[DOI]10.3969/j.issn.1001-9057.2024.09.021
http://www.lcnkzz.com/CN/10.3969/j.issn.1001-9057.2024.09.021

· 继续教育园地 ·

血脂水平及降脂药物与恶性肿瘤的相关性研究进展

罗婷　邱令智　易东　鄢华

[摘要]　恶性肿瘤是威胁人类健康的主要原因之一,带来了全球范围内巨大的医疗负担。随着对恶性肿瘤研究的不断深入,发现脂代谢与细胞周期、细胞增殖、迁移和细胞凋亡密切相关,血脂水平可反映恶性肿瘤的进展,并可在一定程度上预测恶性肿瘤的预后。为探索恶性肿瘤治疗的新靶点、新策略,降脂药物与恶性肿瘤相关性的研究也越来越多。本文通过综述血脂水平与不同类型恶性肿瘤的关系,并阐述降脂药物对恶性肿瘤风险和预后的影响及其潜在机制,以期为探索防治恶性肿瘤新思路提供重要支撑。

[关键词]　血脂;　降脂药物;　肿瘤
[中图分类号]　R73　　[文献标识码]　A

恶性肿瘤是威胁全球人群健康的主要原因之一,给家庭及社会带来了巨大的生理及经济负担。根据最新数据,2022 年中国约有 482 万新发恶性肿瘤患者,其中约 321 万患者死亡[1]。预计到 2040 年全球恶性肿瘤患者将达到 2 840 万,比 2020 年增加 47%[2]。血脂水平可反应体内脂质代谢情况,血脂异常可通过影响免疫细胞的分化和功能来影响免疫系统功能进而影响其抗肿瘤活性。因此,血脂水平改变可能与恶性肿瘤有关。他汀类药物是目前应用较广泛的降脂药,可抑制肿瘤细胞的生长和转移,与癌症分级、癌症风险和癌症特异性死亡率呈负相关。贝特类降脂药通过上调过氧化物酶体增殖物激活受体 α(PPARα)表达来抑制细胞增殖,进而抑制肿瘤细胞生长。新型

基金项目:武汉市科技局知识创新专项基础研究项目(2022020801010576)

作者单位:430022,武汉亚洲心脏病医院心内科
通讯作者:鄢华,E-mail:yanhua0807@aliyun.com

[4] Chandran RK, Geetha N, Sakthivel KM, et al. Differential gene expression changes and their implication on the disease progression in patients with Chronic Myeloid Leukemia[J]. Blood Cells Mol Dis, 2019, 77: 51-60.
[5] Palandri F, Castagnetti F, Testoni N, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up[J]. Haematologica, 2008, 93(12): 1792-1796.
[6] 王建祥,黄晓军,吴德沛,等. 中国 15 家医院慢性粒细胞白血病发病状况及目前诊断治疗模式调查分析[J]. 中华血液学杂志, 2009, 30(11): 721-725.
[7] 谭琳,刘琳,谢瑜,等. 尼洛替尼联合 IFNα-2b 治疗进展期慢性髓系白血病患者的疗效评估及对血清 LDH、α-HBDH 和 ALP 的影响[J]. 国际检验医学杂志, 2019, 40(17): 2159-2162.
[8] Saglio G, Hochhaus A, Goh YT, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacyand tolerability of 140 milligrams once daily and 70 milligrams twice daily[J]. Cancer, 2010, 116(16): 3852-3861.
[9] Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors[J]. Am J Hematol, 2015, 90(9): 755-768.
[10] Atilla E, Ataca P, Ozyurek E, et al, Successful Bosutinib Experience in an Elderly Acute Lymphoblastic Leukemia Patient with Suspected Central Nervous System Involvement Transformed from Chronic Myeloid Leukemia[J]. Case Rep Hematol, 2015, 2015: 689423.
[11] 王娟,宋永平. 高三尖杉酯碱在慢性髓性白血病治疗中的作用机制[J]. 中华临床医师杂志(电子版), 2016, 10(17): 2653-2656.
[12] Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias[J]. N Engl J Med, 2012, 367(22): 2075-2088.
[13] Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias[J]. N Engl J Med, 2013, 369(19): 1783-1796.
[14] Sasaki H, Mitani S, Kusumoto S, et al. Pre-and post-transplant ponatinib for a patient with acute megakaryoblastic blast phase chronic myeloid leukemia with T315I mutation who underwent allogeneic hematopoietic stem cell transplantation[J]. Int J Hematol, 2019, 110(1): 119-123.
[15] Jain P, Kantarjian HM, Gorab A, et al. Prognostic factors and survival outcomes in patients with chronicmyeloid leukemia in blast phase in the tyrosine kinase inhibitor era: cohortstudy of 477 patients[J]. Cancer, 2017, 123(22): 4391-4402.
[16] 余锋,姚子龙,李猛,等. 慢性髓系白血病急髓变临床回顾性分析[J]. 中国实验血液杂志, 2019, 27(4): 995-1000.
[17] Jiang H, Xu LP, Liu DH, et al. Allogeneic hematopoietic SCT in combination with tyrosine kinase inhibitor treatment compared with TKI treatment alone in CML blast crisis[J]. Bone Marrow Transplant, 2014, 49(9): 1146-1154.
[18] Gratwohl A, Brand R, Apperley J, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)[J]. Haematologica, 2006, 91(4): 513-521.
[19] Radujkovic A, Dietrich S, Blok HJ, et al. Allogeneic Stem Cell Transplantation for Blast Crisis Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors: A Retrospective Study by the EBMT Chronic Malignancies Working Party[J]. Biol Blood Marrow Transplant, 2019, 25(10): 2008-2016.
[20] Lübking A, Dreimane A, Sandin F, et al. Allogeneic stem cell transplantation for chronic myeloid leukemia in the TKI era: population-based data from the Swedish CML registry[J]. Bone Marrow Transplant, 2019, 54(11): 1764-1774.
[21] Deotare U, Kim DD, Lipton JH, et al. Management of Elderly Patients with Newly Diagnosed Chronic Myeloid Leukemia in the Accelerated or BlasticPhase[J]. Drugs Aging, 2016, 33(5): 335-345.
[22] Venkataraman V, Casey KS, Onozato M, et al. Long: molecular tracking of CML with bilineal inv(16) myeloid and del(9) lymphoid blast crisis and durable response to CD19-directed CAR-T therapy[J]. Leukemia, 2020, 34(11): 3050-3054.
[23] Zhou L, Shi H, Shi W, et al. Durable Molecular Remission in a Lymphoid BP-CML Patient Harboring T315I Mutation Treated with Anti-CD19 CAR-T Therapy[J]. Onco Targets Ther, 2019, 12: 10989-10995.

(收稿日期:2021-03-07)
(本文编辑:余晓曼)

降脂药前蛋白转化酶枯草杆菌素(PCSK9)抑制剂通过下调PCSK9水平来抑制肿瘤细胞的增殖和侵袭。本文通过综述血脂水平与不同类型恶性肿瘤的关系,并阐述降脂药物对恶性肿瘤发病风险和预后的影响及其潜在机制,以期为改善恶性肿瘤患者预后提供更多治疗思路。

一、血脂与肿瘤

血脂主要成分为甘油三酯(TG)、总胆固醇(TC)、极低密度脂蛋白胆固醇(VLDL-C)、低密度脂蛋白胆固醇(LDL-C)和高密度脂蛋白胆固醇(HDL-C)。脂质在能量储存、细胞增殖和细胞生物学的许多方面都必不可少,可作为转录因子激动剂或拮抗剂维持细胞稳态;可调节细胞周期,影响细胞增殖、迁移和细胞凋亡[3]。

高水平 TG 可以激活细胞信号转导通路[如丝裂原激活蛋白激酶(MEK)/细胞外信号调节激酶和丝氨酸(ERK)和苏氨酸激酶(AKT)通路],促进氧化应激反应,而氧化应激与恶性肿瘤密切相关,因此 TG 水平升高可能与恶性肿瘤细胞的增殖和进展有关。胆固醇稳态是免疫细胞功能调节的重要影响因子,胆固醇水平异常可导致蛋白质功能障碍、氧化还原障碍和免疫功能失调,从而促进肿瘤细胞增殖和血管生成,抑制肿瘤细胞凋亡[4-5]。LDL-C 颗粒激活血小板并损伤血管内皮,引发细胞持续性炎症反应,而炎症与恶性肿瘤密切相关,因此 LDL-C 水平升高可能与恶性肿瘤相关。HDL-C 具有抗炎、抗氧化和抗增殖作用,可能具有抗肿瘤活性[6]。

二、血脂与恶性肿瘤

1909 年有研究者在肿瘤病理切片中找到“脂肪性”晶体,初次发现了血脂与肿瘤的相关性[7]。脂质对肿瘤细胞的增殖、侵袭、迁移有重要影响,因此研究血脂与恶性肿瘤的相关性对于探索防治恶性肿瘤新思路具有重要意义。

1. TG 与恶性肿瘤:TG 与结直肠癌、宫颈癌、子宫内膜癌、卵巢癌的发病风险及预后均呈正相关,而与前列腺癌无显著相关性。TG 与结直肠癌的发生、发展有关[8]。研究结果显示,高 TG(男性≥1.53 mmol/L,女性≥1.58 mmol/L.)和高载脂蛋白 B(≥0.73 mmol/l)与结直肠癌患者总生存期和无病生存期均呈显著负相关,表明 TG 和载脂蛋白 B 水平可能是评估根治性手术后结直肠癌患者预后的血清标志物[9]。一项共纳入 1 713 例宫颈癌患者的研究证明,TG 是宫颈癌患者总生存期和无复发生存期的独立预测因子,且高 TG 是宫颈癌预后不良的独立指标[10],这与 Lin 等[11]的研究相一致。一项回顾性研究证实,TG 水平与子宫内膜癌及卵巢癌风险呈正相关[12]。然而多项研究显示,TG 与前列腺癌死亡风险及肿瘤复发无显著相关性[13-14]。

2. TC 与恶性肿瘤:TC 与前列腺癌、结肠癌、食管癌、乳腺癌、卵巢癌、子宫内膜癌、宫颈癌的发病风险及预后均呈正相关,而与肝癌、胃癌的发病率均呈负相关。一项动物研究表明,TC 与乳腺癌密切相关,高 TC 可促进乳腺癌细胞的生长及转移[15]。一项大型前瞻性研究探讨了 1 189 719 例成年人 TC 与癌症发病率之间的关系,结果显示高 TC 与前列腺癌、结肠癌、乳腺癌发病风险均呈正相关,与男性肺癌、肝癌、胃癌发病风险均呈负相关[16]。这与多项 Meta 分析结果一致[17-18]。一项回顾性研究发现,高 TC 与宫颈癌患者总生存期呈负相关,可作为宫颈癌不良预后的独立预测因子[19]。

3. LDL-C 与恶性肿瘤:LDL-C 与小细胞肺癌、非小细胞肺癌、前列腺癌、胰腺癌、乳腺癌的发病风险均呈正相关。一项回顾性研究发现,LDL-C 水平升高与小细胞肺癌进展相关且 LDL-C的升高程度与进展部位的数量呈正相关[20]。最近一项研究发现,非小细胞肺癌患者血清中 LDL-C 及凝集素型氧化 LDL 受体-1(s-LOX1)水平与肿瘤分期及转移密切相关,且 s-LOX1联合癌胚抗原可使诊断特异性从 72.8% 提高至 97.5%,提示脂质代谢紊乱可能通过 sLOX-1 促进非小细胞肺癌的进展,sLOX-1 可能是一种潜在的具有诊断价值的血清学标志物[21]。此外,氧化 LDL-C 水平鉴别良性前列腺增生和前列腺癌的特异性为 88.24%[22]。LDL-C 还可上调多种致癌基因产物的表达,促进癌细胞的增殖、迁移和侵袭,促进前列腺癌、胰腺癌和乳腺癌的进展[23-24]。

4. HDL-C 与恶性肿瘤:HDL-C 与大多数恶性肿瘤(乳腺癌、血液系统恶性肿瘤、神经系统恶性肿瘤、肺癌、胆囊癌、结肠癌、肾癌、卵巢癌)均呈负相关,是恶性肿瘤患者总生存期的保护因素。高 HDL-C/TC 比值(≥0.35)的三阴乳腺癌患者与低比值(≤0.27)者相比总死亡风险降低了 67%,提示 HDL-C/TC 比值可能是一种对三阴乳腺癌预后有潜在预测价值的指标[25]。一项大型前瞻性研究对 10 734 例普通人随访 25 年,发现低HDL-C 与多发性骨髓瘤、神经系统恶性肿瘤、非霍奇金淋巴瘤、乳腺癌、骨髓增生性肿瘤和肺癌风险增加相关,且恶性血液病和神经系统恶性肿瘤的风险增加最为明显[26]。这与 Jeong 等[27]的研究结果相符,提示低 HDL-C 水平是血液系统恶性肿瘤的独立危险因素和早期诊断标志物。低 HDL-C 水平还与胆囊癌、结肠癌、肾癌、卵巢癌患者的不良预后相关[28-30]。

三、降脂药物与恶性肿瘤

1. 他汀类降脂药物与恶性肿瘤:肿瘤细胞通过裂解固醇调节元件结合蛋白,随后将 3-羟基-3-甲基戊二酰辅酶 a(HMG-CoA)转化为甲羟戊酸盐来上调胆固醇合成,形成高脂血症肿瘤微环境,诱导肿瘤浸润性 $CD8^+$ T 细胞衰竭,使抗肿瘤免疫功能丧失。他汀类降脂药最常用于降低胆固醇,通过抑制 HMG-CoA 还原酶来抑制肿瘤细胞的高脂血症微环境,从而提高抗肿瘤免疫功能。一项前瞻性研究共纳入 163 662 例接受他汀类药物治疗的患者,分析显示他汀类药物使用 >6 个月可使肺癌风险降低 55%,提示他汀类药物对肺癌的发展具有保护作用[31]。另外,辛伐他汀治疗能降低前列腺癌和胰腺癌肿瘤细胞的活力和迁移能力[23]。

2. 贝特类降脂药物与恶性肿瘤:贝特类药物可上调 PPARα 表达,PPARα 通过影响灭活核因子-κB 信号通路来抑制细胞增殖,诱导细胞凋亡,从而抑制肿瘤细胞生长。贝特类药物对肝癌、乳腺癌均有显著保护作用[32]。贝特类药物通过增加活性氧水平和细胞内谷胱甘肽消耗来破坏线粒体功能和细胞内钙离子稳态,进而诱导肝癌细胞的死亡。此外,贝特类药物可能通过下调环氧化酶基因表达来抑制乳腺癌细胞的增殖、迁移,抑

制癌症进展。

3. PCSK9 抑制剂与恶性肿瘤：新型降脂药物 PCSK9 抑制剂通过特异性结合 PCSK9，抑制其与低密度脂蛋白受体（LDL-R）结合，从而增加肝脏 LDL-R 表达，增加 LDL-C 清除，最终降低 LDL-C 水平。研究显示 PCSK9 抑制剂可用于控制激素依赖性乳腺癌的进展和复发[33]。此外，有研究发现，低 PCSK9 水平与非小细胞肺癌患者的无进展生存期独立相关，是接受免疫检查点抑制剂治疗的晚期非小细胞肺癌患者预后良好的预测因子[34-35]。

四、结语

国内外研究已表明血脂水平与恶性肿瘤相关，血脂水平可反映恶性肿瘤的分期、分级及转移，并可在一定程度上预测恶性肿瘤的预后。TG 与结直肠癌、宫颈癌、子宫内膜癌、卵巢癌的发病风险及预后均呈正相关。TC 与前列腺癌、结肠癌、食管癌、乳腺癌、卵巢癌、子宫内膜癌、宫颈癌的发病风险及预后均呈正相关，而与肝癌、胃癌的发病率均呈负相关。LDL-C 与小细胞肺癌、非小细胞肺癌、前列腺癌、胰腺癌、乳腺癌的发病风险及预后均呈正相关。HDL-C 与大多数恶性肿瘤发病风险及预后均呈负相关，是恶性肿瘤患者预后的保护因素。此外，研究发现血脂水平是某些恶性肿瘤的早期诊断标志物及预后标志物，对恶性肿瘤的防治有重要价值。降脂药物对部分恶性肿瘤的发生、发展具有保护作用，但仍需大量前瞻性研究来明确降脂药物的抗肿瘤机制及降脂药物与更多类型恶性肿瘤的相关性。通过进一步研究，我们或许可以发现恶性肿瘤防治的新思路，也可为恶性肿瘤患者准确应用降脂药物提供更多依据。

参 考 文 献

[1] Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants[J]. Chin Med J (Engl), 2022, 135(5): 584-590.

[2] Trabert B, Hathaway CA, Rice MS, et al. Ovarian cancer risk in relation to blood cholesterol and triglycerides[J]. Cancer Epidemiol Biomarkers Prev, 2021, 30(11): 2044-2051.

[3] Kim D, Chung H, Lee JE, et al. Immunologic aspects of dyslipidemia: A critical regulator of adaptive immunity and immune disorders[J]. J Lipid Atheroscler, 2021, 10(2): 184-201.

[4] Radisauskas R, Kuzmickiene I, Milinaviciene E, et al. Hypertension, serum lipids and cancer risk: a review of epidemiological evidence[J]. Medicina, 2016, 52(2): 89-98.

[5] Kuzu OF, Noory MA, Robertson GP. The role of cholesterol in Cancer [J]. Cancer Res, 2016, 76(8): 2063-2070.

[6] Mangaraj M, Nanda R, Panda S, et al. A molecule of diverse function [J]. Indian J Clin Biochem, 2016, 31(3): 253-259.

[7] 毛雪杨，谷宁，胡海瑞，等. 肿瘤与血脂相关性分析及降脂药在肿瘤中的研究进展[J]. 中国医药导报，2023，20(10)：45-49.

[8] Yarla N, Madka V, Rao C. Targeting triglyceride metabolism for colorectal cancer prevention and therapy[J]. Curr Drug Targets, 2022, 23(6): 628-635.

[9] Chen XQ, Wu PW, Liu DH, et al. Prognostic significance of high triglyceride and apolipoprotein B levels in patients with stage Ⅲ and high-risk stage Ⅱ colorectal cancer undergoing curative surgery[J]. Oncol Lett, 2020, 20(1): 705-714.

[10] Jiang Q, Wang L, Jin M, et al. The clinical value of lipid abnormalities in early stage cervical cancer[J]. Int J Gen Med, 2022, 15: 3903-3914.

[11] Lin F, Zheng R, Yu C, et al. Predictive role of serum cholesterol and triglycerides in cervical cancer survival[J]. Int J Gynecol Cancer, 2021, 31(2): 171-176.

[12] Luo YZ, Yang Z, Qiu YL, et al. Pretreatment triglycerides-to-high density lipoprotein cholesterol ratio in postmenopausal women with endometrial cancer[J]. Kaohsiung J Med Sci, 2019, 35(5): 303-309.

[13] Ma HQ, Cui LH, Li CC, et al. Effects of serum triglycerides on prostate cancer and breast cancer risk: A meta-analysis of prospective studies [J]. Nutr Cancer, 2016, 68(7): 1073-1082.

[14] Cheng S, Zheng Q, Ding G, et al. Influence of serum total cholesterol, LDL, HDL, and triglyceride on prostate cancer recurrence after radical prostatectomy[J]. Cancer Manag Res, 2019, 11: 6651-6661.

[15] Santos CR, Domingues G, Matias I, et al. LDL-cholesterol signaling induces breast cancer proliferation and invasion[J]. Lipids Health Dis, 2014, 13: 16.

[16] Kitahara CM, De González AB, Freedman ND, et al. Total cholesterol and cancer risk in a large prospective study in Korea[J]. J Clin Oncol, 2011, 29(12): 1592-1598.

[17] Li C, Yang L, Zhang D, et al. Systematic review and meta-analysis suggest that dietary cholesterol intake increases risk of breast cancer[J]. Nutr Res 2016, 36(7): 627-35.

[18] Zhou P, Li B, Liu B, et al. Prognostic role of serum total cholesterol and high-density lipoprotein cholesterol in cancer survivors: a systematic review and meta-analysis[J]. Clin Chim Acta, 2018, 477: 94-104.

[19] Lin F, Zheng R, Yu C, et al. Predictive role of serum cholesterol and triglycerides in cervical cancer survival[J]. Gynecol Cancer 2021, 31(2): 171-176.

[20] Liu T, Zhou T, Luo F, et al. Clinical significance of kinetics of low-density lipoprotein cholesterol and its prognostic value in limited stage small cell lung cancer patients [J]. Cancer Control, 2021, 28: 10732748211028257.

[21] Hao F, Chen J, Wu J, et al. Expression of serum sLOX-1 in patients with non-small-cell lung cancer and its correlation with lipidmetabolism[J]. Can RespirJ, 2022, 2022: 6619331.

[22] Asare GA, Owusu-Boateng E, Asiedu B, et al. Oxidised low-density lipoprotein, a possible distinguishing lipid profile biomolecule between prostate cancer and benign prostatic hyperplasia[J]. Andrologia, 2019, 51(8): e13321.

[23] Jung YY, Ko JH, Um JY, et al. LDL cholesterol promotes the proliferation of prostate and pancreatic cancer cells by activating the STAT3 pathway[J]. J Cell Physiol, 2021, 236(7): 5253-5264.

[24] Guan X, Liu Z, Zhao Z, et al. Emerging roles of low-density lipoprotein in the development and treatment of breast cancer[J]. Lipids Health Dis, 2019, 18(1): 137.

[25] Lofterd T, Mortensen ES, Nalwoga H, et al. Impact of pre-diagnostic triglycerides and HDL-cholesterol on breast cancer recurrence and survival by breast cancer subtypes[J]. BMC Cancer, 2018, 18(1): 654.

[26] Pedersen KM, Çolak Y, Bojesen SE, et al. Low high-density lipoprotein and increased risk of several cancers: 2 population-based cohort studies including 116 728 individuals[J]. J Hematol Oncol, 2020, 13(1): 129.

[27] Jeong SM, Choi T, Kim D, et al. Association between high-density lipoprotein cholesterol level and risk of hematologic malignancy[J]. Leukemia, 2021, 35(5): 1356-1364.

[28] Yuan B, Fu J, Yu WL, et al. Prognostic value of serum high-density lipoprotein cholesterol in patients with gallbladder cancer[J]. Rev Esp Enferm Dig, 2019, 111(11): 839-845.

[29] Wang Y, Sun X, Lin H, et al. Correlation between immune signature and high-density lipoprotein cholesterol level in stage Ⅱ/Ⅲ colorectal cancer[J]. Cancer Med, 2019, 8(3): 1209-1217.

[30] Lin Q, Liu W, Xu S, et al. Associations of preoperative serum high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels with the prognosis of ovarian cancer[J]. Arch Gynecol Obstet, 2022, 305(3): 683-691.

[31] Khurana V, Bejjanki HR, Caldito G, et al. Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans[J]. Chest, 2007, 131(5): 1282-1288.

[32] Li IH, Shih JH, Tsai CS, et al. Inverse association of fibrates and liver cancer: a population-based case-control study in Taiwan [J]. J Clin Pharmacol, 2019, 59(9): 1170-1176.

[33] Abdelwahed KS, Siddique AB, Mohyeldin MM, et al. Pseurotin A as a novel suppressor of hormone dependent breast cancer progression and recurrence by inhibiting PCSK9 secretion and interaction with LDL receptor[J]. Pharmacol Res, 2020, 158: 104847.

[34] Xie M, Yu X, Chu X, et al. Low baseline plasma PCSK9 level is associated with good clinical outcomes of immune checkpoint inhibitors in advanced non-small cell lung cancer[J]. Thorac Cancer, 2022, 13(3): 353-360.

[35] 辛海光，谢青. 晚期肝细胞肝癌系统抗肿瘤治疗不良反应管理[J]. 临床内科杂志，2022，39(12)：806-810.

（收稿日期：2023-07-03）

（本文编辑：李丹青）