPS≥10 组中,帕博利珠单抗单药治疗与安慰剂联合化疗相比,显著延长了患者的中位 OS(中位 OS 分别为 17.4 个月、10.8 个月),而帕博利珠单抗联合化疗与安慰剂联合化疗相比,中位 OS 差异不大。MSI 的状态可能是预测晚期 G/GEJ 癌症患者中帕博利珠单抗治疗效果的一个生物标志物,对 H-MSI 的患者,在 CPS≥1 或者更高的组中,对比单纯化疗,使用帕博利珠单抗单药治疗或帕博利珠单抗联合化疗均显著延长了患者的中位 OS[22]。在 KEYNOTE-811[23]试验中也表明帕博利珠单抗与曲妥珠单抗和化疗联合使用在人体表皮生长因子受体-2(human epidermal growth factor receptor-2, HER-2)阳性的 G/GEJ 腺癌患者的一线治疗中提供了显著的临床益处和可控的毒性。除此之外,KEYNOTE-659[24]试验也证明了帕博利珠单抗联合化疗[替吉奥和奥沙利铂(SOX)]在晚期 G/GEJ 的一线治疗中具有良好的抗肿瘤活性和可控的安全性。目前,KEYNOTE-859[25]试验也正在研究帕博利珠单抗联合化疗在晚期 G/GEJ 腺癌患者一线治疗中的作用。因此,帕博利珠单

抗联合化疗在晚期 G/GEJ 腺癌患者的一线治疗中具有广阔的应用前景。

虽然 KEYNOTE-059 和 KEYNOTE-061 等系列研究结果证明,帕博丽珠单抗在晚期 G/GEJ 腺癌患者的二线或后线治疗中卓有成效,但目前尚没有将帕博利珠单抗联合化疗应用于晚期 G/GEJ 腺癌的二线或后线治疗中的报道。期望在不久的将来,帕博利珠单抗联合化疗可以为既往接受过治疗的晚期 G/GEJ 腺癌患者的治疗带来希望。

3　纳武利尤单抗联合化疗

纳武利尤单抗是一种全人类 IgG4,可延长晚期黑色素瘤、非小细胞肺癌和非霍奇金淋巴瘤患者的进展时间,提高患者的生存率[26]。2014 年,美国食品药品监督管理局批准了针对 PD-1 的单克隆抗体纳武利尤单抗用于治疗晚期黑色素瘤和肺鳞癌[27]。在 ATTRACTION-02[28] 的研究中,首次证明了纳武利尤单抗在进展期 G/GEJ 腺癌的患者中具有可控的安全性和良好的抗肿瘤活性。纳武利尤单抗已经被几个国家批准为治疗晚期 G/GEJ 癌症的第三线或后线治疗方案[29],并于 2021 年 4 月获得 FDA 批准,与氟尿嘧啶和铂类化疗联合用于晚期或转移性胃癌患者的一线治疗[30]。在 CheckMate 649 试验中将纳武利尤单抗联合 CapeOX 化疗方案或联合亚叶酸钙、氟尿嘧啶和奥沙利铂化疗方案与单纯化疗方案在一线治疗晚期 G/GEJ 腺癌的患者进行了直接对比,结果表明,与使用单纯化疗方案的患者相比,使用纳武利尤单抗联合化疗的患者有着更长的生存期和更高的生活质量[31]。在对 CheckMate 649 试验进行了更长期的观察和随访后,更加证实先前的研究结果:与单纯化疗的相比,纳武利尤单抗联合化疗具有长期临床上有意义的 OS 和 PFS 获益、可获得持久的抗肿瘤反应、使患者具有相对健康的生活质量以及可接受的安全性[32]。ATTRACTION-04[29] 试验中评估了纳武利尤单抗联合 SOX/CapeOX 化疗方案治疗先前未经治疗、无法切除、晚期或复发性 G/GEJ 腺癌患者的安全性和疗效,结果表明纳武利尤单抗联合 SOX/CapeOX 化疗方案在晚期 G/GEJ 腺癌患者一线治疗中的疗效显著。更有研究指出,纳武利尤单抗联合化疗代表了我国 HER-2 阴性的晚期 G/GEJ 患者的新标准一线治疗[33]。

纳武利尤单抗联合化疗不仅被推荐用于晚期胃癌患者的一线治疗中,在晚期胃癌患者的二线治疗中也具有不可或缺的作用。在一项Ⅰ/Ⅱ期临床试验中将纳武利尤单抗与紫杉醇和雷莫西尤单抗联合用于既往化疗难治的晚期胃癌患者中,结果显示:入组的 43 例患者中 12 个月和 18 个月的总生存率分别为 55.8%和 32.1%,高于使用雷莫西尤单抗联合紫杉醇的总生存率[34]。由此可以看出,纳武利尤单抗联合化疗在晚期胃癌的二线乃至是后线治疗中也将发挥巨大作用。

4　卡瑞利珠单抗联合化疗

卡瑞利珠单抗(艾瑞卡®)是江苏恒瑞医药开发的一种 PD-1 抑制剂,最近在中国获得批准,用于治疗复发或难治性经典霍奇金淋巴瘤[35]。卡瑞利珠单抗可在多种肿瘤中表现出广泛的抗肿瘤活性,在我国晚期 G/GEJ 癌症患者中也显示出了显著的疗效[36]。有研究表明卡瑞利珠单抗联合阿帕替尼在晚期 G/GEJ 腺癌患者的毒性可控[37]。在晚期 G/GEJ 腺癌患者的治疗方案中,卡瑞利珠单抗联合化疗的重要性越来越大。一项研究评估了先将卡瑞利珠单抗与 CapeOX 联合化疗 4~6 个疗程后再用卡瑞利珠单抗联合阿帕替尼一线治疗晚期 G/GEJ 腺癌的安全性和有效性[38],结果显示该联合方案的 ORR 为 58.3%,中位缓解持续时间为 5.7 个月,中位 OS 为 14.9 个月,中位 PFS 为 6.8 个月。还有研究将卡瑞利珠单抗联合化疗在晚期 G/GEJ 腺癌患者一线治疗中的疗效与单独化疗的疗效进行对比[39],结果显示联合治疗组的 ORR 和 DCR 均优于单独化疗组,联合组的 PFS 显著长于化疗组。对 HER-2 阳性的晚期胃癌患者,曲妥珠单抗联合化疗是标准的一线治疗方案。有研究将卡瑞利珠单抗联合曲妥珠单抗和化疗与曲妥珠单抗联合化疗在 HER-2 阳性晚期胃癌的一线治疗中进行了对比,结果显示卡瑞利珠单抗联合组的治疗效果显著优于曲妥珠单抗联合化疗组[40]。在晚期胃癌的新辅助治疗中,Tang 等[41] 将卡瑞利珠单抗与同步放化疗联用取得了显著的效果。Lin[42] 等将卡瑞利珠单抗与紫杉醇和替吉奥化疗方案用于 T3 期浆膜浸润胃癌患者的新辅助治疗中,结果显示,与 SOX 方案和紫杉醇联合替吉奥方案相比,卡瑞利珠单抗联合化疗方案不仅可以降低肿瘤分期,还可显著提高患者的 PCR 率。目前,还有一些卡瑞利珠单抗联合化疗在晚期胃癌一线治疗中的研究正在进展之中,如 Wang 等[43] 和 Pan 等[44] 的卡瑞利珠单抗与低剂量阿帕替尼和 SOX 联合治疗方案,Zhou 等[45] 的卡瑞利珠单抗联合卡培他滨化疗方案以及 Zheng 等[46] 的围术期卡瑞利珠单抗联合 SOX 治疗方案。

卡瑞利珠单抗联合化疗不仅在晚期 G/GEJ 腺癌患者的一线治疗中应用十分广泛,对晚期 G/GEJ 腺癌患者的二线或后线治疗也有极其重要的作用。在一项Ⅱ期临床试验中将卡瑞利珠单抗与阿帕替尼和替吉奥联用用于晚期 G/GEJ 的二线治疗,共纳入 24 例患者,ORR 为 29.2%,中位 PFS 为 6.5 个月。Dong 等[47] 正在研究使用卡瑞利珠单抗联合多西紫杉醇和替吉奥化疗方案在 EB 病毒阳性、错配修复缺陷且 CPS≥5 的Ⅲ期胃癌的术后辅助治疗中的安全性和有效性,期望研究的结果可以为晚期 G/GEJ 腺癌患者的二线或后线治疗带来希望。

5　替雷利珠单抗联合化疗

替雷利珠单抗是一种抗 PD-1 单克隆 IgG4 抗体,作为一种具有免疫治疗作用的抗肿瘤药物,替雷利珠单抗在 2019 年 12 月被中国批准用于治疗二线或后线化疗后复发或难治的经典霍奇金淋巴瘤患者[48]。替雷利珠单抗在多种实体瘤中表现出持久的抗肿瘤效应,其中就包括晚期 G/GEJ 腺癌[49]。替雷利珠单抗联合化疗在晚期 G/GEJ 腺癌中的研究也正在进展之中,有研究将替雷利珠单抗与 CapeOX 联合一线治疗晚期 G/GEJ 腺癌患者,结果显示替雷利珠单抗联合化疗在晚

期 G/GEJ 腺癌患者中的 ORR 为 DCR 分别为 46.7% 和 80%[50]。与传统化疗相比,替雷利珠单抗联合化疗不仅可以提高晚期 G/GEJ 腺癌患者的生存率,还能延长患者的生存时间[51]。一项Ⅱ期临床研究将替雷利珠单抗与化疗联合用于晚期 G/GEJ 腺癌的新辅助治疗中,32 例患者入组,最终发现有 17 名(53.1%)治疗后达到 MPR,8 名(25%)患者治疗后达到 PCR,1 年总生存率和 1 年无复发生存率更是分别高达 91.4%和 90%[52]。目前尚未发现将替雷利珠单抗联合化疗用于晚期 G/GEJ 腺癌患者二线或后线治疗中的相关报道。

6　总结与展望

胃癌是全球发病率较高的人类癌症之一[53],早期胃癌患者接受根治性手术后进行化疗,术后 5 年生存率为可达到 90%。然而,由于许多患者缺乏早期胃癌的特定体征,检出率较低,因此,有超过 70% 的患者在确诊时肿瘤已为晚期[54]。然而,晚期胃癌的治疗手段十分有限。近年来,随着免疫治疗的不断发展,免疫联合化疗已成为继手术、化疗、放疗和靶向治疗和免疫治疗后的又一种全新的治疗模式。目前全球范围内正积极开展有关免疫检查点抑制剂联合化疗的临床研究。从上述几种 PD-1 抑制剂联合化疗的研究进展中可以看到,将 PD-1 抑制剂与化疗联合在晚期 G/GEJ 腺癌患者的一线治疗中应用十分广泛,许多国家已经开始推荐将此方案应用于晚期 G/GEJ 腺癌患者的一线治疗。虽然到目前为止,有关 PD-1 抑制剂联合化疗在晚期 G/GEJ 腺癌患者的二线或后线治疗中的研究相对较少,但是仍有许多国家正在开展有关免疫治疗联合化疗在晚期实体瘤二线或后线治疗中的研究。随着免疫治疗的不断发展,在这个免疫治疗的时代笔者坚信 PD-1 抑制剂联合化疗可以为晚期 G/GEJ 腺癌患者的后线治疗带来光明的前景。

利益冲突　无

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(上接第 1341 页)

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