● 综述 ●

肿瘤治疗相关血管并发症诊疗进展

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[摘要] 在过去数十年中,肿瘤治疗手段不断拓展,但同时也带来了各种心血管并发症。本文将综述各种肿瘤治疗引起的血管毒性效应的发生机制及治疗策略,主要从肿瘤治疗相关高血压、冠状动脉疾病及血栓栓塞疾病三大方面阐述目前肿瘤治疗相关血管并发症的研究现状,以期使临床医师更好地认识肿瘤治疗相关血管并发症,及时识别、正确处理。

[关键词] 肿瘤治疗;血管并发症;高血压;冠状动脉疾病;血栓栓塞
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Vascular Complications Related to Cancer Therapies: Advances in Diagnosis and Treatment

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[**Abstract**] The spectrum of therapies of cancer has broadened considerably over the past decade and also results in several cardiovascular complications. This article will review vascular toxic effects associated with cancer therapies, potential mechanisms and treatment strategies, focusing on current status of cancer therapy-related hypertension, coronary artery disease and thromboembolic disease, with the aim of giving a better understanding of cancer therapy-related vascular complications and assisting physicians to identify and manage patients with vascular complications in their daily practice.

[**Key words**] Cancer therapy; Vascular complication; Hypertension; Coronary artery disease; Thromboembolic disease

对于肿瘤患者,血管并发症是常见的肿瘤治疗引发的并发症,且极大地影响患者生存质量及预后。依据《2016 年欧洲心脏病学会肿瘤治疗与心血管毒性指南》,肿瘤治疗相关的血管并发症主要包括:冠状动脉疾病、高血压、血栓栓塞与外周血管疾病,其中最常见的血管并发症为高血压[1]。本文回顾已发表的临床研究及指南,阐述肿瘤治疗的血管毒性效应,并对可能导致血管并发症的治疗药物及方法进行梳理,总结治疗策略,希望为临床工作实践提供指导。

1 肿瘤治疗相关高血压并发症

高血压是许多化疗药物、靶向治疗药物的常见并发症,尤其是血管生成抑制剂。约 1/3 的肿瘤患者在病程中会出现新发高血压[2]。对于肿瘤患者,高血压并发症的发生除与化疗、靶向治疗相关外,某些恶性肿瘤本身也会对血压造成影响,如肾癌。一项前瞻性队列研究显示,儿童癌症幸存者与一般人群相比,高血压患病率较高,且患病率随年龄增长显著增加,30 岁时儿童癌症幸存者高血压患病率为 13%,40 岁时达到 37%,50 岁时则超过 70%[3]。

1.1 常见引起高血压的肿瘤治疗方式

1.1.1 分子靶向血管生成抑制剂 分子靶向血管生成抑制剂对诱发新发高血压风险较高,并可能使既往已控制的血压升高,造成血压控制不佳,甚至诱发高血压急症或亚急症。目前认为血管生成抑制剂引起高血压的机制为此类药物可导致内皮功能异常和血管生成异常,包括毛细血管减少、微血管网改

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变、血管壁顺应性降低、一氧化氮的生物活性降低等[2]。现有的血管生成抑制剂都可能导致高血压的发生,荟萃分析报道的使用血管生成抑制剂治疗患者的高血压发生率见表 1。

表 1 分子靶向血管生成抑制剂相关高血压发生率

Table 1. Incidence of Molecularly Targeted Antiangiogenic Agents-Related Hypertension

Molecularly targeted antiangiogenic agents	Incidence
Bevacizumab[4]	23.6%
Ramucirumab[5]	21.3%
Sunitinib[6]	21.6%
mSorafenib[7]	15.3%
Axitinib[8]	40.1%
Vandetanib[9]	24.2%
Regorafenib[10]	44.4%
Pazopanib[11]	35.9%
Apatinib[12]	45.4%

虽然高血压为血管生成抑制剂的主要副作用,但有研究发现药物相关的血压升高与抗肿瘤治疗效果、疾病预后存在相关性[13-16]。若患者出现治疗相关高血压,则预示抗肿瘤治疗有效。可能的原因为血管生成抑制剂所致血压升高提示该药有效阻断血管生成通路,因而可能产生较好的抗肿瘤治疗效果。然而,目前这一观点并未得到广泛的证实[17],仍有待进一步研究验证血压升高可否作为血管生成抑制剂治疗疗效的有效预测指标。

1.1.2 *蛋白酶体抑制剂* 蛋白酶体抑制剂是一种作用于泛素-蛋白酶体通路从而诱导肿瘤细胞凋亡的化疗药物。卡非佐米(carfilzomib)是第二代蛋白酶体抑制剂,用于治疗多发性骨髓瘤。卡非佐米相关高血压发生率高于一代蛋白酶体抑制剂硼替佐米(bortezomib)(15% *vs* 3%)[18],高血压是其最常见的心血管不良反应[19]。在其临床试验中,新发高血压的发生率为 14.3% ~25%[20]。近期的一项前瞻性研究显示,在接受卡非佐米治疗的多发性骨髓瘤患者中约 5% 的患者因出现难以控制的高血压,而暂停卡非佐米的治疗[21]。

1.1.3 *磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase, PI3K)抑制剂* PI3K 在细胞生长、增殖和凋亡过程中起关键作用,与肿瘤的发生发展密切相关。库潘尼西(copanlisib)是一种 PI3K 抑制剂,它能抑制 PI3K-α 和 PI3K-δ 两种激酶亚型。在正常人体内,PI3K 介导的信号通路在细胞生长、存活和代谢方面都有很重要的作用,该药主要用于治疗复发性滤泡性淋巴瘤。血压的一过性升高是库潘尼西常见的副作用。在库潘尼西治疗复发或难治性淋巴瘤的二期临床试验中,30% ~58% 的患者出现一过性高血压[22-23]。研究表明库潘尼西相关高血压通常发生在第一次静脉给药时,静脉给药 2 小时后血压升高达到峰值,后血压逐渐下降,患者多在给药后 24h 内恢复正常血压,收缩压和舒张压分别平均升高 16.8mmHg 和 7.8mmHg[24]。

1.2 监测与治疗

抗肿瘤药物使用患者一旦开始使用这些可能导致高血压的药物,即应定期监测血压,尤其在治疗早期阶段应更密切地监测血压[25]。控制高血压的首要目的是降低靶器官损害的风险。除此之外,血压的良好控制与管理是保障抗肿瘤药物持续使用的前提条件,如果血压过高或难以控制将迫使肿瘤治疗终止。肿瘤治疗相关高血压的降压治疗与常规高血压治疗类似。对于正在接受抗肿瘤治疗的患者,血管紧张素转化酶抑制剂(angiotensin-converting enzyme inhibitors, ACEI)或血管紧张素Ⅱ受体阻滞剂(angiotensin Ⅱ receptor blockers, ARBs)、二氢吡啶类钙通道阻滞剂为首选的降压药物[26]。在选择降压药物时,应尽量避免药物相互作用,例如索拉非尼通过细胞色素 p450 系统(主要为 CYP3A4)代谢,对于正在使用索拉非尼的高血压患者应避免使用地尔硫卓、维拉帕米等非二氢吡啶类钙通道阻滞剂。该类药物抑制 CYP3A4 同工酶,可能使药物血药浓度升高,应避免使用[1]。如果出现严重的、难治性高血压,应及时中断抗肿瘤药物治疗。

2 肿瘤治疗相关冠状动脉疾病

放射治疗、化疗及靶向治疗,均与加速发展冠状动脉疾病和/或急性冠状动脉综合征(acute coronary syndrome, ACS)相关。抗肿瘤治疗引起心肌缺血机制是多种多样的,包括血管痉挛、内皮损伤、急性动脉血栓形成,以及长期脂质代谢异常和随之而来的动脉粥样硬化加速发展。此外,既往纵隔放疗亦可加速药物相关性冠状动脉损伤[1]。

2.1 常见引起冠状动脉疾病的肿瘤治疗方式

2.1.1 *化疗* 常见的可能引起冠状动脉疾病的化疗药物有:氟尿嘧啶、卡培他滨、来那度胺、紫杉醇等。近期一项研究纳入 527 名接受氟尿嘧啶或卡培他滨化疗的肿瘤患者,19.9% 的患者在治疗后出现心电图缺血性改变,1.1% 的患者发生心肌梗死[27]。有研究表明氟尿嘧啶的不同给药方式所致胸痛特点

不同。氟尿嘧啶通过静脉注射给药时,胸痛通常发生在推注过程中或给药完成后数分钟内,为典型的心绞痛症状,心电图伴有 ST 段抬高。而静脉缓慢滴注氟尿嘧啶,胸痛通常在第 1 ~2 化疗周期输注完成后的 24 ~72h 出现,心绞痛症状不典型,胸痛间断出现,可忍受,心电图检查多无特殊改变[28]。铂类药物也会造成血管内皮损伤[29]。在接受紫杉醇治疗的患者中,约有 3% 的患者发生心肌缺血、心肌梗塞[30]。

2.1.2　*放疗*　辅助性放射治疗在早期乳腺癌、霍奇金病和其他胸部恶性肿瘤的治疗中能够使患者生存率显著改善。但同时,放射治疗亦可引起冠状动脉疾病。放疗相关冠状动脉粥样硬化通常发生在放疗后的 10 ~15 年[31]。其可能机制为,血管受到辐射后,毛细血管壁通透性增加,同时激活血管炎症级联反应,随之导致内膜增生,胶原沉积和纤维化。上述变化可导致冠状动脉狭窄及动脉粥样硬化斑块形成。

纵膈放疗的晚期心血管并发症是霍奇金病幸存者继肿瘤复发的第 2 常见死亡的原因,占治愈患者死亡原因的 25%,心肌梗死是该亚组最常见的死因[32]。并且,仍有研究发现接受胸部放射治疗的长期存活者其心血管疾病发病率显著增加,需要进行冠状动脉搭桥手术和经皮冠状动脉介入治疗的概率增加,分别为未接受放疗患者的 3.2 倍和 1.6 倍[32]。乳腺癌及肺癌患者在接受放疗期间,心脏不可避免暴露于电离辐射,这也增加了患者缺血性心脏病的发生率,增加的风险与心脏所接受辐射的平均剂量成正比[33-34]。接受左侧乳腺放疗的患者,与接受右侧乳腺放疗的患者相比,发生缺血性心脏病的风险增高 1.2 倍[35-36]。

2.1.3　*分子靶向血管生成抑制剂*　接受血管生成抑制剂治疗的肿瘤患者,可能出现心绞痛[25],且其心肌缺血及心肌梗塞的风险也明显增高。在一项纳入 903 名晚期肾细胞癌患者的临床研究中,接受索拉非尼治疗的患者中有 2.9% 发生心肌缺血或梗死,而接受安慰剂治疗的患者中的发生率为 0.4%[37]。荟萃分析提示贝伐珠单抗治疗使肿瘤患者发生心肌缺血的风险增高。与对照组相比,治疗组患者其发生严重心肌缺血的风险增高 2.14 倍[38]。

2.2　监测与治疗

既往存在冠状动脉疾病是化疗引起 ACS 的独立危险因素。在治疗前,应了解患者既往是否有冠状动脉疾病史,及相关危险因素,对于高危患者在治疗过程中应动态监测心肌标志物及心电图变化[39]。与非肿瘤患者相比,肿瘤患者发生急性冠脉综合征时临床表现常不典型,约 30% 的肿瘤 ACS 患者出现胸痛,44% 出现呼吸困难,23% 出现低血压[39]。肿瘤患者的最常见心肌梗死类型为非 ST 段抬高型心肌梗死,约占 67%[40]。对于所有怀疑 ACS 的患者均应根据 ACS 指南进行诊断和治疗,包括:使用他汀类药物和 β 受体阻滞剂、经皮冠状动脉介入治疗以及抗血小板和抗凝药物治疗,并暂时停止抗肿瘤治疗[41]。需要注意的是,经皮冠状动脉介入、抗血小板和抗凝药物治疗都会显著增加癌症患者的出血风险,因此对于该类药物及治疗方式的使用应根据病情综合评估。

3　肿瘤治疗相关血栓栓塞性疾病

恶性肿瘤患者的血栓形成和出血的风险均较正常人显著增加[42-43]。约 20% 的肿瘤患者会发生血栓栓塞事件[44]。肿瘤患者血栓形成风险增加的可能机制主要是由于组织因子、粘蛋白和半胱氨酸蛋白酶等血栓形成前因子释放到血液中激活凝血级联反应[45-46]。血栓栓塞的风险在某些肿瘤中发生率更高(如:多发性骨髓瘤、肺癌、结直肠癌等)。接受抗肿瘤治疗可使其血栓风险进一步增加[47]。

3.1　常见增加血栓栓塞风险的肿瘤治疗方式

3.1.1　*分子靶向血管生成抑制剂*　研究表明,接受血管生成抑制剂治疗的肿瘤患者动脉血栓栓塞事件(arterial thrombosis event, ATE)发生率显著增加[42]。血管生成抑制剂可改变血管止血平衡,干扰内皮细胞的再生能力,并引起血管内皮层的缺陷,导致血栓和出血。贝伐珠单抗被证实可显著增加肿瘤患者的动脉血栓栓塞事件的风险。与单纯化疗相比,化疗联合贝伐珠单抗治疗的 ATE 风险增加了两倍[48]。年龄 65 岁以上和既往 ATE 病史是再次发生 ATE 的独立危险因素。对于年龄大于 65 岁、有 ATE 病史的患者,贝伐珠单抗治疗相关的 ATE 风险从 2% 增加到 18%。舒尼替尼和索拉非尼也被证实与动脉血栓栓塞事件相关。在纳入 10 255 名接受索拉非尼或舒尼替尼治疗患者的荟萃分析中,索拉非尼和舒尼替尼的 ATE 发生率分别为 1.7% 和 1.4%[49]。

贝伐珠单抗是否增加静脉血栓栓塞事件(venous thrombosis event, VTE)的风险尚无定论。不同研究显示出不同的结果。Hurwitz 等[50]的荟萃分析提示贝伐珠单抗联合化疗与单纯化疗相比,VTE 风

险未增加。而另外两项荟萃分析显示化疗联合贝伐珠单抗与单纯化疗相比，VTE 风险增加，相对危险度分别为 1.33 和 1.14[51-52]。酪氨酸激酶抑制剂与 VTE 之间的关系也尚不确定。在纳入 7 441 名实体瘤患者的荟萃分析中，未发现接受舒尼替尼、索拉非尼、帕佐帕尼、凡德他尼及阿西替尼治疗的肿瘤患者的静脉血栓事件增加[53]。近期有学者通过荟萃分析，对比双盲研究与开放式非盲研究中血管生成抑制剂的 VTE 的比值比(odds ratio，OR)，发现纳入非盲研究的 OR 为 1.53，而在双盲研究中 OR 值为 0.99[54]。

3.1.2 *沙利度胺和来那度胺* 沙利度胺及其前体药物来那度胺会增加血栓栓塞的风险[55]。使用来那度胺发生血栓栓塞的风险在不同文献报道中为 3% ~75%，而沙利度胺的风险为 1% ~58% [56]。沙利度胺可引起凝血因子 VIII、凝血因子 IX、血管性血友病因子、纤维蛋白原升高和可溶性血栓调节蛋白降低，这是其引起血栓栓塞风险增加的可能原因[56-57]。而来那度胺与地塞米松联合使用时，血栓风险则会进一步增加[58]。

3.2 预防与治疗

肿瘤患者血栓的发现主要基于患者的临床症状。对患者进行常规动静脉血栓筛查并未显示出获益。患者进行肿瘤影像学检查时(如胸部 CT)，可能偶然发现肺栓塞或静脉血栓。但如何处理无临床症状的静脉血栓尚无定论[1]。由于肿瘤患者的血栓栓塞风险和出血风险同时存在，抗血小板药物或抗凝剂是否应用对于临床医师来说是一个两难的选择，需充分评估患者的血栓栓塞风险和出血风险后再行决定治疗方案。使用阿司匹林、华法林(国际标准化比率为 2.0 ~3.0)或治疗剂量的低分子肝素可以减少静脉血栓栓塞的风险[59-60]。肿瘤患者使用新型口服抗凝药的临床研究数据有限。近期发表的几项研究显示，依度沙班在治疗肿瘤患者静脉血栓的效果不劣于低分子肝素 [61]。在门诊高危血栓风险的肿瘤患者中预防性使用利伐沙班未能显著降低静脉血栓事件的发生率[62]。高危血栓风险的肿瘤患者预防性使用抗凝药物能否带来获益目前尚无定论。

4 总 结

肿瘤治疗相关血管并发症，主要包括最常见的高血压，冠状动脉疾病及血栓栓塞疾病 3 大类。肿瘤本身也是血栓栓塞的危险因素，某些肿瘤也可引起高血压。对于肿瘤患者而言，接受放疗、化疗、靶向治疗均可能使血管并发症的风险增加。血管并发症影响患者生存质量及预后。针对肿瘤患者，如何合理有效地评估抗肿瘤治疗相关血管并发症风险尚无相关共识、指南，仍有待进一步探索研究。对于已经发生的血管并发症，治疗原则遵循并发症相关指南，同时应结合患者情况，制定个体化治疗方案。

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