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周莉,上海交通大学医学院附属松江医院肿瘤科主任,主任医师,副教授,硕士研究生导师。长期从事肿瘤临床诊疗工作,擅长常见恶性肿瘤,如乳腺癌、胃癌、结直肠癌、肺癌以及肝胆胰恶性肿瘤的诊断、化疗、靶向治疗、免疫治疗及综合治疗。研究方向为三阴性乳腺癌脑转移相关机制研究。Emory大学医学院访问学者,曾入选上海市高级中西医结合人才培养计划及浦东新区学科带头人培养计划。主持国家自然科学基金面上项目和上海市自然科学基金面上项目等多项,省部级课题3项,主编教材2部,发表学术论文及SCI论文20余篇。

三阴性乳腺癌免疫联合治疗新策略

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摘 要:三阴性乳腺癌(triple-negative breast cancer,TNBC)是乳腺癌中预后最差的亚型之一,由于缺乏明确的治疗靶点,长期以来化疗是其核心治疗方案,但疗效有限且易产生耐药。近年来,免疫检查点抑制剂(immune checkpoint inhibitors,ICIs)的出现为TNBC治疗带来了突破性变革。本综述系统阐述了免疫治疗,特别是免疫联合策略在TNBC中的最新进展;重点分析了免疫联合化疗在早期新辅助及晚期转移性阶段取得的显著临床获益,并深入探讨了免疫治疗与多聚ADP-核糖聚合酶(poly ADP-ribose polymerase,PARP)抑制剂、抗血管生成药物、周期蛋白依赖性激酶(cyclin-dependent kinases,CDKs)4/6抑制剂及抗体药物偶联物(antibody-drug conjugates,ADCs)等靶向药物联合的协同机制与应用前景。文章最后总结了当前面临的挑战,如生物标志物挖掘、耐药机制克服及毒性管理等,并对未来研究方向进行了展望,旨在为TNBC的精准免疫治疗提供理论参考。

关键词:三阴性乳腺癌;免疫治疗;联合治疗;抗体-药物偶联物
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A new combined immunotherapy strategy for triple-negative breast cancer

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Abstract: Triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor, progesterone receptor, and HER2, represents 5%-20% of breast cancers and is associated with aggressive clinical behavior, early recurrence, and poor prognosis. The lack of actionable targets has historically made chemotherapy the cornerstone of systemic therapy, albeit with limitations due to toxicity and acquired resistance. The advent of immune checkpoint inhibitors (ICIs), particularly agents targeting the PD-1/PD-L1 axis, has revolutionized the therapeutic landscape for TNBC. This subtype exhibits a comparatively higher level of immunogenicity, often featuring a tumor-infiltrating lymphocyte-rich microenvironment, which provides a rationale for immunotherapy. However, single-agent ICI response rate remains modest, driving the development of combination strategies to synergistically enhance anti-tumor immunity. Immunotherapy combined with chemotherapy has established a new standard of care. Chemotherapy not only exerts direct cytotoxic effects but also can induce immunogenic cell death, promoting antigen presentation and T-cell

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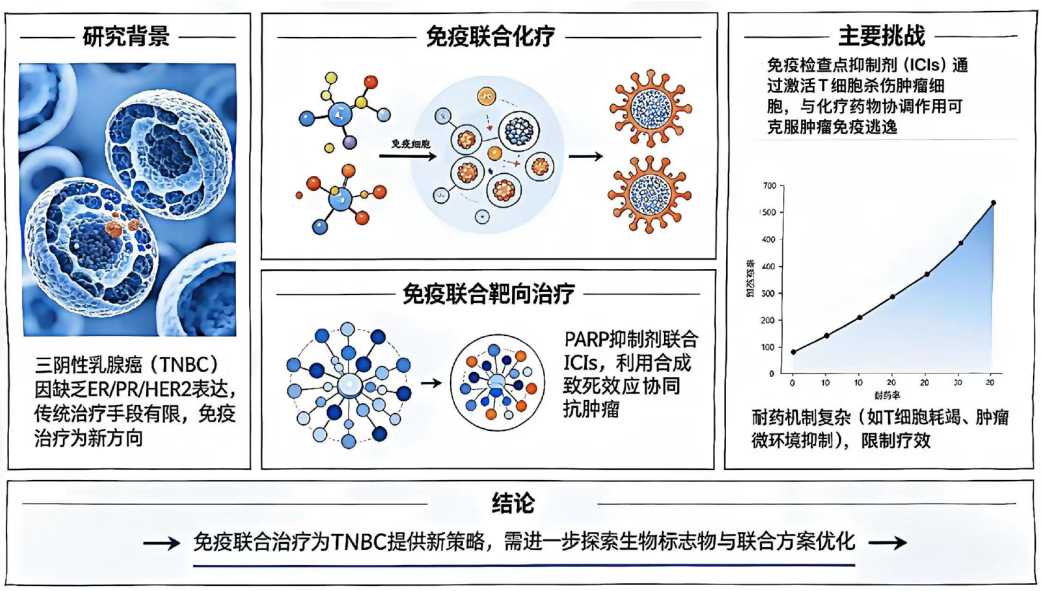
activation. In the neoadjuvant setting for early-stage, high-risk TNBC, the KEYNOTE-522 trial demonstrated that adding pembrolizumab to chemotherapy significantly improved pathological complete response (pCR) rate and event-free survival (EFS), leading to its regulatory approval. Similarly, in metastatic TNBC, both the IMpassion130 (atezolizumab+nab-paclitaxel) and KEYNOTE-355 (pembrolizumab+chemotherapy) trials established overall survival benefits for PD-L1-positive patients, solidifying the role of chemoimmunotherapy in the first-line setting. PD-L1 expression remains a key, albeit imperfect, predictive biomarker. The combination of ICIs with targeted therapies represents a highly promising frontier. For patients with germline BRCA1/2 mutations, poly ADP-ribose polymerase (PARP) inhibitors like olaparib induce synthetic lethality and may enhance tumor immunogenicity via the cGAS-STING pathway. Early clinical data suggest encouraging activity for PARP inhibitor-ICI combinations. Furthermore, antibody-drug conjugates (ADCs) are redefining treatment paradigms. Sacituzumab govitecan, a Trop-2-directed ADC, improves survival in pretreated metastatic TNBC. Notably, the HER2-directed ADC trastuzumab deruxtecan demonstrates potent activity even in tumors with low HER2 expression (HER2-low), a category encompassing many TNBCs. Its ″bystander effect″ allows for cytotoxic payload delivery to antigen-heterogeneous tumors, creating potential for synergy with ICIs. Other combinations under investigation include ICIs with anti-angiogenic agents (e.g., bevacizumab) which may normalize vasculature and alleviate immune suppression, and those with tyrosine kinase inhibitors (e.g., lenvatinib) or CDK4/6 inhibitors which possess immunomodulatory properties. Despite significant progress, major challenges persist. Predictive biomarkers beyond PD-L1, such as integrated multi-omics profiles, dynamic immune cell monitoring, and gut microbiome analysis, are needed for better patient stratification. Mechanisms of primary and acquired resistance, involving upregulation of alternative immune checkpoints (e.g., LAG-3, TIM-3), expansion of immunosuppressive cells (e.g., MDSCs), and loss of antigen presentation, require further elucidation. Strategies to overcome resistance include next-generation bispecific antibodies and agents targeting the immunosuppressive tumor microenvironment. Furthermore, managing the overlapping toxicities of combination regimens remains a critical clinical consideration. In conclusion, immunotherapy-based combinations have fundamentally transformed TNBC management, moving it from a chemotherapy-centric model into a new combination era. While immuno-chemotherapy is now standard, combinations with targeted agents like PARP inhibitors and ADCs show immense potential. Future efforts must focus on optimizing combination strategies through a deeper understanding of the tumor-immune cycle, developing refined predictive biomarkers, and carefully balancing efficacy with toxicity to realize the goal of personalized and durable treatment responses for TNBC patients.



Key words: triple-negative breast cancer; immunotherapy; combined therapy; antibody-drug conjugate

乳腺癌(breast cancer,BC)是女性最常见的癌症,也是全球癌症相关死亡率的第二大原因。根据雌激素受体(estrogen receptor,ER)、孕激素受体(progesterone receptor,PR)和人表皮生长因子受体2(human epidermal growth factor receptor 2,HER2)等分子标志物,BC可分为激素受体(hormone receptor,HR)阳性、HER2阳性和三阴性乳腺癌(triple-negative breast cancer,TNBC)3种主要亚型,TNBC约占所有乳腺癌的15%~20%[1-3],具有侵袭性强、易早期复发转移、预后差的特点[4]。由于缺

乏有效的治疗靶点,化疗一直是TNBC系统性治疗的基石[5]。然而,化疗药物易产生耐药性,且毒副作用显著,患者长期生存获益进入平台期[6]。

肿瘤免疫治疗,尤其是针对程序性死亡蛋白-1(programmed death-1,PD-1)及其配体(programmed cell death ligand 1,PD-L1)的免疫检查点抑制剂(immune checkpoint inhibitors,ICIs)的发展,为TNBC患者带来了新的希望[7,8]。目前国内外临床应用的ICIs主要针对PD-1/PD-L1和细胞毒性T淋巴细胞相关抗原4(cytotoxic T-lymphocyte-associated protein 4,CTLA-4)通路,通过解除肿瘤微环境中的免疫抑制状态,增强T细胞抗肿瘤活性[9-11]。在乳腺癌中,TNBC患者从免疫治疗中获益最大。与其他乳腺癌亚型相比,TNBC具有更高的免疫原性水平。帕博利珠单抗(Pembrolizumab)作为代表性药物,其作用机制为阻断PD-1与PD-L1的结合,恢复T细胞功能。KEYNOTE-355试验证实[12],对于PD-L1阳性(联合阳性评分CPS≥10)的转移性TNBC患者,帕博利珠单抗联合化疗可显著延长无进展生存期(progression-free survival,PFS)和总生存期(overall survival,OS),中位OS达23.0个月,较化疗组提升43.5%。基于此,美国FDA已批准其用于PD-L1阳性晚期TNBC的一线治疗[10]。阿替利珠单抗(Atezolizumab)是另一款PD-L1抑制剂,其IMpassion130试验虽在转移性TNBC中显示生存获益,但后续IMpassion031研究未能在辅助治疗中复现疗效,提示其需严格筛选入组人群[13]。CTLA-4抑制剂如伊匹木单抗(Ipilimumab)在TNBC中的研究相对有限,主要因其单药疗效较低且毒性较高,目前可探索与PD-1抑制剂的联合策略[14]。研究表明,部分TNBC肿瘤微环境(tumor microenvironment,TME)中存在肿瘤浸润淋巴细胞(tumor infiltrating lymphocytes,TILs),具备"免疫炎性"特征,为ICIs的应用提供了生物学基础[15]。然而,单药ICIs应答率有限,因此,将免疫治疗与其他治疗模式(如化疗、靶向治疗等)联合,通过协同作用逆转免疫抑制微环境、激发和维持有效的抗肿瘤免疫应答,已成为当前TNBC治疗领域最富前景的研究策略[16]。

1 免疫联合化疗

化疗药物不仅能直接杀伤肿瘤细胞,还能通过诱导免疫原性细胞死亡,释放肿瘤相关抗原和损伤相关分子模式,促进树突状细胞成熟和T细胞活化,从而将化疗的细胞毒性作用与免疫系统的长期记忆功能相结合[17,18]。这一机制为免疫联合化疗提供了坚实的理论依据。

1.1 在新辅助治疗中的突破

新辅助治疗是评估早期TNBC新方案疗效的"快速通道"[11,19]。其中KEYNOTE-522 III期研究是一项里程碑式的试验,共有1 174例新诊断的TNBC患者被随机分组,分别接受帕博利珠单抗+化疗或安慰剂+化疗,这些患者有淋巴结受累(N1~N2),或肿瘤大小≥2 cm。在化疗后,患者继续接受手术,并在术后继续接受另外9个周期的帕博利珠单抗/安慰剂治疗。研究结果显示,加用帕博利珠单抗提高了病理完全缓解率(pathological complete response rate,pCR;可作为改善长期生存结果的中间替代终点;63%(95%置信区间59.5%~66.4%)vs 56%(50.6%~60.6%))和3年无事件生存期(event free survival,EFS;帕博利珠单抗组发生EFS事件的123例(16%)vs单独化疗组93例(24%),风险比0.63(95%可信区间0.48~0.82),P<0.001)。在转移性肿瘤中,免疫治疗的获益仅限于PD-L1阳性的TNBC患者[12]。重要的是,达到pCR的患者无论是否接受了帕博利珠单抗治疗,结局均同样良好,但与接受单独化疗的患者相比,接受帕博利珠单抗治疗的有残留病变患者的EFS有改善。这证实了在化疗基础上联合PD-1抑制剂帕博利珠单抗,可显著提高pCR,并延长EFS,这一成果使该方案成为高危早期TNBC新辅助治疗的新标准[10,12,20]。多项Meta分析进一步证实,ICIs联合化疗能将总体pCR率提升约13%,绝对获益显著[21]。

1.2 在晚期治疗中的生存获益

对于转移性TNBC,IMpassion130研究首次证实了PD-L1抑制剂阿替利珠单抗联合白蛋白紫杉醇一线治疗,可为PD-L1阳性患者带来无进展生存期和总生存期的双重获益[22,23]。随后的KEYNOTE-355研究进一步验证了帕博利珠单抗联合化疗在PD-L1高表达(CPS≥10)患者中的总生存优势[24]。这些研究共同确立了免疫联合化疗在晚期TNBC一线治疗中的地位[25]。

尽管免疫联合化疗取得了成功,但其疗效仍存在异质性。PD-L1表达是目前最常用的生物标志物,但并非完美。探索更精准的预测指标是优化该

策略的关键。

2 免疫联合靶向治疗

2.1 联合多聚ADP-核糖聚合酶抑制剂

除免疫治疗外,TNBC靶向治疗领域最具影响的进展之一是针对携带BRCA1/2突变患者的ADP-核糖聚合酶(poly ADP-ribose polymerase,PARP)抑制剂的开发。对于携带BRCA1/2等基因突变的TNBC患者,PARP抑制剂通过“合成致死”效应诱导DNA损伤累积[26]。此外,它能激活cGAS-STING通路,增强肿瘤免疫原性。与标准化疗相比,PARP抑制剂改善了PFS,并使总缓解率增加了一倍[27]。临床前及早期临床研究显示,在OlympiA试验的1 836例有胚系BRCA1/2突变的相关乳腺癌(包括有残留病变的TNBC)患者中,与安慰剂相比,1年的奥拉帕利辅助治疗改善了无浸润性癌生存期(风险比0.58,99.5%置信区间0.41-0.82;P<0.001)和总生存期(0.68,95%置信区间0.47-0.97;P=0.009)[19]。PARP抑制剂(如奥拉帕利)与PD-1抑制剂联合,在BRCA1/2突变型晚期TNBC中展现出令人鼓舞的客观缓解率和疾病控制率[28,29]。

2.2 联合抗体药物偶联物药物

抗体-药物偶联物(antibody-drug conjugates,ADCs)的开发正在进一步重新定义转移性乳腺癌的治疗格局。这些药物将针对特定肿瘤抗原的单克隆抗体与细胞毒性载荷连接起来,从而使细胞毒性药物能够更有效地递送到肿瘤微环境[30-32]。靶向Trop-2的戈沙妥珠单抗,是第一种与标准化疗相比,可显著改善转移性TNBC患者总生存期的ADC类药物[30]。随后,靶向HER2的ADC药物德曲妥珠单抗的临床运用,使我们将HER2作为生物标志物的思维模式发生了转变。之前的HER2靶向治疗方法仅在HER2过表达或扩增的肿瘤中显示出抗肿瘤活性[33],在这些肿瘤中,HER2激活可触发促进肿瘤生长的下游信号通路。相比之下,德曲妥珠单抗不仅在传统HER2过表达的乳腺癌中显示出稳健的抗肿瘤活性,而且在HER2表达水平较低的肿瘤中也显示出稳健的抗肿瘤活性。这些肿瘤之前被称为HER2阴性,现在被更名为“HER2低表达型”,它们的生长不依赖于HER2信号,似乎也不是一个独特的生物学实体,但它们对德曲妥珠单抗也有应答[30,32]。考虑到之前认为HER2阴性的肿瘤中有多达50%属于这一新的HER2低表达肿瘤类别,包括许多TNBC患者[34],因此这一影响是显著的。在这些肿瘤中,细胞表面的HER2蛋白与德曲妥珠单抗通过特异性的连接子相连,使复合物可以进入任何表达HER2的细胞(即使是低水平)。重要的是,德曲妥珠单抗等新一代ADCs通过可裂解连接子装载了可穿透膜的细胞毒性药物,这两种特征使得抗体可在细胞内释放有效载荷,并自由地穿过可能不表达HER2的邻近细胞的细胞膜。这种所谓的“旁观者效应”被认为可能是这些化合物在靶抗原不均匀表达的各种环境中具有强大活性的原因。

2.3 联合抗血管生成药物及其他靶向药物

血管内皮生长因子(vascular endothelial growth factor,VEGF)不仅能促进血管生成,还参与营造免疫抑制微环境。抗VEGF药物(如贝伐珠单抗)可通过“血管正常化”改善T细胞浸润,并减少免疫抑制性细胞,如调节性T细胞(regulatory T cells,Tregs)的聚集。IMpassion031等针对早期TNBC的研究证实,阿替利珠单抗联合化疗在新辅助治疗中能进一步提高pCR率。

周期蛋白依赖性激酶(cyclin-dependent kinases,CDKs)4/6抑制剂尽管在HR阳性乳腺癌中成功,但其在TNBC中的作用仍在探索。研究发现CDK4/6抑制剂可诱导肿瘤细胞衰老并增强抗原呈递,与ICIs联用可能逆转免疫逃逸[35]。

3 挑战与未来方向

尽管免疫联合策略前景广阔,但是当前依赖的PD-L1表达和TMB等生物标志物预测疗效不完全,因此仍面临多重挑战。未来需整合多组学信息,如肿瘤浸润淋巴细胞密度、基因表达谱、肠道微生物组以及外周血中动态变化的免疫细胞亚群(如TAA特异性T细胞),以构建更精准的预测模型。耐药是目前临床上TNBC治疗失败的主要原因,机制涉及其他免疫检查点(如淋巴细胞激活基因3、T细胞免疫球蛋白)的上调、免疫抑制性细胞(如骨髓来源的抑制性细胞)的富集以及抗原呈递机制的缺失等。针对这些机制,开发新一代ICIs双抗、靶向TME中免疫抑制细胞的药物等是重要方向。在接下来的研究中,多种强效药物的联合必然伴随毒副作用的叠加,如何优化给药顺序、剂量和疗程,在最大化疗效的同时最小化免疫相关不良事件和靶向药物毒性,是临

床实践中必须解决的难题。

4 结论

免疫联合治疗彻底改变了TNBC的治疗格局，从以化疗为主的单一模式进入了以免疫为核心的“联合时代”。免疫联合化疗已确立标准治疗地位，而免疫治疗与各类靶向药物的联合则展现出巨大的潜力。未来的研究焦点将从是否联合转向如何更好地联合，通过深化对肿瘤免疫循环的理解，利用精准的生物标志物指导患者分层，并创新性地设计联合方案，最终实现TNBC个体化免疫治疗的成功，为患者带来长期生存的希望。

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