抗肿瘤药物相关毛细血管渗漏综合征发生率的 Meta 分析Δ

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摘　要　目的:对抗肿瘤药物治疗过程中出现毛细血管渗漏综合征(CLS)相关不良反应的发生率进行 Meta 分析,为临床安全用药提供参考。方法:检索 Embase、the Cochrane Library、PubMed 和中国知网等数据平台,收集抗肿瘤药物治疗过程中发生 CLS 的观察性研究和随机对照试验,检索时间为建库至 2024 年 4 月 1 日。纳入符合标准的文献并进行质量评价,采用 RevMan 5.4 软件进行 Meta 分析。结果:共纳入 70 篇文献,合计 3 002 例患者。Meta 分析结果显示,白细胞介素 2 单独使用或联合其他药物引起 CLS 的发生率最高(为 29%),其次为白细胞介素 1、白细胞介素 3 和白细胞介素 4(为 23%),抗 CD 单克隆抗体类药物、粒细胞-巨噬细胞集落刺激因子和吉西他滨引起 CLS 的发生率分别为 21%、10%和 3%。结论:白细胞介素类药物最易引发 CLS,应重点监护该类患者的不良反应,提高用药安全性。

关键词　毛细血管渗漏综合征;抗肿瘤药物;免疫调节剂;不良反应;Meta 分析

Meta-Analysis on the Incidence of Capillary Leakage Syndrome Induced by Anti-Tumor DrugsΔ

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ABSTRACT　OBJECTIVE: To perform Meta-analysis on the incidence of adverse drug reactions associated with capillary leakage syndrome (CLS) during the treatment of anti-tumor drugs, and provide reference for safe medication in the clinic. METHODS: Embase, the Cochrane library, PubMed, and CNKI were retrieved to collect randomized controlled trials (RCT) of CLS during the treatment of anti-tumor drugs up to Apr. 1st, 2024. Literature that met the criteria was included and evaluated for quality, and RevMan 5.4 software was used for Meta-analysis. RESULTS: A total of 70 articles were enrolled, including 3 002 patients. Meta-analysis showed that interleukin-2 alone or in combination with other drugs had the highest incidence of CLS (29%), followed by interleukin-1, interleukin-3 and interleukin-4 (23%). The incidence of CLS induced by anti-CD monoclonal antibody drugs, granulocyte-macrophage colony-stimulating factor and gemcitabine was 21%, 10% and 3%, respectively. CONCLUSIONS: Interleukin drugs are most likely to cause CLS, and it is important to monitor adverse drug reactions to improve medication safety.

KEYWORDS　Capillary leakage syndrome; Anti-tumor drug; Immunomodulator; Adverse reaction; Meta-analysis

毛细血管渗漏综合征(capillary leakage syndrome,CLS)是一种罕见的可危及生命的疾病,主要与毛细血管对蛋白质的通透性增加有关,临床典型表现为低血压、水肿和血细胞比容升高,严重的 CLS 病例可发生低血容量性休克、多器官功能障碍综合征,甚至死亡[1]。其最常见的并发症为急性肾损伤,发生于 28%~62%的 CLS 患者中[2]。对于接受抗肿瘤治疗的患者,药物诱导是引发 CLS 的重要原因,尤其是在使用抗代谢药物、免疫刺激剂和单克隆抗体时[3]。然而,由于这种疾病的非特异性症状,尚未有抗肿瘤药物相关 CLS 发生率的系统性研究。本研究旨在系统评价抗肿瘤药物治疗过程中 CLS 相关不良反应的发生率,以期帮助临床尽早识别体征并及时进行治疗。

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1　资料与方法

1.1　纳入与排除标准

收集抗肿瘤药物治疗过程中发生 CLS 相关不良反应的观察性研究和随机对照试验。(1)纳入标准:①年龄≥18 岁的恶性肿瘤患者,性别不限;②使用抗肿瘤药物进行治疗;③治疗过程中出现 CLS 结局指标。(2)排除标准:①重复发表及不能获得全文或结局指标的文献;②3 种及以上药物联合应用;③动物实验;④会议记录、综述。

1.2　文献检索与筛选

计算机检索建库至 2024 年 4 月 1 日 the Cochrane Library、PubMed、Embase 和中国知网等数据库,英文检索词为"(Capillary Leak Syndrome OR Vascular leak) AND (cancer OR carcinoma OR neoplasm OR tumor)",中文检索策略为"(毛细血管渗漏或血管渗漏)和(癌症或肿瘤)"。利用 EndNote 软件对得到的相关文献进行整合,由 2 名研究员独立进行筛选,产生分歧时,联合第 3 名研究员讨论解决。

1.3　文献质量评估

非随机对照试验通过 MINORS 量表进行质量评价,共

8 个条目，内容包括明确给出了研究目的、纳入患者的连贯性、预期数据的收集、终点指标能恰当反映研究目的、终点指标评价的客观性、随访时间是否充足、失访率<5%以及是否估算了样本量，每个条目为 0~2 分，总分为 16 分。随机对照试验采用 Cochrane 风险评估工具进行质量评价。

1.4 统计学方法

采用 RevMan 5.4 软件进行 Meta 分析，当样本整体不符合正态分布时，需对结果进行转化以估计实际发病率。CLS 发生率(P)及其标准误 *SE*(P)的计算公式：P=ln(odds)=In[*X*/(*n*−*X*)]，*SE*(P)= *SE*[ln(odds)]=[1/*X*+1/(*n*−*X*)]$^{1/2}$，其中 *X* 为 CLS 发生例数，*n* 为样本量；换算后所得的发病率用 *Pt* 表示：*Pt*=*OR*/(1+*OR*)；95%*CI* 下限：LL=*LLOR*/(1+*LLOR*)；95%*CI* 上限：UL=*ULOR*/(1+*ULOR*)。对数据进行异质性检验，结果具有同质性($P\geq0.10$ 且 $I^2\leq50\%$)时，使用固定效应模型进行处理；结果具有异质性($P<0.10$ 且 $I^2>50\%$)时，则使用随机效应模型进行处理。

2 结果

2.1 文献筛选结果与纳入文献的基本特征

初步检索得到 1 799 篇文献，其中 the Cochrane Library 2 篇，PubMed 1 788 篇，Embase 9 篇，中国知网 0 篇；筛选后最终纳入 70 篇[4-73]，均为单臂临床研究，合计 3 002 例患者。纳入文献的基本特征见表 1。

表 1 纳入文献的基本特征

药物类别	国家	样本量/例	CLS/例	CLS 发生率/%	参考文献
白细胞介素(IL)2	美国、以色列、日本、法国、英国、中国	4~408	1~92	4.0~100.0	[4-25]
IL-2 联合其他药物	以色列、英国、法国、爱尔兰、瑞士、美国	3~226	0~51	0~100.0	[5,8,21,26-33]
IL-1、IL-3、IL-4	美国	9~47	2~9	10.3~44.4	[34-39]
粒细胞-巨噬细胞集落刺激因子	法国、意大利、美国、英国	14~44	1~3	6.8~15.0	[40-42]
吉西他滨	法国、日本、美国	23~36	1	2.8~4.3	[43-46]
抗 CD 单克隆抗体类药物	美国、瑞士、德国、	5~80	1~18	2.5~100.0	[47-64]
其他类	美国、英国、其他欧洲国家	5~56	1~12	2.2~80.0	[65-73]

2.2 文献质量评价

采用 MINORS 量表对纳入的文献进行质量评价，结果显示，1 篇文献评分为 12 分，31 篇文献评分为 13 分，29 篇文献评分为 14 分，9 篇文献评分为 15 分，纳入的文献整体质量较高。

2.3 Meta 分析结果

2.3.1 IL-2：22 篇文献[4-25](共 23 项研究)报告了 IL-2 引起 CLS 的发生率，采用随机效应模型进行 Meta 分析。结果显示，经换算得到总体 *Pt* 估计为 29%(95%*CI*=19%~40%)，见图 1。

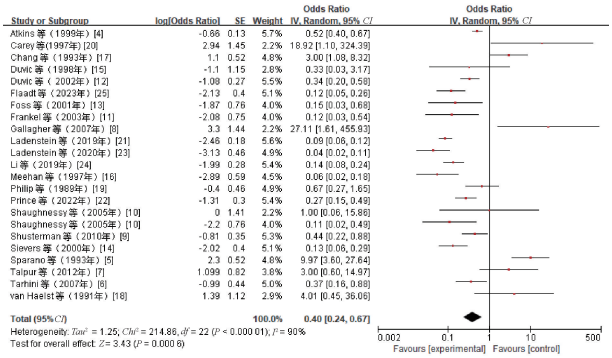

图 1 IL-2 引起 CLS 发生率的森林图

2.3.2 IL-2 联合其他药物：11 篇文献[5,8,21,26-33](共 13 项研究)报告了 IL-2 联合其他药物引起 CLS 的发生率，采用随机效应模型进行 Meta 分析。经换算得到总体 *Pt* 估计为 29%(95%*CI*=16%~46%)，其中 IL-2+贝伐珠单抗引起 CLS 的发生率为 100%[8]，IL-2+α 干扰素(IFN-α)引起 CLS 的发生率为 81%[5]，见图 2。

2.3.3 IL-1、IL-3、IL-4：6 篇文献[34-39]报告了 IL-1、IL-3、IL-4 引起 CLS 的发生率，采用固定效应模型进行 Meta 分析。经换算得到总体 *Pt* 估计为 23%(95%*CI*=17%~31%)，见图 3。

2.3.4 粒细胞-巨噬细胞集落刺激因子：3 篇文献[40-42]报告了粒细胞-巨噬细胞集落刺激因子引起 CLS 的发生率，采用固定效应模型进行 Meta 分析。经换算得到总体 *Pt* 估计为 10%(95%*CI*=5%~19%)，见图 4。

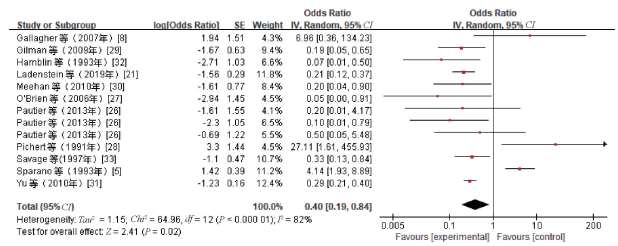

图 2 IL-2 联合其他药物引起 CLS 发生率的森林图

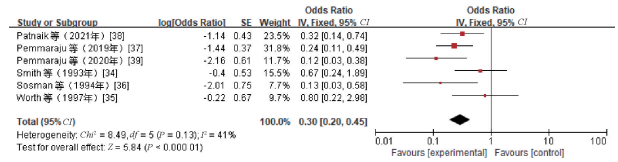

图 3 IL-1、IL-3、IL4 引起 CLS 发生率的森林图

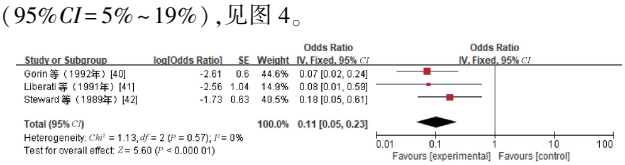

图 4 粒细胞-巨噬细胞集落刺激因子引起 CLS 发生率的森林图

2.3.5 吉西他滨：4 篇文献[43-46]报告了吉西他滨引起 CLS 的发生率，采用固定效应模型进行 Meta 分析。经换算得到总体 *Pt* 估计为 3%(95%*CI*=1%~8%)，见图 5。

2.3.6 抗 CD 单克隆抗体类药物：18 篇文献[47-64]报告了抗 CD 单克隆抗体类药物引起 CLS 的发生率，采用随机效应模型进行 Meta 分析。经换算得到总体 *Pt* 估计为 21%(95%*CI*=12%~33%)，见图 6。

2.3.7 其他类：9 篇文献[65-73](共 10 项研究)报告了其他抗肿瘤药物与 CLS 的相关性，CLS 的发生率为 3%~80%。其中，使

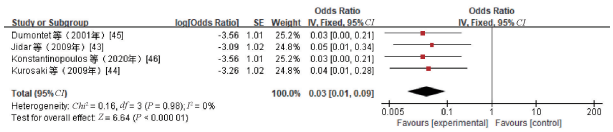

图 5　吉西他滨引起 CLS 发生率的森林图

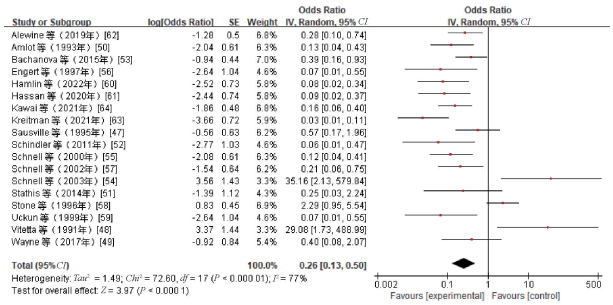

图 6　抗 CD 单克隆抗体类药物引起 CLS 发生率的森林图

用吡咯并苯二氮䓬类药物[67]（1 项研究，CLS 发生率为 63%）及紫杉醇[69]（1 项研究，CLS 发生率为 80%）时，CLS 发生率较高。

3　讨论

CLS 是由于毛细血管对蛋白质的通透性增加而引起的一系列病理表现，其具体机制尚不清楚，且没有特定的治疗方法。当前许多研究结果表明，CLS 常作为恶性肿瘤治疗中的不良反应/事件出现，药物是引起继发性 CLS 的主要原因，特别是抗肿瘤药物，这可能与抗肿瘤药物对内皮细胞的直接侵袭相关[74]。

IL-2 作为一种恶性肿瘤免疫疗法，其引起 CLS 的发病率为 34.7%～43.9%，且 IL-2 的剂量与 CLS 的总发生率之间没有相关性[75]。动物实验研究结果显示，IL-2 可能通过增强中性粒细胞黏附和生成活性氧中间体、蛋白酶及促炎细胞因子（如肿瘤坏死因子 α），引起正常组织急性损伤，从而导致血管渗漏[76]。在使用抗肿瘤药物引发 CLS 的病例中，人粒细胞刺激因子（CLS 发生率为 14.6%）和 IL-2（CLS 发生率为 11.4%）是最常见的相关药物[77]。

本研究通过 Meta 分析的方法，系统评价了抗肿瘤药物引起 CLS 的发生率，结果显示，IL-2 单独使用或联合其他药物使用时引发 CLS 的概率最高（为 29%）；其他 IL 类、抗 CD 单克隆抗体类药物、粒细胞-巨噬细胞集落刺激因子和吉西他滨引起 CLS 的发生率分别为 23%、21%、10%和 3%；IL-2+贝伐珠单抗及 IL-2+IFN-α 引起 CLS 的发生率较高（分别为 100%、81%）；IL-2+甲磺酸伊马替尼（3 项研究）和抗 CD22 单克隆抗体（8 项研究）引起 CLS 的发生率呈剂量依赖性升高。上述结果提示，临床医师在选择抗肿瘤治疗药物时应充分考虑 CLS 相关不良反应的风险，密切关注患者状态，及早预防并及时采取有效措施。

异质性分析：（1）本研究纳入的文献时间跨度较大，为 1982—2023 年，期间诸多因素（如环境、医疗条件）会影响结果的稳定性；（2）不同恶性肿瘤类别，不同分型、不同给药剂量和疗程，均会增加异质性，使结果出现偏倚；（3）部分研究之间样本量相差较大，容易产生误差。

本研究的局限性：（1）吉西他滨、粒细胞-巨噬细胞集落刺激因子的相关研究较少，可能导致 Meta 分析的结果不准确；（2）未检索到中文相关文献，纳入的研究以美国和欧洲地区为主，亚洲仅有 2 篇，结果可能存在片面性；（3）纳入的研究较多，未进行敏感性分析和亚组分析，可能影响结果的准确性。

综上所述，CLS 是恶性肿瘤治疗过程中常见的不良反应，使用抗肿瘤药物是引发 CLS 的关键危险因素，了解该类药物与 CLS 发生率的相关性有助于提早预防并及时采取有效治疗措施，改善患者预后。

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