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癌症治疗中免疫相关不良事件文献可视化分析*

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摘要:目的 为免疫检查点抑制剂(ICI)用于癌症治疗中免疫相关不良事件(irAEs)的进一步研究提供参考。方法 计算机检索 Web of Science 数据库, 检索时限为自建库起至 2023 年 2 月 1 日。运用 Excel 2016 版和 VOSviewer 1.6.18 版软件, 对纳入文献的发表年份、发表期刊、作者及研究机构、文献共被引及关键词共现等进行文献计量学分析。结果 共纳入 2 735 篇文献, 始发于 2012 年, 2015 年后发文量和引用频次呈逐年递增趋势。发文量最大的国家及研究机构分别是美国(1 058 篇, 38.68%)及美国德克萨斯大学 MD 安德森癌症中心(137 篇, 5.01%); 发文量最大、文献被引频次最高的作者分别为 JOHNSON(32 篇, 1.17%), POSTOW(3 144 次), 期刊均为 *Journal for Immuno Therapy of Cancer*(117 篇, 4.28%, 4 720 次); 27 篇高被引(被引频次 ≥ 200 次)文献聚焦于纳武利尤单抗、帕博利珠单抗和伊匹木单抗等在黑色素瘤、肾癌及肺癌等实体瘤中的免疫治疗研究, 以及 ICI 的 irAEs 的特征与预后、毒性管理指南、系统综述与荟萃分析等研究; 关键词可聚为 4 类, 主要包括免疫治疗、癌症、双盲临床试验、安全性等主题。结论 采用文献计量学方法可清晰、直观地了解全球 ICI 用于癌症免疫治疗中 irAEs 的研究现状及热点。

关键词:文献计量学; 免疫检查点抑制剂; 癌症治疗; 药品不良反应; 免疫相关不良事件

Visualization Analysis of Literature on Immune-Related Adverse Events in Cancer Therapy

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Abstract: Objective To provide a reference for further research on the immune-related adverse events (irAEs) in cancer therapy by immune checkpoint inhibitors (ICIs). **Methods** Relevant literature in the Web of Science database from the inception to February 1, 2023 was searched. Bibliometric analysis was performed on the publication year, journal, author, research institution, co-citation and keyword co-occurrence of the included literature by the Excel 2016 and VOSviewer 1.6.18 softwares. **Results** A total of 2 735 literature was included, the first one was published in 2012, the quantity of publications and citation frequency showed an increasing trend year by year after 2015. The United States and the University of Texas MD Anderson Cancer Center was the country and research institution with the largest quantity of publications, publishing 1 058 literature (38.68%) and 137 literature (5.01%) respectively. JOHNSON was the author with the largest quantity of publications (32 literature, 1.17%), and POSTOW was the author with the highest citation frequency of literature (3 144 times). The *Journal for Immuno Therapy of Cancer* was the journal with the largest quantity of publications (117 literature, 4.28%) and the highest citation frequency of literature (4 720 times). Twenty-seven literature with high citation (frequency ≥ 200 times) focused on the immunotherapy research of nivolumab, pembrolizumab and ipilimumab in solid tumors such as melanoma, kidney cancer and lung cancer, as well as the characteristics and prognosis, toxicity management guidelines, systematic reviews and Meta-analyses of irAEs of ICIs. Keywords could be grouped into four categories, mainly including these topics such as immunotherapy, cancer, double-blind clinical trials and safety. **Conclusion** Bibliometric study can provide a clear and intuitive understanding of the current research status and hot spots of irAEs in cancer immunotherapy by ICIs in the world.

Key words: bibliometrics; immune checkpoint inhibitor; cancer therapy; adverse drug reaction; immune-related adverse event

癌症是世界范围内的主要公共卫生问题, 是美国人口第二大死亡原因^[1]。2022 年, 中国预期癌症新发病例数约为美国的 2 倍, 预期死亡数约为美国的 5 倍^[2]。免疫治疗发展迅速, 被认为是继手术、放射治疗(简称放

疗)、化学药物治疗(简称化疗)和靶向治疗后癌症治疗的“第五支柱”^[3]。近年来, 免疫检查点抑制剂(ICI)在癌症治疗中的应用, 使部分患者的生存期延长, 给癌症治疗带来了新的方向。然而 ICI 对肿瘤淋巴细胞无选择

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性,可能在所有器官中诱导免疫“攻击”,从而产生了一种新的毒性谱,称为免疫相关不良事件(irAEs)。几乎所有器官均为潜在靶点,故irAEs极其多样,可累及皮肤、肠道、内分泌腺、肺、肝等组织^[4-6]。对irAEs的疗效预测因子、发病机制、病理表现等进行深入研究,有助于临床对药品不良反应(ADR)进行早期诊治,也对检测和管理不良事件及在某些情况下预防致命结果至关重要。近年来,国内外学者开展了许多关于irAEs的研究,发表的文献日益增多,但有关该领域的研究热点与发展趋势可视化研究报道较少。本研究中对癌症治疗中irAEs相关文献进行统计分析,梳理其研究概况,了解其研究热点及趋势,以期为未来相关研究的开展提供借鉴。现报道如下。

1 资料与方法

1.1 数据来源

计算机检索Web of Science(WOS)数据库核心合集中癌症治疗中ICI irAEs相关文献,设定高级检索,主题词为“immune - related adverse event”“immune checkpoint inhibitor”“cancer or tumor or carcinoma or neoplasm”。检索时限为自建库起至2023年2月1日,1 d内完成搜索(避免数据更新所致偏差)。语言限定为英语,剔除修订类、书籍章节和重复发表的文献。作者、标题、摘要、关键词、出版物来源、引文等全部数据以.ciw和.txt格式从WOS数据库中下载。

1.2 研究方法

提取.ciw格式数据,导入EndNote软件中进行数据清洗、去重、分析;.txt格式数据导入VOSviewer 1.6.18版软件进行文献计量学分析,得到可视化图谱。提取WOS数据库中年度发文量及引文量相关数据,采用Excel 2016软件进行分析。分析检索所得文献的产出、国家、机构、作者、来源期刊、关键词共现、期刊共被引等,探索癌症治疗中ICI irAEs的研究热点和趋势。

2 结果

2.1 年度发文量与引用频次统计

相应文献始发于2012年,但到2014年期间年发文量不足5篇,引用频次也较低。自2015年起,其引用频次稳定增长,2018年起更是呈爆发式增长趋势,到2022年达峰值。2022年的发文量虽有所减少,但2021年至2022年引用频次仍保持缓慢增长,2023年(截至2023年2月1日)已发表相关文献15篇。详见图1。提示国际上对此课题研究近5年来发展迅速,目前可能已较全面,虽出现减缓趋势,但相关研究仍保持在较高水平。

2.2 国家/地区、机构及作者合作分析

国家/地区合作网络:2 735篇文献涉及61个国家/地区,其中合作发表了10篇以上文献的有32个(见图2)。

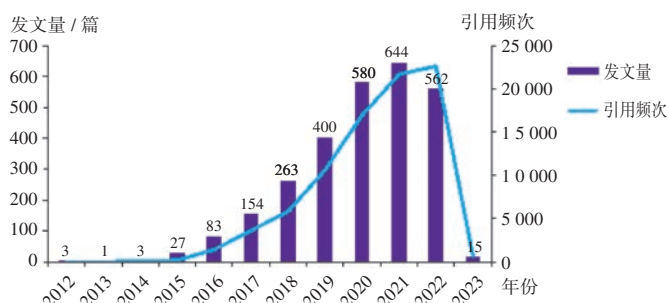


图1 年度发文量及引用频次

Fig. 1 Annual quantity of publications and citation frequency

美国发文量位列第一(1 058篇、38.68%),其次为中国(415篇、15.17%)、日本(334篇、12.21%)、法国(211篇、7.71%)、意大利(209篇、7.64%)。被引次数最多的是美国(5 3251次),其次为法国(15 330次)、英国(10 504次)、德国(9 487次)和加拿大(8 689次)。整体来看,欧美国家在此研究领域贡献较突出。

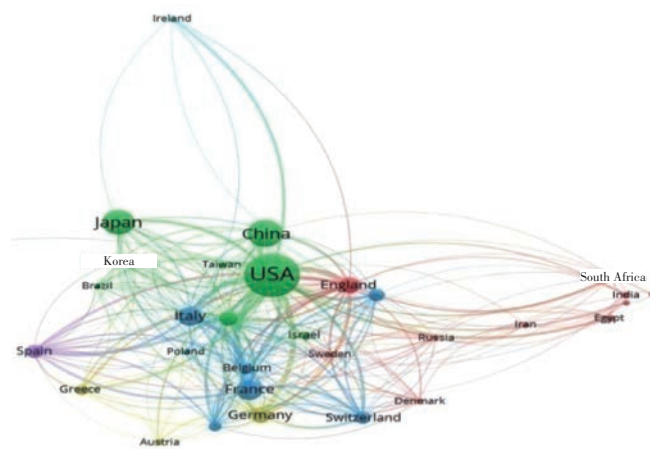


图2 发文国家/地区合作网络图

Fig. 2 Network of publishing country/region cooperation

机构合作网络:共有3 362个研究机构。其中合作发文量 ≥ 20 篇的机构有43个(见图3),排名前5的依次为University of Texas MD Anderson Cancer Center(德克萨斯大学MD安德森癌症中心,137篇),Harvard Medical School(哈佛医学院,102篇),Memorial Sloan - Kettering Cancer Center(斯隆 - 凯特琳癌症中心,84篇),Massachusetts General Hospital(麻省总医院,77篇),Johns Hopkins University(约翰斯霍普金斯大学,72篇)。上述5个研究机构均来自美国,提示美国研究机构在此领域的研究中注重合作,且取得显著成果。中国发文量位列前茅的机构有中国医学科学院北京协和医学院(40篇,第11),上海交通大学(26篇,第22),四川大学(25篇,第26),中山大学(23篇,第29),浙江大学(21篇,第34)。提示中国也很重视该领域的研究与合作,特别是一些实力强劲的高校体现出资金和人才上的优势,获得了更多研究成果。



图3 发文机构合作网络图

Fig. 3 Network of publishing institution cooperation

作者合作网络:共有15 935名作者,发文量 ≥ 10 篇的作者有54位,其中11位作者与其余作者间无联系,另43位作者的合作关系网络图见图4。作者发文量以JOHNSON居首(32篇、1.17%),其后依次为LAMBOTTE(25篇、0.09%)、NAIDOO(24篇、0.09%),HODI(21篇、0.08%)、MICHOT(18篇、0.07%)。高产作者的节点大,发文量多,同时处在复杂网络结构中,提示其为该领域研究中的关键作者,且与他人合作紧密。从该领域文献的被引用频次来看,POSTOW位居首位(3 144次),其次为JOHNSON(2 212次)、LAMBOTTE(2 015次)、BRAHMER(1 861次)、NAIDOO(1 813次),提示这些作者的研究成果得到了更多研究者的认可,在该领域的影响力较大。

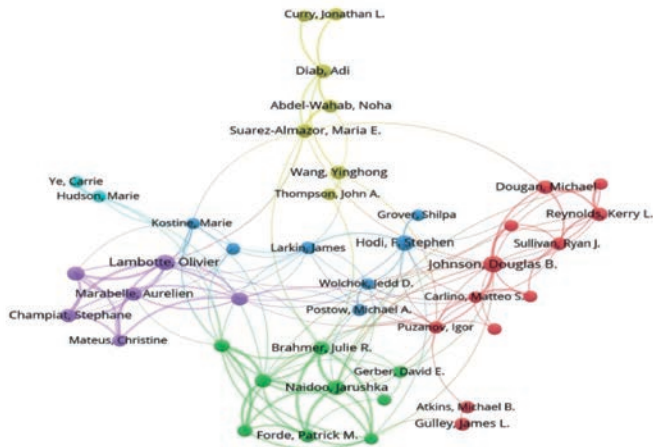


图4 文献作者合作网络图

Fig. 4 Network of author cooperation

2.3 发文期刊分析

2 735篇文献来自654个期刊。发文量排名前10的期刊共发表文献638篇,占总发文量的23.33%。其中*Journal for Immuno Therapy of Cancer* 发文量(117篇,4.28%)及被引频次(4 720次)均居首。*European Journal of Cancer*, *Journal of Immunotherapy*, *Cancer Immunology Immunotherapy* 和 *Frontiers in Pharmacology* 的发文量及

表1 发文量排名前10的期刊

Tab. 1 Top 10 journals with the large quantity of publications

排序	期刊	发文量(篇)	影响因子(2021)
1	<i>Journal for Immunotherapy of Cancer</i>	117	12.485
2	<i>Frontiers in Immunology</i>	85	8.787
3	<i>Cancers</i>	81	6.575
4	<i>European Journal of Cancer</i>	61	10.002
5	<i>Journal of Immunotherapy</i>	60	4.912
6	<i>Immunotherapy</i>	60	4.040
7	<i>Cancer Immunology Immunotherapy</i>	51	6.630
8	<i>Frontiers in Pharmacology</i>	43	5.988
9	<i>Thoracic Cancer</i>	42	3.223
10	<i>Frontiers In Oncology</i>	38	5.738

表2 被引频次排名前10的期刊

Tab. 2 Top 10 journals with the high citation frequency of literature

排序	期刊	被引频次	影响因子(2021)
1	<i>Journal for Immuno Therapy of Cancer</i>	4 720	12.485
2	<i>European Journal of Cancer</i>	3 987	10.002
3	<i>JAMA Oncology</i>	2 788	33.012
4	<i>Oncologist</i>	1 722	5.837
5	<i>Clinical Cancer Research</i>	1 400	13.801
6	<i>Cancer Immunology Immunotherapy</i>	1 034	6.63
7	<i>Frontiers in Pharmacology</i>	1 033	5.988
8	<i>Journal of Immunotherapy</i>	876	4.912
9	<i>Annals of The Rheumatic Diseases</i>	868	28.003
10	<i>Cancer</i>	827	6.921

被引频次均位居前列,提示这些期刊在此研究领域内影响力较大。详见表1、表2。

2.4 参考文献共被引分析

46 969篇参考文献中,高被引(被引频次 ≥ 200 次)的有27篇,均为2010年后发表,其中14篇发表在*New England Journal of Medicine*。被引频次最高的为2018年发表在*J Clin Oncol*的《Management of Immune - Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline》,共被引580次。根据27篇高被引参考文献的内容,将相关文献归为两类:第一类14篇,主要为纳武利尤单抗、帕博利珠单抗、伊匹木单抗等在黑色素瘤、肾癌及肺癌等实体瘤中的免疫治疗研究;第二类13篇,主要为ICI的irAEs的特征与预后、毒性管理指南和系统综述与荟萃分析等研究。详见图5。

2.5 关键词共现分析

2 735篇文献中,涉及此领域的关键词共有5 267个,取出现频次不少于50次的72个关键词进行分析,并对同义词进行合并,得到54个关键词共现聚类网络图(见图6)

次,可能有非英文的相关文章未被纳入。因此,本研究中所得结果可能不适用于以其他语言发表的研究。第三,由于一些作者有相同的名字缩写,一些关键词有不同的表达方式,分析结果可能存在偏差。今后可扩大范围检索多个数据库,形成更加全面的文献研究。

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