抗肿瘤药物的心血管毒性及其防治的研究进展

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摘要: 肿瘤和心血管疾病是全球导致死亡的两大主要原因。抗肿瘤药物的应用明显改善患者的预后, 而其引起的心血管毒性已经成为影响肿瘤患者生存和预后的重要因素, 因此对肿瘤治疗相关心血管并发症的防治日益重要。抗肿瘤药物相关的心血管毒性显示出不同的临床表现, 涉及多种病理机制。本文从抗肿瘤药物所致心血管毒性的特点、分子机制、防治策略等角度回顾了当前的研究进展, 对其进行简要综述。

关键词: 抗肿瘤药物; 心脏毒性; 血管毒性; 病理机制; 预防和治疗

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Research progress on cardiovascular toxicity associated with anti-tumor drugs and its prevention and treatment

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Abstract: Cancer and cardiovascular diseases are the two major causes of death worldwide. The application of anti-tumor drugs has significantly improved the prognosis of patients, the cardiovascular toxicity caused by the application of them has become an important factor affecting the survival and prognosis of cancer patients. Therefore, the prevention and treatment of cardiovascular toxicity related to cancer treatment is increasingly important. The cardiovascular toxicity associated with anti-tumor drugs exhibits different clinical manifestations and involves multiple pathological mechanisms. This article reviews the current research progress from the perspective of the characteristics, molecular mechanisms and prevention and treatment strategies of cardiovascular toxicity caused by cancer drugs.

Key words: anti-tumor drug; cardiac toxicity; vascular toxicity; pathological mechanism; prevention and treatment

肿瘤和心血管疾病是全球发病率和死亡率最高的两大疾病, 预计到2040年, 全球肿瘤患者将达到2 840万例, 比2020年增加47%[1]。肿瘤治疗领域已取得的巨大进展使肿瘤患者的预后显著改善。然而, 这些治疗产生的毒性可能对患者产生短期或长期的不良影响。与肿瘤治疗相关的心血管毒性 (cancer therapy-related cardiovascular toxicity, CTR-CVT) 是癌症患者治疗和管理中最大的挑战之一, 影响患者的生活质量和长期预后。此类不良事件不仅与蒽环类等较老的化

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疗药物有关, 还与许多靶向治疗和免疫治疗有关。本综述将对抗肿瘤药物引起的心血管毒性、预防与治疗策略、未来研究方向等进行阐述。

1 抗肿瘤药物的心血管毒性

1.1 心脏毒性

1.1.1 蒽环类药物

蒽环类药物 (anthracyclines, ANTs) 如多柔比星 (doxorubicin, DOX)、表柔比星、柔红霉素等, 是最有效和应用最广泛的抗肿瘤药物之一。但临床发现其应用会引起左心室功能不全和心力衰竭 (heart failure, HF)[2]。DOX 引起的慢性心脏毒性具有剂量依赖性, 当累积剂量为 400 mg·m^{-2} 时, HF 的发生率为 3%～5%, 550 mg·m^{-2} 时为 7%～26%, 700 mg·m^{-2} 时为 18%～48%[3]。组织学上, ANTs 引起心肌间质纤维化和心肌细胞坏死, 最终导致心脏扩张、心室壁变薄和左心室功能降低[4]。

基础研究发现, ANTs 引起心脏毒性的机制主要涉及加重氧化应激、干扰铁代谢及与拓扑异构酶 II 相互作用等。DOX 诱导心脏长期毒性, 导致心脏不可逆的功能障碍, DOX 通过产生活性氧与活性氮, 增加氧化应激, 破坏 DNA、引起蛋白质羰基化和脂质过氧化, 导致线粒体受损和心肌细胞死亡[5]。DOX 与氧化还原活性铁池作用干扰铁代谢, 并增加线粒体铁蛋白的含量, 诱导活性氧产生, 加剧氧化应激损伤[6]; 同时 DOX 也抑制两种拓扑异构酶—2A (topoisomerase 2A, TOP 2A) 和 2B (topoisomerase 2B, TOP 2B) 的功能, 阻断 DNA 复制和转录。另外, DOX 与心肌细胞中的 TOP2B 结合, 形成 TOP2B/DOX/DNA 复合物, 导致 DNA 双链断裂, 刺激 p53 相关基因的表达, 抑制过氧化物酶体增殖激活受体 γ 辅激活因子 1α, 导致线粒体功能障碍, 诱导心肌细胞死亡[7]。细胞凋亡和自噬缺陷也是 DOX 诱导心脏毒性的原因。DOX 通过抑制腺苷酸活化蛋白激酶 [adenosine 5′-monophosphate (AMP)-activated protein kinase, AMPK] 信号通路, 导致心肌肥厚、能量应激[8]。DOX 抑制磷脂酰肌醇 3-激酶/蛋白激酶 B/哺乳动物雷帕霉素靶蛋白 [phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/the mammalian target of rapamycin (mTOR), PI3K/Akt/mTOR] 信号通路的活化, 并诱导半胱氨酸天冬氨酸蛋白酶-3 的活化, 导致细胞凋亡[9]。此外, DOX 还可通过下调 Bcl-2 的蛋白表达, 抑制 Bcl-2/Beclin1 的相互作用启动自噬过程, 导致细胞死亡[10]。

1.1.2 分子靶向药物

1.1.2.1 人表皮生长因子受体 2 抑制剂 人表皮生长因子受体 2 (human epidermal growth factor receptor 2, HER2 或 ErbB2) 抑制剂, 如曲妥珠单抗, 显著改善 HER2 阳性乳腺癌患者的预后。临床中发现接受曲妥珠单抗辅助治疗的患者中, 13.5% 的患者由于心脏毒性中断治疗 [30% 为 HF, 70% 为无症状左心室射血分数 (left ventricular ejection fraction, LVEF) 下降][3]。其危险因素包括老年、肥胖、既往 ANTs 治疗、高血压、LVEF 较低。不同 HER2 的抑制剂诱发的心肌病和 HF 发生率存在差异, 曲妥珠单抗分别为 2%～18% 和 0.3%～4%, 帕妥珠单抗分别为 3%～7% 和 0.3%～1%[11]。在 APHINITY 研究中, 曲妥珠单抗/帕妥珠单抗组 15 例患者 (0.6%) 和曲妥珠单抗/安慰剂组 6 例患者 (0.2%) 出现 NYHA III 或 IV 级 HF 和 LVEF 显著下降, 在曲妥珠单抗治疗的基础上增加帕妥珠单抗并未明显增加心脏毒性[12]。

HER/ErbB 家族包括 ErbB1、ErbB2、ErbB3 和 ErbB4。基础研究机制表明 ErbB2 在心肌细胞发育中发挥重要作用。曲妥珠单抗抑制心肌细胞 ErbB2 的信号转导被认为是产生心脏毒性的核心机制之一。心脏神经调节蛋白 1 (neuregulin 1, NRG1) 与心肌细胞上的 ErbB4 结合, ErbB2 与 ErbB4 异源二聚体自磷酸化, 激活丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)、PI3K、蛋白激酶 C 和信号传导及转录激活蛋白等, 发挥对心脏的应激保护作用, 曲妥珠单抗抑制 NRG1 通路, 导致心脏毒性发生[13]。同时, 抗 ErbB2 抗体诱导的 Bcl-xS/Bcl-xL 增加可能引发 Bax 寡聚、线粒体膜去极化、ATP 耗尽和心脏收缩功能障碍[14]。因此, 曲妥珠单抗会促进氧化应激, 导致 DNA 断裂和诱导线粒体凋亡途径。ErbB2 抑制还可通过诱导活性氧产生来促进 ANTs 的心脏毒性, 其机制仍不清楚[15]。

1.1.2.2 血管内皮生长因子抑制剂 血管生成是肿瘤细胞增殖、侵袭和转移的重要环节, 血管内皮生长因子抑制剂 (vascular endothelial growth factor inhibitors, VEGFIs) 的出现是实体器官恶性肿瘤患者治疗领域的一个重大进展。临床发现 VEGFIs 相关的心脏毒性从无症状左室收缩功能不全 (left ventricular systolic dysfunction, LVSD) 到 HF、心源性休克和死亡, 但其真实发生率尚未明确[16]。VEGFIs 相关的心脏毒性具有可逆性, 60%～80% 患者停药后损伤的心脏可恢复[17]。冠状动脉疾病 (coronary artery disease, CAD)、高血压是 VEGFIs 相关心脏毒性的危险因素, 继往或同时使用其他心脏毒性药物 (如 ANTs)、心脏后负荷增加、甲状腺功能减退、糖尿病也会增加 VEGFIs 诱导心脏毒性的风险[18]。在一项大型前瞻性临床研究中, 使用 VEGF-A 特异性血管生成抑制剂贝伐珠单抗治疗的患

者的心功能下降的发生率为2%, NYHA 3级或4级HF的发生率为1%[19]。贝伐珠单抗与ANTs合用时, LVSD和HF的风险增加。在MAIN试验, 接受R-CHOP治疗 (利妥昔单抗、环磷酰胺、多柔比星、长春新碱和泼尼松龙) 加贝伐珠单抗治疗组的患者发生LVSD和HF的风险是R-CHOP加安慰剂组的3倍, 发生率分别为18% *vs* 8%和16% *vs* 7%[20]。抑制血管内皮生长因子 (vascular endothelial growth factor, VEGF) 的酪氨酸激酶抑制剂 (tyrosine kinase inhibitors, TKIs) 如舒尼替尼、索拉菲尼是多激酶抑制剂。在接受舒尼替尼和索拉菲尼治疗的患者中, HF发生率大约为4.1%和1%[21]。

同时有研究比较了被美国食品和药物管理局 (Food and Drug Administration, FDA) 批准的9种VEGFR-TKI在实体瘤患者中的心血管风险。凡德他尼具有显著的QT间期延长作用 (16%～18%), QT间期 > 500 ms的加权发生率为2.6%[22]。有研究报道凡德他尼可延长多能干细胞分化的心肌细胞动作电位, 抑制hERG (human ether-a-go-go related gene) 钾通道电流, 同时抑制钠电流和钙电流[23]。

与VEGF相关的信号通路在维持血管稳态、心脏发育和功能方面起着关键作用[24]。VEGFIs相关LVSD和HF的发生机制可能涉及多种心肌损伤的联合作用。心脏毒性机制可能源于对VEGF直接抑制的"靶向"效应或抑制其他TKIs引起的"脱靶"效应, 由其选择性程度和作用方式决定[16]。心肌细胞特异性VEGF敲除的小鼠, 子宫内活胎率有限, 少量出生的小鼠心室壁变薄, 心脏功能受损, 这表明VEGFI可能具有直接的心肌细胞毒性作用[25]。VEGF-TKIs导致大约80种激酶失调, 常常诱发其"脱靶"效应[26]。舒尼替尼的主要靶点是VEGFR1-3, 但其也可下调AMPK, 增加心肌细胞能量消耗, 并启动线粒体凋亡途径, 是其引起心肌病/HF的重要机制[27]。AMPK下调可能是VEGFI的脱靶效应。另外, 索拉菲尼抑制至少15种激酶, 临床前研究显示索拉菲尼对原癌基因丝氨酸/苏氨酸蛋白激酶的抑制与心肌凋亡和心脏功能受损有关[28]。

1.1.2.3 表皮生长因子酪氨酸激酶抑制剂 口服的第三代不可逆表皮生长因子受体–酪氨酸激酶抑制剂 (epidermal growth factor receptor tyrosine kinase inhibitor, EGFR-TKI) 奥希替尼, 已成为EGFR突变的非小细胞肺癌 (non-small cell lung cancer, NSCLC) 患者的首选TKI[29]。但研究发现奥希替尼治疗可导致显著的心脏毒性。在一项药物警戒研究中, 接受奥希替尼治疗的患者发生HF的可能性是其他EGFR-TKI (如厄洛替尼、阿法替尼和吉非替尼) 的2倍, HF事件的中位发生时间为29天[30]。在服用奥希替尼时, 应监测患者HF的体征和症状。FLAURA临床试验研究发现奥希替尼的QT间期延长率 (10%) 高于吉非替尼和厄洛替尼 (5%)[31]。一项针对NSCLC靶向治疗相关心脏毒性的药物警戒分析的研究发现, 奥希替尼与QT间期延长的相关性较强, 其发生风险是其他EGFR抑制剂的49倍, 且约有4%的病例死亡[32]。因此, 对于既往有QT间期延长病史或同时使用其他延长QT间期的药物的患者, 在考虑使用奥希替尼时, 应监测QT间期。

在体外细胞实验中, 奥希替尼显示出对心脏hERG钾通道弱抑制, 这可能是奥希替尼诱导QT间期延长的机制[33]。奥希替尼对EGFR具有高度特异性, 但小鼠模型显示其对ErbB2 (HER2) 有抑制作用, 这种效应是否是增加心脏毒性的原因需要进一步探索[34]。

1.1.2.4 蛋白酶体抑制剂 硼替佐米、卡非佐米和艾沙佐米是治疗多发性骨髓瘤的蛋白酶体抑制剂 (proteasome inhibitors, PIs)。在临床使用的PIs中, 卡非佐米导致HF的风险显著升高 (25%)[35]。近期一项大型药物警戒研究表明, 使用卡非佐米可导致多种心血管不良事件发生, 包括全身性高血压、缺血性心脏病、血栓栓塞事件等。心血管事件中位发病时间为41天, 缺血性心脏病中位发病时间最短为16天[36]。HF是导致卡非佐米停药的最常见的不良事件[37]。多发性骨髓瘤患者多为老年人, 往往伴随心血管合并症, 卡非佐米治疗期间发生心血管不良事件的风险与卡非佐米的剂量、输注时间有关[35,38]。同卡非佐米相比, 硼替佐米HF的发生率相对较低 (4%), 主要取决于该药物是否用于已有显著心血管疾病风险因素的患者, 以及患者是否曾接触过心脏毒性药物 (如ANTs)[39]。

在心肌细胞和血管平滑肌内皮中, 蛋白酶体抑制促进蛋白聚集并改变核因子-κB (nuclear factor-κB, NF-κB) 靶标的转录激活, 促进细胞凋亡信号级联, 下调自噬水平, 改变一氧化氮信号稳态, 可能与PIs的心脏毒性相关[40]。AMPKα的失活和自噬相关蛋白的下调是卡非佐米诱导心脏毒性的主要机制[41]。体内和体外研究表明, 硼替佐米可能诱导线粒体缺陷, 但其致病机制仍有待阐明[42]。

1.1.2.5 布鲁顿酪氨酸激酶抑制剂 伊布替尼是一种新型强效布鲁顿酪氨酸激酶 (Bruton's tyrosine kinase, BTK) 抑制剂, 抑制恶性B细胞的增殖和存活。临床发现暴露于伊布替尼的患者可发生严重和致命的心脏事件, 包括心律失常、HF等[43]。伊布替尼相关的心房颤动 (atrial fibrillation, AF) 常见于65岁以上和/或有心血管危险因素的患者, 多发生在启动伊布替尼治疗的

1年内[44]。AF是伊布替尼最明显的心脏毒性, 发生率为5%～16%, 是导致停用伊布替尼的最常见原因, 其停药率可高达32%[45]。在2021年对366.33万例TKIs病例报告的分析中, 伊布替尼与AF的相关性最强, 总风险增加了9倍[46]。

基础研究表明, 除了对心脏BTK的直接靶向抑制作用外, 伊布替尼对TEC蛋白酪氨酸激酶 (TEC protein tyrosine kinase) 也有间接的脱靶抑制作用。PI3K-Akt是BTK和TEC调控的通路之一, 在应激条件下可发挥心脏保护作用; 伊布替尼下调或抑制该通路增加了对房性心律失常的易感性[47]。伊布替尼影响I-Na通道损伤心房传导, 增加AF的发生[48]。近期有研究提出非BTK靶机制导致心脏毒性的观点。Jiang等[49]的小鼠模型数据表明, 伊布替尼可通过增加钙/钙调素蛋白依赖的蛋白激酶II (Ca/calmodulin-dependent protein kinases or CaM kinases II, CaMK II) 的活性来增加心房纤维化和重构, 增加AF和其他心律失常的易感性。Xiao等[50]研究显示伊布替尼脱靶抑制C末端Src激酶, 导致炎症和纤维化增加, 使心脏易发生AF。同时, 伊布替尼抑制至少19种其他激酶, 因此伊布替尼相关的AF也可能涉及其他信号通路[51]。

1.1.2.6 BCR-ABL激酶抑制剂 在过去的20年中, 国内外已有近10种BCR-ABL激酶抑制剂获批用于治疗慢性粒细胞白血病, 包括伊马替尼、达沙替尼、帕纳替尼和尼罗替尼等。在服用达沙替尼的中位时间为6个月的患者中, 有4%的患者发生左室功能障碍或充血性心力衰竭, 其中一半为NYHA III或IV级 (中度至重度, 需要治疗)[52]。一项评估激酶抑制剂治疗引起的心律失常的报告发现, 帕纳替尼 (ROR = 3.0; 95% CI: 2.21～4.14)、尼罗替尼 (ROR = 2.96; 95% CI: 2.47～3.53) 与AF的显著增加有关。同时, 尼罗替尼具有促室性心律失常的倾向[46]。

由于激酶抑制谱和非酪氨酸激酶靶点不同, 这些药物具有不同的心血管安全性。在心肌细胞中, ABL维持内质网的稳态。伊马替尼抑制ABL激酶诱导内质网应激, 最终导致线粒体去极化、ATP耗尽、细胞色素c的释放, 细胞坏死和凋亡[53]。

1.1.3 免疫检查点抑制剂

免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 如PD-1/PD-L1抑制剂, 激活抗肿瘤免疫反应, 显著提高肿瘤患者的生存率。然而, ICIs对免疫系统的非特异性激活可导致免疫相关不良事件。ICIs相关的心脏毒性包括心肌炎、心包炎、HF、心律失常和血管炎[54]。近期一项荟萃分析报告了心血管irAEs的发生率, ICI单药治疗为3.1%, ICI联合治疗为5.8%[55]。心肌炎是ICIs最常见的心血管irAE, ICIs相关的心肌炎发病率为0.5%～1.7%, 但病死率约50%[56]。Xu等[57]研究纳入了52名诊断为ICIs相关心肌炎的患者, 平均发病时间为30天, G1～2级患者平均发病时间为50天, G3～4级患者平均发病时间为24天, 引起的主要心脏不良事件 (major adverse cardiac events, MACEs) 包括心源性死亡、严重心律失常、心源性休克等。

ICIs引起心肌炎的确切机制尚未完全阐明, 效应T细胞对未知心脏抗原的反应增加可能是其机制之一[58]。

1.1.4 嵌合抗原受体T细胞免疫疗法

嵌合抗原受体T细胞免疫疗法 (chimeric antigen receptor T-cell immunotherapy, CAR-T) 已成为难治性和复发性血液系统恶性肿瘤的一种极具前景的治疗方法。尽管其临床疗效显著, 但仍可引起心脏毒性。CAR-T的心血管并发症包括: 左室功能障碍、心律失常和心源性猝死[59]。在2017～2019年FDA不良事件报告系统所报告的CAR-T疗法相关的CVEs (n = 196) 中, CVEs的全因死亡率为30%, 心律失常是最常见的CVE (77.6%)[60]。另外, 患者在输注CAR-T细胞之前接受预处理的化疗药物主要是氟达拉滨和环磷酰胺, 环磷酰胺本身可能会引起左室功能障碍和HF。

CAR-T疗法导致细胞因子在全身大量释放, 包括白细胞介素6 (interleukin-6, IL-6)、肿瘤坏死因子α (tumor necrosis factor-α, TNF-α) 和干扰素γ (interferon-γ, IFN-γ) 引起前列腺素激活, 诱发细胞因子释放综合征 (cytokine release syndrome, CRS)。近期的药物警戒数据显示, 在接受CAR-T治疗时, 发生心血管和肺部不良事件的患者死亡率为30.9%, 而发生CRS的患者死亡率为17.4%[61]。CRS与CAR-T治疗相关的心血管毒性之间存在显著关联, 心脏毒性尤其见于既往有心血管疾病的患者或患有严重CRS的患者。

1.2 血管毒性

1.2.1 血管内皮生长因子抑制剂

高血压是VEGFIs最常见的心血管不良反应, VEGFIs使高血压/重度高血压的发生风险增加5.3/5.6倍[62]。贝伐珠单抗的高血压总发病率为20%～25%[63]。乐伐替尼与高血压 (所有级别和严重程度) 的发生率也有较高相关性[64]。高血压也是凡德他尼临床试验报告中常见不良事件, 发生率为16%～56%[65]。有研究评估接受索拉菲尼治疗的肝癌患者发现, 27%的患者 (n = 299) 出现高血压或原有高血压恶化, 进而导致其他心血管并发症的发生[66]。VEGF是血管生成的关键调节剂。多种基础研究表明VEGF诱导一氧化氮 (nitrogen monoxide, NO) 和前列腺素I2两种血管扩

张因子的产生, 并减少缩血管因子内皮素-1 的产生。VEFGIs 诱导活性氧产生, 引起氧化应激, 减少内皮 NO 的合成, 导致血管舒缩失衡, 引发血压升高[67]。遗传学研究还阐明 VEGFIs 引起的高血压与 VEGF 信号传导通路的多态性有关[68]。

肿瘤治疗的血管毒性具有多样性, 血管反应性改变、血管血栓形成、动脉粥样硬化和血管炎导致血管管腔阻塞和血流减少[69]。贝伐珠单抗可导致较高的静脉 (11.9%) 和动脉 (3.3%) 血栓栓塞发生率[70]。多受体 TKIs (VEGFR 和血小板源性生长因子受体抑制剂) 可破坏冠状动脉微血管内皮网络的稳定性, 降低冠状动脉血流储备, 导致血栓形成和动脉缺血事件 (心肌梗死和缺血性卒中) 的风险增加[71]。

1.2.2 BCR-ABL 激酶抑制剂

BCR-ABL 激酶抑制剂尼罗替尼和帕纳替尼也可抑制 VEGF 信号通路, 诱导内皮功能障碍, 继而血压升高[72]。尤其是在接受帕纳替尼治疗的患者中, 高血压发生率为 17%, 相对风险为 9.0[73]。另外, 使用尼罗替尼、帕纳替尼治疗的患者即使没有心血管疾病危险因素, 下肢也可能发生严重的动脉粥样硬化性和非动脉粥样硬化性外周动脉疾病 (高达 30%)[74]。近期的一项荟萃分析中, 接受尼罗替尼和帕纳替尼治疗的患者的动脉事件的发生率分别为 8.1% 和 7.1%[75]。尼罗替尼诱导的血管事件与加速进展的动脉粥样硬化和血管内皮功能障碍有关[76]。而帕纳替尼相关的血管事件由血栓性微血管病所致[77]。

1.2.3 免疫检查点抑制剂

接受 ICIs 治疗的患者也存在血管不良事件。PD1/PDL1 缺乏会导致免疫检查点功能失调, 会增加 T 细胞聚集和细胞因子的产生, 导致动脉壁炎症和重塑[78]。除了血管炎, 越来越多的证据表明, ICIs 可能通过改变斑块组成加速动脉粥样硬化并促进急性冠状动脉综合征的发生。在肿瘤患者的匹配病例对照研究中, 同未使用 ICIs 治疗的患者相比, ICIs 引起动脉粥样硬化心血管事件 (心肌梗死、冠状动脉血运重建和缺血性卒中) 的风险高 3 倍[79]。同时, 在接受 ICIs 治疗的患者中观察到静脉血栓栓塞事件的风险更高[80]。在临床治疗方案中, ICIs 常与其他 ICIs 和/或其他抗肿瘤药物联合使用, 如 VEGFIs 联合 ICIs 被推荐用于晚期肾细胞癌的治疗, VEGFIs 是否会增强 ICIs 的心血管毒性作用, 特别是动脉粥样硬化和斑块炎症仍不清楚, 亟待临床进一步分析[81]。

2 抗肿瘤药物相关心血管毒性的防治

2.1 危险因素

针对肿瘤治疗相关心血管毒性的一级和二级预防, 根据相关的指南和共识, 建议进行基线心血管评估以识别心血管毒性高风险的患者, 积极管理危险因素 (如吸烟、高血压、糖尿病、血脂异常、肥胖), 可以根据基线风险、肿瘤治疗的方案及预先存在的心脏病, 确定治疗期间进行心脏监测 (LVEF、血清生物标志物水平、超声心动图、心脏磁共振等) 的频率[82]。

大多数心血管药物和抗肿瘤药物药理学特征复杂, 治疗指数窄, 患者间个体差异较大。具有心血管疾病的肿瘤患者应避免药物相互作用 (drug interactions, DIs)。如伊布替尼与抗凝血和抗心律失常药物 (如利伐沙班、维拉帕米/地尔硫卓) 之间通过 CYP450 代谢途径产生复杂的 DIs。肿瘤患者在 AF 时发生 HF 和血栓栓塞的风险增加, 当发生伊布替尼相关的 AF 时, 优选 β 受体阻滞剂和 IC 类抗心律失常药物[83]。

2.2 心血管保护药物联用

多种西药或中药具有防治抗肿瘤药物心血管毒性的潜力。在患者计划接受心脏毒性药物治疗时, 预防性使用 ACEIs 或 ARB 和/或选择性 β 受体阻滞剂可减少心脏毒性的发生[84]。对于计划接受大剂量 ANTs (如多柔比星 $\geqslant$ 250 mg·m^{-2}, 表柔比星 $\geqslant$ 600 mg·m^{-2}) 治疗的患者, 临床医师可采用多种策略预防心脏毒性, 包括使用心脏保护剂右雷佐生、持续输注或使用多柔比星脂质体制剂[85]。研究表明降糖药物二甲双胍可通过多种机制拮抗 DOX 引起的心脏毒性, 包括减少活性氧生成和氧化应激, 抑制线粒体损伤, 维持能量产生[86]。临床前研究显示二甲双胍可以激活 AMPK 发挥对 DOX 心脏毒性的保护作用[87], 这使其成为降低 DOX 心脏毒性有前途的辅助药物。

使用天然药物防治抗肿瘤药物的心血管毒性是一种新兴的方法。有研究表明脂联素、姜黄素、白藜芦醇、五味子 B 等及其他新型植物化学物质显示出对 DOX 诱导的心脏毒性有保护作用, 并可以降低肿瘤患者的死亡率[88]。脂联素可通过降低血清肌酸激酶、乳酸脱氢酶和羟丁酸脱氢酶水平来预防 DOX 引起的心脏毒性, 还可保护心肌免受凋亡和氧化应激[89]。姜黄素是一种天然化合物, 来源于植物姜黄, 具有抗炎作用, 姜黄素以 PI3K/Akt/mTOR 依赖性方式调节细胞自噬和凋亡; 姜黄素还通过调节核苷酸寡聚化结构域样受体家族 3、半胱天冬酶 1 和 IL-18 等促焦亡标志物来抑制焦亡, 并对 DOX 诱导的心脏毒性显示出心脏保护作用[90]。白藜芦醇具有抗氧化和抗炎作用, 降低活性氧水平, 升高超氧化物歧化酶、过氧化氢酶水平, 通过激活 AMPK 减轻 DOX 诱导的心脏毒性中的氧化应激、细胞凋亡和改善心肌纤维化, 发挥心脏保护活性[91]。研究表明, 五味子 B 以剂量依赖性方式减弱

DOX诱导的小鼠心脏p38 MAPK激活, 还降低DOX诱导的心脏组织中IL-1β、IL-16和TNF-α等促炎因子的表达[92]。小檗碱是一种天然的异喹啉生物碱, 也可通过平衡心肌细胞自噬和细胞凋亡来改善DOX诱导的心脏毒性[93]。天然产物在防治抗肿瘤药物心血管毒性中展示了明显的作用, 但仍需进一步的临床研究。

近年来, 对心脏毒性新治疗靶点的探索取得了新的进展, 环状RNA具有作为下一代基于RNA的心衰治疗药物的转化潜力。Lu等[94]的研究发现源自胰岛素受体基因的环状RNA (circular RNA molecule derived from the host gene encoding the insulin receptor, Circ-INSR) 的过表达可以逆转DOX诱导的心脏毒性, 维持线粒体功能。因此, Circ-INSR是预防抗肿瘤药物引起的心脏毒性的一个很有前景的靶点。

3 展望

随着新型抗肿瘤药物的出现, 需要不断改进CTR-CVT的预防、诊断和治疗。从临床问题出发, 探索检测早期CTR-CVT的新方法, 评估CTR-CVT风险预测的遗传谱, 运用系统生物学和精准医学方法可以更好地了解患者的风险, 提供更好的毒性预防和监测。抗肿瘤药物引起心血管毒性的临床表现及潜在机制的总结详见表1。大多数肿瘤治疗I～III期临床试验研究中无心血管不良反应的标准化记录, 应以心血管事件为终点, 开展大规模的前瞻性临床试验, 基于真实世界数据展开药物警戒研究、多组学研究等, 对CRT-CVT的管理至关重要。同时应进一步了解CRT-CVT的潜

Table 1 Summary of the clinical manifestations and potential mechanisms of cardiovascular toxicity of anti-tumor drugs

Cardiovascular toxicity	Classification	Clinical manifestation	Name of anti-tumor drug	The potential mechanism
Cardiac toxicity	ANTs	Left ventricular dysfunction, HF	DOX	Exacerbate oxidative stress, interfere with iron metabolism, interact with topoisomerase II, and induce apoptosis and autophagy defects
	HER2 inhibitors	LVEF, HF	Trastuzumab, pertuzumab	Inhibit ErbB2 signaling in cardiomyocytes, induce an increase in Bcl-xS/Bcl-xL, promote oxidative stress, and induce mitochondrial dysfunction
	VEGFIs	LVSD, HF	Sunitinib	Inhibit ribosomal S6 kinase and downregulate AMPK
			Sorafenib	Inhibit Raf-1 proto-oncogene, serine/threonine kinase
		QT prolongation	Vandetanie	Inhibit the hERG current, inhibit the sodium, and calcium currents
	EGFR-TKI	HF, QT prolongation	Osimertinib	Inhibit EGFR signaling and cardiac hERG potassium channel
	PIs	HF	Carfilzomib	Inhibit the proteasome, inactivate AMPKα, and down-regulate autophagy-related proteins
	The BTK inhibitor	AF	Ibrutinib	Inhibit BTK and TEC, increase CaMK II activity, and inhibit C-Src tyrosine kinase
	BCR-ABL kinase inhibitors	Left ventricular dysfunction, congestive heart failure	Dasatinib	Unknown
		AF	Ponatinib, nilotinib	Unknown
	ICIs	Myocarditis	PD-1/PD-L1 inhibitors	Effector T cell responses to unknown cardiac antigens are increased
	CAR-T	Left ventricular dysfunction, arrhythmia	CAR-T	Cytokines IL-6, TNF-α, and IFN-γ are released in large quantities, causing prostaglandin activation and triggering CRS
Vascular toxicity	VEGFIs	Hypertension	Bevacizumab, lenvatinib, vandetanib, sorafenib	Inhibition of VEGF signaling pathway and reduction of endothelial NO synthesis lead to vasomotor imbalance and increase of reactive oxygen species
	BCR-ABL kinase inhibitors	Hypertension	Nilotinib, ponatinib	Inhibit VEGF signaling pathway and induce endothelial dysfunction
	VEGFI	Venous and arterial thromboembolism	Bevacizumab	Inhibit VEGF signaling pathway, destroy the stability of coronary microvascular endothelial network, and reduce coronary flow reserve
	ICIs	Venous and arterial thromboembolism	PD-1/PD-L1 inhibitors	T cells drive inflammation
	BCR-ABL kinase inhibitor	Peripheral arterial disease	Nilotinib	Accelerate atherosclerosis progression and vascular endothelial dysfunction
			Ponatinib	Thrombotic microangiopathy
	ICIs	Large vessel inflammation	PD-1/PD-L1 inhibitors	PD1/PDL1 deficiency leads to immune checkpoint dysfunction and increases T-cell aggregation and cytokine production, leading to arterial wall inflammation and remodeling
		Atherosclerotic events	PD-1/PD-L1 inhibitors	Changes in plaque composition accelerate atherosclerosis

在病理机制, 加强临床前的基础研究和转化研究, 探索新的靶点及可能的最佳治疗策略。由于许多天然药物在其治疗上的优势, 在寻找能减毒增效的创新型药物方面提供了一个很好的研究方向。未来也需要心脏学专家、肿瘤学专家、放射科专家、药剂师、护士等共同努力与协作, 关注抗肿瘤药物临床应用, 完善肿瘤治疗相关心血管事件的监测、预防和治疗措施, 使肿瘤治疗更加安全、有效。

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