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Hans汉斯

他汀类药物在抗肿瘤药物引起的心脏毒性中的保护作用

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摘　要

他汀类药物属于羟甲基戊二酰辅酶A (HMG-CoA)还原酶抑制剂，可抑制胆固醇生物合成，抗动脉粥样硬化，已经广泛用于冠状动脉粥样硬化性心脏病的治疗，近年来有研究发现他汀类药物在抗肿瘤药物所致心脏毒性中有保护作用。本文对相关报道进行综述，以期对肿瘤患者心血管损伤的预防、治疗提供思路。

关键词

他汀类药物，心脏保护，抗肿瘤药物

Protective Effect of Statins on Cardiotoxicity Induced by Antitumor Drugs

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Abstract

Statins are hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors, which can inhibit

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cholesterol biosynthesis and anti-atherosclerosis, and have been widely used in the treatment of coronary atherosclerotic heart disease. In recent years, studies have found that statins have a protective effect on cardiotoxicity caused by anti-tumor drugs. In this paper, related reports are reviewed in order to provide ideas for the prevention and treatment of cardiovascular injury in cancer patients.

Keywords

Statins, Cardioprotection, Antitumor Drug

1. 引言

心血管疾病和恶性肿瘤分别是全世界第一和第二大死亡原因。随着医疗水平的不断提高，肿瘤患者生存率显著提高。在抗肿瘤治疗过程中，一个常见的问题是化疗、免疫、靶向和放射治疗引起的心脏毒性，可表现为急性冠状动脉综合征、心肌炎、心律失常、瓣膜病或心力衰竭等，心血管疾病是癌症幸存者死亡的主要原因之一[1] [2]。他汀类药物也被称为羟甲基戊二酰辅酶 A (HMG-CoA)还原酶抑制剂，抑制胆固醇生物合成。通常用于治疗高胆固醇血症，是心血管领域常用药。他汀类药物在 20 多年前被引入治疗，并迅速成为世界上最常见的处方药物之一[3]。他汀类药物具有许多有益作用，包括抗氧化、抗炎和抗血栓作用[4]。有研究发现他汀类药物不仅在心血管疾病中发挥作用，还具有抗肿瘤作用。他汀类药物可在肿瘤细胞中诱导细胞凋亡，但不影响正常骨髓或脐血中来源的祖细胞的细胞凋亡，保持其正常增殖[5]。另外，他汀类药物具有抗血管生成特性，在抑制肿瘤进程中发挥作用[6] [7] [8] [9]。由于他汀的上述作用，人们开始关注其在抗肿瘤治疗过程中的心脏保护作用，其中抗肿瘤药物在肿瘤治疗中的应用比例大，心脏毒性发生率高，本文对近年来他汀类药物在抗肿瘤药物引起的心脏毒性中的保护性作用研究进行综述。

1.1. 蒽环类药物所致心脏毒性

蒽环类药物自 20 世纪 50 年代被发现以来，由于其高效性，已成为肿瘤学中的化疗基石之一，但其较高的心脏毒性导致临床用药受限。其心脏毒性机制仍不完全清楚，目前存在两个公认的假说：1) 氧化应激，在铁存在的情况下，产生活性氧，导致细胞膜脂质过氧化，导致心肌细胞损伤；2) 拓扑异构酶 IIβ 在静止不增殖的心肌细胞中具有活性，其抑制可导致细胞死亡途径的激活和线粒体生物合成发生的抑制[10] [11] [12]。

一些实验室研究发现他汀类药物可以减轻蒽环类药物导致的心脏毒性。在细胞模型中，Pecoraro 等人用阿霉素处理心肌细胞产生心脏毒性，加用辛伐他汀，发现可连接蛋白 43 从质膜转移到胞质溶胶中，导致连接蛋白 43 在线粒体膜上表达减少，进而调节线粒体中储存的钙水平，除此之外，还可通过增加连接蛋白 43 磷酸化水平，影响细胞间的间隙连接，来阻断阿霉素诱导的有害刺激的传播[13]；Jaewon 等人研究发现生存素可通过 FOXO1/信号转导与转录因子 3 (STAT3)/特异性蛋白 1 (Sp1)转录通路介导他汀类药物的心脏保护作用[14]；Henninger 等人用低剂量的阿霉素处理小鼠导致白细胞介素 6 (IL-6)、结缔组织生长因子(CTGF)、脑钠肽(BNP)和热休克蛋白 A1B (Hspa1b) RNA 的持续上调，处理三个月后，在洛伐他

汀联合治疗的情况下，心肌细胞的这些持续(慢性)应激反应减少，通过电子显微镜观察到对照组和单用他汀类药组线粒体数量无明显差异，阿霉素治疗组增加了肌原纤维之间的线粒体数量，而阿霉素、洛伐他汀联合治疗的动物的心脏中没有显示出这种线粒体过度增殖[15]；Kim 等人发现接受高剂量瑞舒伐他汀治疗的大鼠血清肌钙蛋白 I 浓度明显低于单用阿霉素处理组，联合使用瑞舒伐他汀和低剂量卡维地洛可部分抑制氧化应激，与单用阿霉素处理组相比，接受低剂量瑞舒伐他汀治疗组显示出较少的纤维化变化[16]；Dadson 等人发现瑞舒伐他汀在心脏中保留了丝氨酸/苏氨酸激酶(Akt)依赖性信号，直接影响钙稳态，预防阿霉素诱导的早期心脏毒性[17]。

一些临床研究也发现他汀在蒽环类药物导致的心脏毒性中具有保护作用。一项纳入 2262 名癌症患者的荟萃分析显示，与非他汀类药物组相比，他汀类药物治疗组左心室射血分数(LVEF)下降更小，心脏毒性风险显著降低，说明他汀类药物在预防蒽环类药物诱导的心脏毒性方面具有保护作用[18]；一项共有 51 名患有乳腺癌症、白血病或淋巴瘤的参与者(33 名女性和 18 名男性，年龄 48 ± 2 岁)研究中，有 14 名患者同时接受了他汀类药物治疗，相比未接受他汀治疗的患者，蒽环类诱导的 LVEF 降低显著改善[19]；一项对来自 4 项随机对照试验和 3 项队列研究的 2511 名服用蒽环类药物的癌症患者的荟萃分析表明，与未接受他汀类药物治疗的癌症患者相比，服用他汀类药物的患者的心脏毒性发生率显著较低。相比之下，他汀类药物处方组与未服用他汀类药物组相比，LVEF 的变化与基线相比没有差异，不同类型的癌症并没有改变他汀类药物治疗的效果[20]；在一项包括 110 名接受蒽环类药物化疗的女性乳腺癌患者的前瞻性、随机、单盲试验中，通过在接受化疗前进行了全面的超声心动图检查，6 个月后行 3D 超声心动图评估 LVEF，发现预防性使用阿托伐他汀可以预防癌症治疗相关心功能障碍的发展[21]；此外，一项包含 300 名成年淋巴瘤患者的试验中，参与者随机接受阿托伐他汀，40 mg/d (n = 150)，或安慰剂(n = 150) 12 个月，阿托伐他汀组心功能下降(从化疗前到 12 个月后，LVEF 下降≥10%，研究期间的最终值 < 55%)的患者比例为 9%，而安慰剂组的比例为 22%，这一发现可能支持阿托伐他汀用于蒽环类药物引起心功能障碍高风险的淋巴瘤患者[22]。

以上研究表明他汀类药物在蒽环类药物引起的心脏毒性中具有保护作用。

1.2. HER-2 信号通路的抑制剂所致心脏毒性

人表皮生长因子受体 2 (HER-2)，在许多癌症中表达上调，包括大约 20%~25%的乳腺癌。然而 HER-2 也存在于心肌细胞中，参与调节心肌细胞凋亡、肥大、有丝分裂、细胞－细胞粘附、血管生成和对肾上腺素能信号的敏感性[23]。因此，阻断 HER-2 可能对心脏有害。

一项动物实验发现，在曲妥珠单抗诱导小鼠心脏毒性的模型中，瑞舒伐他汀可抑制曲妥珠单抗导致的活性氧(ROS)和谷胱甘肽的产生来改善心脏毒性[24]。最近的一项回顾性研究，共有 129 例 HER2 阳性乳腺癌症患者接受了曲妥珠单抗治疗。在癌症治疗期间，有 43 名患者接受了他汀类药物治疗，与未接受他汀药物组相比，他汀类药物减轻了曲妥珠单抗引起的 LVEF 下降[25]。另一项回顾性队列研究发现，曲妥珠单抗治疗的女性癌症患者中，接受他汀治疗的患者因心力衰竭导致住院的风险较低，但这一趋势并不显著[26]。

以上研究表明他汀类药物在 HER-2 信号通路的抑制剂引起的心脏毒性中具有一定保护作用。

1.3. 其他抗肿瘤药所致心脏毒性

接受环磷酰胺治疗的癌症患者中，7%~28%的患者会产生心脏毒性(如充血性心力衰竭、心律失常、心脏压塞和心肌功能障碍)，在高剂量给药时更常见[27]。环磷酰胺心脏毒性与炎症、内皮功能障碍、钙调节失调、内质网和线粒体损伤有关[28]。有研究发现辛伐他汀可通过调节炎性小体/半胱天冬酶 1

(caspase1)/白细胞介素 1β 通路对环磷酰胺诱导的心脏毒性具有保护作用[29]；铂类化疗药导致的心脏毒性事表现为心律失常以及心电图改变、心肌炎和心肌病等，其诱导的心脏毒性的发病机制可能与氧化应激、内质网应激和细胞凋亡有关[30] [31]。Saleh 等人在鼠模型中发现瑞舒伐他汀和辛伐他汀通过阻断内质网应激介导的凋亡或死亡来减轻顺铂诱导的心脏毒性[32]；5-氟尿嘧啶引起的心脏毒性可表现为心绞痛样短暂性心肌缺血、充血性心力衰竭、心肌病、心包炎、心律失常、心源性休克和猝死[33] [34]，机制包括冠状动脉痉挛、内皮损伤、血栓形成效应和直接心肌毒性诱导的坏死[35]，Muhammad 等人发现 5-氟尿嘧啶可激活 Rho 激酶/Akt/内皮型一氧化碳合成酶(eNOS)和内皮素 1 (ET-1)/胞外信号调节激酶(ERK)途径诱导心脏毒性，辛伐他汀通过其调节这些通路来发挥心脏保护作用[36]。抗微管剂、血管内皮生长因子抑制剂、蛋白酶体抑制剂、免疫检查点抑制剂、酪氨酸激酶抑制剂等抗肿瘤药物亦可导致心脏毒性[37]-[49]，但他汀类药物是否对其导致的心脏毒性有保护作用目前没有研究。

2. 小结

随着科学技术发展及医疗水平提高，恶性肿瘤患者的生存期明显延长，治疗肿瘤所带来的心血管毒性引起关注，其导致肿瘤患者心血管疾病发病率和死亡率升高，且可导致治疗中断，使得我们必须寻找一些方法来减轻抗肿瘤过程中的心脏毒性。目前一些实验室及临床回顾性研究发现他汀类药物在抗肿瘤药物所致心脏毒性中有保护作用，但其保护作用机制研究较少，且其临床研究中，应用他汀类药物患者本身可能有更高的心血管疾病风险，导致结果可能有所偏倚。除此之外，大多数研究使用了不同的他汀类药物或剂量，无法确定他汀类药物作为心脏保护剂的“预防性”剂量或方案。为确定他汀类药在抗肿瘤药物导致的心脏毒性中的保护作用及增加临床循证医学证据，还需进行更多的基础研究及多中心、前瞻性研究，以期能为临床提供新的治疗思路，使肿瘤患者获益。

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