Advances in Clinical Medicine 临床医学进展, 2022, 12(8), 7292-7299
Published Online August 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.1281053

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免疫抑制剂联合治疗毒副反应相关最新进展分析

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收稿日期：2022年7月8日；录用日期：2022年8月3日；发布日期：2022年8月10日

摘 要

恶性肿瘤是在发病率和死亡率方面仅次于心血管疾病的第二大类疾患，世界卫生组织国际癌症研究机构(International Agency for Research on Cancer, IARC)发布了2020年世界最新的癌症负担数据，全世界癌症新发病例总共1929万例，全球癌症死亡病例996万例，我国癌症新发病例占比23.7%，死亡病例占比30.2%，二者均位列第一。恶性肿瘤传统的常见治疗方式包括化学治疗、内分泌治疗、靶向治疗、放射治疗、外科手术治疗，但上述治疗模式已进入了停滞阶段。2018年，免疫治疗首次进入我国，相比于传统肿瘤疗法，免疫治疗可大幅提高患者的晚期生存率，尤其对于恶性黑色素瘤、肾癌及非小细胞肺癌患者，其生存率的提高效果更为明显，部分患者甚至可维持5~10年。尤其胸膜间皮瘤、小细胞肺癌、肝癌肿瘤中，突破了多年治疗无明显进展的局面，带来生存的获益。免疫治疗包括免疫检查点抑制剂和过继细胞治疗，通过操纵免疫系统来识别和攻击癌细胞。这些疗法有可能在多种实体和血液系统恶性肿瘤中诱导持久的反应，从而改变了对多种瘤种的治疗模式。其中，免疫检查点抑制剂(immune checkpoint inhibitors, ICI)为目前临床常用的免疫治疗模式之一，ICI包括程序化死亡受体-1 (programmed cell death protein-1, PD-1)/(programmed cell death-ligand 1, PD-L) 1和细胞毒性T淋巴细胞相关蛋白4 (cytotoxic T-lymphocyte-associated protein 4, CTLA-4)，同时在免疫检查点抑制剂引起的相关不良反应也不容忽视。本文为将对ICI相关的不良反应展开综述。

关键词

PD-1，毒副反应，机制，发生率，治疗

Recent Developments Related to the Toxic Side Effects of Immunosuppressive Combination Therapy

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文章引用：费鹏飞，李瑜英. 免疫抑制剂联合治疗毒副反应相关最新进展分析[J]. 临床医学进展，2022，12(8): 7292-7299. DOI: 10.12677/acm.2022.1281053

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Received: Jul. 8th, 2022; accepted: Aug. 3rd, 2022; published: Aug. 10th, 2022

Abstract

Malignant neoplasm is the second most common type of disease after cardiovascular disease in terms of morbidity and mortality. The International Agency for Research on Cancer (IARC) of the World Health Organization has released the latest data on the burden of cancer in the world in 2020. The International Agency for Research on Cancer (IARC) released the latest data on the burden of cancer in the world in 2020, with a total of 19.29 million new cancer cases and 9.96 million cancer deaths worldwide. The traditional common treatment modalities for malignant tumors include chemotherapy, endocrine therapy, targeted therapy, radiation therapy, surgical treatment, but the above treatment modalities have entered a stagnant stage. In 2018, immunotherapy entered China for the first time, and compared with traditional tumor therapy, immunotherapy can significantly improve the late survival rate of patients, especially for patients with malignant melanoma, kidney cancer and non-small cell lung cancer. In particular, for patients with malignant melanoma, kidney cancer and non-small cell lung cancer, the improvement of survival rate is more obvious, and some patients can even sustain 5~10 years. Especially in pleural mesothelioma, small cell lung cancer and liver cancer tumors, the breakthrough of years of treatment without significant progress has brought survival benefits. Immunotherapy, which includes immune checkpoint inhibitors and pericyte therapy, recognizes and attacks cancer cells by manipulating the immune system. These therapies have the potential to induce durable responses in a wide range of solid and hematologic malignancies, thus changing the treatment paradigm for a wide range of tumor types. Among them, immune checkpoint inhibitors (ICI) are one of the immunotherapy modalities commonly used in clinical practice, including programmed cell death receptor-1 (PD-1)/(programmed cell death-ligand 1 (PD-1)), Death-ligand 1 (PD-L) 1 and (cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)), and the associated adverse effects caused by immune checkpoint inhibitors should not be ignored. In this paper, we review the adverse effects associated with ICI.

Keywords

PD-1, Side Effects, Mechanism, Incidence, Treatment

1. 相关机制

早期的抗癌药物通过损害防御机制而导致不良事件，而新的免疫疗法则通过激活免疫效应器和/或降低其耐受性来攻击癌细胞。这一类的免疫治疗新方法可能会诱发压倒性的炎症反应和自身免疫。可能与以下的作用机制有关，免疫疗法通常通过缓解淋巴结和外周组织中激活的 T 淋巴细胞的抑制作用，从而增强淋巴细胞的活化和 T 细胞介导的对表达自身抗原的正常细胞的破坏，并诱导炎症和自身免疫反应导致 irAEs (immune relate adverse effects) [1]。在临床中 CTLA-4 抗体、PD-1 抗体以及 PD-L1 抗体和的药物

相继应用于临床治疗，不同作用机制的免疫药物间其毒副反应不同，而且目前研究提示同一作用机制的免疫检查点抑制剂，生产厂家不一样，其毒副反应亦有所不同，同一 PD-1 抗体对不同的瘤种免疫毒副反应也可不一样[2] [3] [4]。免疫治疗模式包括：免疫双联合，免疫联合靶向(包括联合贝伐珠单抗，雷莫芦单抗，重组人血管内皮抑制素以及抗 EGFR 类药物)，免疫联合放疗，免疫联合化疗。联合治疗背后的一个关键策略是通过各种方法，使冷肿瘤升温，如通过化疗、放疗、疫苗和肿瘤内策略，吸引 T 细胞进入肿瘤，通过诱导免疫原性、减轻与化疗相关的肿瘤诱导的免疫抑制，或使肿瘤更容易受到细胞毒性 T 细胞的攻击来增强免疫反应[5]。

2. 毒性谱及发生率

免疫抑制剂相关毒副反应是由于其对免疫系统的激活而产生的非特异性反应，可受累几乎全身全部的器官组织。多见作用的靶器官包括心脏，肺部，肝脏、皮肤、肠道、内分泌器官。相应的症状包括心功指标升高、肝酶的升高、皮肤瘙痒、腹泻腹痛、甲状腺功能减退、甲状腺功能亢进等，严重者可发生心肌炎、心衰、心肌梗塞，炎症性皮疹，垂体炎，胃肠道炎症，免疫性肝炎，甲状腺风暴。在 2018 年中山大学肿瘤防治中心发表在英国医学杂志一项荟萃分析显示，各种 PD-1 抑制剂的不同给药剂量在其所致毒性方面没有显著差异；在全级别(1~5 级)和严重级别(3~5 级)毒副反应发生率从低到高依次为阿替利珠单抗、纳武利尤单抗、帕博利珠单抗、化疗和联合治疗。阿替利珠单抗、纳武利尤单抗、帕博利珠单抗的 1~5 级毒副反应的总发生率分别为 66.4%、71.8%、75.1%，3~4 级分别为 15.1%、14.1%、19.8% [2]。而我们的国产 PD-1 抑制剂信迪利单抗受限于所批准的适应症，治疗难治或复发性经典霍奇金淋巴瘤可以看到，全级别及 3~4 级毒性发生率分别为 93%、18% (主要包括肺炎/肺部感染和上呼吸道感染)，无治疗相关性死亡[6]。总体上，阿维单抗、西米普利单抗及信迪利单抗具有与其他 PD-1 抑制剂类似的不良事件。Zhou Xiaoxiang 于 2021 年 8 月在柳叶刀肿瘤学发表的一篇 meta 分析显示接受抗 PD-1 免疫抑制剂治疗加化疗的患者发生治疗相关不良事件的风险显著高于接受抗 PD-L1 免疫抑制剂治疗治疗加靶向治疗或免疫治疗的患者[7]。

3. 心脏相关毒性

由免疫检查点抑制引起的心脏免疫相关不良事件相关机制仍不明确，但有以下研究，PD-1 和 PD-L1 都在人体心肌细胞中表达，这一点为淋巴细胞药物治疗的心脏毒性提供了合理性[8]。心肌对免疫现象高度敏感，在 PD-1 基因或药理学缺失后，心肌中 PD-L1 的高水平表达增加，这表明 PD-1/PD-L1 信号通路与保护心脏免受免疫反应的高度相关性[9]。Lars Michel 发表在欧洲心脏病学杂志的一篇期刊提示，经流式细胞术证实，暴露于抗 PD-1 治疗的小鼠后，心脏内皮细胞上的 PD-L1 表达上调，CD44 在 CD8+T 细胞上的表达增加了 1.3 倍，而 CD44 的表达常被认为 T 细胞活性的标志[10]。在实际临床中，免疫治疗引起的相关毒性是十分少见的，据估计，大约 0.09%的患者接受免疫抑制剂治疗发生相关的毒性，联合免疫抑制剂治疗的相关心脏毒性风险是 ICI 单药治疗的 5 倍，尽管真实的发病率可能更高[11] [12] [13]。症状也从心肌酶的升高到心肌病、心包炎、心包积液和心律失常不等。由于症状上呈现出来的不一样，临床上医生的处理也可不同，在发现的初始阶段，可以暂停免疫抑制剂的使用避免 T 细胞的浸润加重，抗胸腺细胞球蛋白可以用于暴发性心肌炎[14]。药物可以用于 PD-1 治疗癌症引起的免疫新心肌炎，但同时也要中止一段时间癌症的治疗，而 TNF-α 可以作为一种预防措施，以避免心脏并发症变得临床明显，同时保持抗癌疗效[15]。

4. 皮肤相关毒性

涉及免疫检查点抑制剂的皮肤毒性的病理生理机制主要尚不清楚，但大多数是 T 细胞介导的，这些

皮肤 irAE 的发展涉及到一种共同抗原的阻断，该抗原在肿瘤细胞和真皮－表皮交界处和或皮肤的其他部位共同表达。它们可能通过重新激活 CD4+/CD8+ T 细胞来瞄准皮肤真皮/表皮的抗原，再和真正的皮肤交叉反应之后产生炎症反应[16]。皮肤是被认为最容易受自身免疫力影响的器官，所以皮肤毒性是最常见的并发症。根据对现有随机对照试验的系统回顾，对于接受抗 PD-1/PD-L1 治疗的患者，皮肤毒性的绝对风险约为 30%~40%，抗 CTLA-4 药物皮肤毒性的发生率为 47%~68%，联合治疗上发生率更高[17] [18]。总的来说，皮肤 irAE 可分为六类毒性：大疱性疹、瘙痒、色素沉着疾病和严重的皮疹/炎症性皮炎。任何这些皮肤不良反应都可能发生，无论所治疗的恶性肿瘤类型如何，而且似乎并不是剂量依赖性的[19]。当病人出现皮肤方面的反应时，应当即时的和皮肤科医生进行联系，对患者的病情做出准确的判断，排除免疫相关的皮肤毒性，避免病情的进一步发展。I 级皮肤毒性是轻微的，可以用局部使用皮质类固醇或抗组胺药治疗。对于 II 级以上的副作用，建议使用口服 1 mg/kg/天的强的松。如果患者在使用全身类固醇时病情继续恶化，应考虑使用额外的免疫调节治疗，如英夫利昔单抗、环磷酰胺和霉酚酸酯。

5. 胃肠相关毒性

免疫检查点抑制剂造成胃肠相关不良反应的关键思想是免疫药物的使用打破免疫稳态，减少 T 细胞耐受[20]。活化的 T 细胞攻击胃肠健康组织，导致具有类似于自身免疫性疾病特征的 irAE。进一步的转录组分析表明，PI3K-AKT-mTOR 通路在结肠炎病变的 CD8+效应 T 细胞中被高度激活[21]。除此之外，现有的证据表明，微生物群参与了肿瘤的发生，以及免疫系统的激活或抑制，这可能有助于肿瘤的控制或逃逸。况且，已经证实胃肠道微生物群的改变可能使患者易患结肠炎，肠道微生物群作为影响胃肠道毒性的一个因素已在多篇研究中提及[22]。一般来说，抗 CTLA-4 药物的胃肠道副作用比 PD-1/PD-L1 抑制剂的发生率和严重程度更高[23] [24]。ICIs 联合治疗的副作用发生率高于 ICIs 单药治疗[25]。在接受伊匹单抗治疗的患者中，大约三分之一的患者发生腹泻，其中 8%~23%发生结肠炎，使用 PD-1 的患者发生胃肠道副作用较不常见，只有不到 4%的患者发生结肠炎[26]。I 级胃肠毒性的治疗很大程度上是支持的，补充液体和电解质。II 级胃肠毒性，应该胃肠科医生的干预和结肠镜检查，确诊之后应考虑添加糖皮质类固醇。对于 III 级和 IV 级结肠炎，PD-1 的使用应立即停止，并开始大剂量使用糖皮质类固醇(1~2 mg/kg/天的甲基泼尼松龙或其同等剂量) [27]。单剂量英夫利昔单抗(5 mg/kg)已成功用于 3~5 天后对皮质类固醇反应无效的病例[28] [29]。此外，mTOR 抑制剂西罗莫司阻断该通路不仅可以抑制肿瘤生长，而且还可以抑制结肠炎病变中的 T 细胞浸润。更为重要的是，与西罗莫司和抗 PD-1 联合使用，通过诱导肿瘤细胞的免疫原性细胞死亡，协同抑制肿瘤生长[21]。

6. 肺部相关毒性

免疫性肺炎(checkpoint inhibitor pneumonitis, CIP)的发生机制可能和一下相关：① 增强和或靶向 T 细胞对肿瘤交叉抗原的活性和正常组织共享可能导致 CIP 的发生[20]。② 炎症因子的参与，白细胞介素-6 (IL-6)、IL-17A、IL-35、C 反应蛋白(CRP)、降钙素原(PCT)、表面活性剂蛋白-D (SP-D)在那些发生免疫性肺炎患者身上更常见[30] [31]。在 ICI 单药治疗的临床试验中，ICI 相关肺炎的总发生率为 2.5%~5.0%，ICI 联合治疗的总发生率范围为 7%~10% [32]，真实世界中的发生率在 7%~19%不等[33]。在非小细胞肺癌中，ICI 相关肺炎的发病率高于其他肿瘤[34]。以前的结论是联合免疫治疗的免疫性肺炎的发生率高于单药免疫组[35]。最近四川大学华西医院 LONG 发表的网状 meta 给出了相反的答案，显示在免疫组对比免疫联合化疗组中，免疫 + 化疗组可降低任何级别的 CIP 风险，在 1~5 级免疫性肺炎和 3~5 级的免疫新肺炎中，免疫组的排名最高，其次是免疫 + 化疗组和化疗组[36]。这和最近报道的两篇荟萃分析的结果一致[37] [38]。对此，免疫性肺炎风险降低的一个可能的解释可能是，当常规化疗药物与免疫抑制剂联

合使用时，化疗是由细胞毒性药物组成的，并耗尽免疫效应细胞和免疫抑制细胞，化疗药物似乎有免疫抑制作用[39]。当然，免疫联合化疗导致相关不良反应的确切机制在当前还未被阐述清楚。如果怀疑有免疫性肺炎，应从停止免疫抑制剂治疗，糖皮质激素开始。

7. 肝脏相关毒性

对于免疫相关的肝脏毒性反应的性质尚不完全了解，目前尚不清楚仅仅免疫检查点抑制剂是否足以驱动显著的肝脏炎症和自身免疫，还是二次的“打击”，如药物或环境触发或异生物对肝毒性是必要的[40]。单药 ICIs 引起的全级别肝毒性发生率为 2%~37%，当 ICIs 联合抗 CTLA-4 或传统化疗时，这种发生率会增加[41]。最近一项关于肝细胞癌检查点抑制剂研究的荟萃分析表明，肝细胞癌患者通过肝酶升高如 ALT 和 AST 测量的肝损伤风险是其他实体肿瘤的 3 倍[42]。其他不太常见的肝毒性实验室发现包括 ALP 升高、肝胆疾病、胆红素升高和 GGT 升高。免疫相关性肝炎病理表现为伴有肝细胞损伤模式的全小叶型肝炎，其临床表现类似于自身免疫样药物诱导的肝损伤，由无症状的肝转氨酶升高组成，严重的肝炎和肝功能衰竭往往很少发生。肝脏毒性的发生率偏低部分原因可能归因于肝脏本身能够通过诱导耐受性来抑制免疫反应，这种现象通常被称为适应[43]。对于 2 级肝炎，免疫治疗应暂时中断，直到血清转氨酶水平出现下降。对于 3 级或 4 级肝炎，应立即停止免疫抑制剂的使用，并开始使用全身糖皮质类固醇。根据已发表的病例报告，霉酚酸酯被推荐给对皮质类固醇无反应的病例，应避免英夫利昔单抗可能诱发暴发性肝炎[44]。

8. 内分泌毒性

除其他因素外，免疫检查点抑制剂引起的内分泌毒性似乎受到多种因素的影响，如免疫药类型、剂量、联合用药、既往是否有自身炎症、自身免疫性疾病病史的影响[45]。甲状腺和垂体功能障碍是 ICI 治疗中最常见的内分泌疾病。其他内分泌腺如肾上腺、甲状旁腺、胰腺更少受到影响，代谢异常也已被描述。在接受 ICI 治疗的患者身上存在 ICI 相关甲状腺功能障碍，在接受抗 PD-1 治疗的患者中更常见。这可能是由于 PD-1 在所有 B 细胞表面的表达相关[46]。垂体炎的发生与 CTLA 免疫药更常见，在剂量上可能是有正相关关系的，在低剂量和高剂量之间，发生率从 1%到 17%不等[47]。抗 PD-1 单抗的发生率为 0.4%，抗 PD-L1 单抗的发生率为 0.1%，联合治疗发生率为 6.4%。且 ICI-垂体炎在男性(特别是 60 岁以上)中的发生率是女性的 2~5 倍。甲状腺功能障碍发生率为 4%~19.5%，多药联合治疗时内分泌毒副反应发生率可升高至 9.9%~22% [48]。内分泌毒性时症状呈现出来是非特异性的，很难被分辨出来，大多数症状可以表现为恶心、呕吐、食欲减退、体重减轻、全身虚弱、疲劳、轻度认知功能障碍、低血压和头痛，此外，其症状与癌症进展或脑转移相似，导致延误诊断。延误诊断可导致致命的副作用，如肾上腺危象、甲状腺风暴、严重的低钙血症和糖尿病酮症酸中毒。所以，在临床上使用时，需要医生对基线值的充分检查方便后面检查数据的对比。虽然大多数免疫毒副反应都是可逆的，需要及时停止治疗和糖皮质激素治疗，但内分泌疾病通常会持续存在，通常需要终身的激素替代。未经治疗的内分泌病可能会危及生命。

9. 结语与展望

免疫治疗在中国进入批准应用的时间尚且不长，但是在肿瘤治疗上已经开创了一个新的格局。同时在临床治疗方面的毒性也已经需要引起临床医生的足够重视了。真实世界中的病人病情复杂多变，不比临床世界的情况，早期发现和及时干预是十分必要的，这就需要对患者病情有清晰的认知，和对免疫药物有充分的了解。目前上来说，对于免疫治疗导致的相关不良反应的具体机制还不是很清楚，免疫联合

治疗往往说来是加重不良反应的，但是在免疫治疗导致肺炎这里，却有着相反的说法。这还需要更多的动物实验来阐明相关机制和更多大型临床试验来验证。

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