•综述•

抗肿瘤分子靶向药物相关性腹泻研究进展

王施元, 王致红, 李春雨*, 李国辉*

(国家癌症中心, 国家肿瘤临床医学研究中心, 中国医学科学院、北京协和医学院肿瘤医院, 北京 100021)

摘要: 近年来, 抗肿瘤药物的研发焦点从细胞毒性药物逐渐转向分子靶向药物, 这类药物通过干扰癌细胞中过度表达或突变的分子, 从而抑制肿瘤生长。与传统的化疗方案相比, 分子靶向治疗是一种高特异性且不良反应较轻的新型治疗方法, 但是分子靶向药物引起的不良反应也不容忽视。腹泻是临床上较为常见的不良反应之一, 不仅降低患者的生活质量, 还会成为临床安全用药的制约因素。本文对近十年来分子靶向药物相关性腹泻的文献进行归纳和分析, 以期为相关研究和临床合理安全用药提供参考。

关键词: 腹泻; 抗肿瘤药物; 分子靶向药物; 酪氨酸激酶抑制剂; 不良反应; 合理用药

中图分类号: R969 **文献标识码**: A **文章编号**: 0513-4870(2021)12-3377-08

Research progress on diarrhea induced by molecular-targeted agents

WANG Shi-yuan, WANG Zhi-hong, LI Chun-yu*, LI Guo-hui*

(*National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China*)

Abstract: In recent years, the focus of anti-cancer agents has gradually shifted from cytotoxic chemotherapy to molecular-targeted agents that interfere with frequently overexpressed or mutated molecules in cancer cells. Compared with cytotoxic chemotherapy, molecular-targeted therapy is a new biological therapy with higher specificity and lower toxicity, however, the adverse reactions caused by molecular-targeted agents cannot be ignored. Diarrhea is one of the most common adverse drug reactions, which could seriously affect the quality of life and even lead to treatment discontinuation and consequently decreased cancer control. To provide a reference for relevant research and clinical medication, we review the current reports on the incidence, pathogenic mechanism, and management of diarrhea induced by the molecular-targeted agents.

Key words: diarrhea; anti-cancer agent; molecular-targeted agent; tyrosine kinase inhibitor; adverse reaction; rational drug use

分子靶向药物是一类在细胞水平上针对恶性肿瘤细胞病理发展过程中关键调控分子而设计的新型抗肿瘤药物, 药物进入人体后特异性结合靶点并发挥作用, 使肿瘤细胞死亡, 但不会对周围的正常组织细胞造成影响。与传统的化疗方案相比, 分子靶向治疗具有高选择性、疗效确切和不良反应轻等优点, 因此被临床广泛应用, 但是分子靶向药物的局限之处也逐渐显现, 表现为皮疹、腹泻、心血管毒性和药物性肝损伤等多种不良反应[1]。其中, 腹泻的总体发生率较高, 影响生活质量的同时还会降低药效, 导致患者的用药依从性下降, 严重时甚至危及生命。本文对近年来中国期刊全文数据库、Web of Science 和 PubMed 中分子靶向药物相关性腹泻的相关研究进行综述, 归纳整理分子靶向药物相关性腹泻的研究现状和应对措施, 以期为相关研究和临床用药提供参考, 使临床获益最大化。

1 分子靶向药物相关性腹泻概述

根据药物的结构, 分子靶向药物主要分为两大类,

收稿日期: 2021-03-24; 修回日期: 2021-04-22.
基金项目: 北京市科技计划项目 (Z181100001618003).
*通讯作者 Tel: 86-10-87788428, E-mail: chunyu_li@126.com;
Tel: 86-10-87788577, E-mail: lgh0603@126.com
DOI: 10.16438/j.0513-4870.2021-0427

小分子靶向药物和大分子单克隆抗体类药物。根据药物的作用靶点, 可以分为表皮生长因子受体 (epidermal growth factor receptor, EGFR) 酪氨酸激酶抑制剂 (tyrosine kinase inhibitors, TKIs)、血管内皮生长因子受体 (vascular endothelial growth factor receptor, VEGFR) 酪氨酸激酶抑制剂、EGFR单克隆抗体、VEGFR单克隆抗体、以白细胞分化抗原-20 (cluster of differentiation-20, CD20) 等特异性抗原分子为靶点的单克隆抗体、有丝分裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号通路抑制剂、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 / protein kinase B / the mammalian target of rapamycin, PI3K/Akt/mTOR) 信号通路相关抑制剂、Bcr-abl (breakpoint cluster region-abl) 激酶抑制剂、组蛋白脱乙酰酶抑制剂、蛋白酶体抑制剂和细胞周期蛋白依赖性激酶4/6 (cyclin-dependent kinase 4/6, CDK4/6) 抑制剂等[2,3]。

腹泻是分子靶向药物的常见不良反应, 发生率较高, 在以EGFR为靶点的小分子靶向药物的不良反应中, 腹泻的发生率仅次于皮疹, 位居第二[4]。《新型抗肿瘤药物临床应用指导原则 (2019年版)》明确指出: 大部分口服小分子靶向药物以及卡瑞利珠单抗、尼妥珠单抗、帕博利珠单抗和信迪利单抗等单克隆单体均会导致不同程度的腹泻[5]。腹泻的临床表现为便次增加和/或稀便或水样便, 常伴有腹胀、腹痛、食欲减退等症状, 长期腹泻可导致脱水、浑身乏力、营养不良、电解质紊乱和肾功能不全, 严重影响肿瘤患者的日常活动, 甚至会导致分子靶向治疗中断, 从而降低疗效, 两项I期临床试验表明当分子靶向药物与化疗药物联用时, 腹泻是具有剂量依赖性的限制因素[6,7]。

在目前已公布的EGFR-TKIs的III期临床试验中, 腹泻的总体发生率为9.5%～95.2%, 3级及其以上的发生率为0.9%～14.4%。一项临床试验汇总分析表明, 与其他EGFR-TKIs相比, 阿法替尼的腹泻发生率更高[8,9], 而且女性、低体重和高龄是阿法替尼诱发严重腹泻的重要危险因素[10]。2020年, 邰新娟等[11]报道了一例仑伐替尼治疗甲状腺癌致严重难治性腹泻, 最终导致停药的案例。在一项随机、开放标签的III期临床试验中, 一名患者在使用达可替尼治疗期间发生严重腹泻, 由于未经治疗导致死亡[12]。多项临床试验表明, 细胞毒性T淋巴细胞相关蛋白-4 (cytotoxic T-lymphocyte-associated protein-4, CTLA-4) 抑制剂易普利姆玛的各级腹泻发生率为43%, 3级及其以上的发生率为15%[13]; PD-1抑制剂帕博利珠单抗的各级腹泻发生率为16%[14]; PD-1抑制剂卡瑞利珠单抗在治疗晚期鳞状食道癌过程中的各级腹泻发生率为5.7%, 3级及其以上的发生率为1%[15]。以上研究均提示, 使用分子靶向药物可能引起不同程度的腹泻, 严重情况下可导致治疗中断, 临床用药时应当严格评估并及时处理 (表1)[12,16-27]。

Table 1 Incidence of diarrhea in clinical trials about different molecular-targeted agents. EGFR: Epidermal growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; Raf: Ras-associated factor; MEK: Mitogen extracellular kinase; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol-3-kinase; Bcr-abl: Breakpoint cluster region-abl; CD20: Cluster of differentiation-20

Target	Agent	Area	Diarrhea	
			All grades%	⩾3 grade%
EGFR	Gefitinib[12]	Japan and Korea	55.8	0.9
	Erlotinib[16,17]	China	27.7	8.5
		Global	41.0	3.7
	Icotinib[18]	China	9.5	7.4
	Afatinib[19,20]	Global	95.2	14.4
		Asia	88.3	5.4
	Dacomitinib[12]	Japan and Korea	86.7	8.4
	Osimertinib[21]	Japan	34.1	2.4
VEGFR	Sorafenib[22]	Japan	53.2	7.3
	Lenvatinib[22]	Japan	37.0	3.7
Raf/MEK/MAPK	Dabrafenib[23]	Global	32.0	2.2
PI3K	Taselisib[24]	Global	44.1	12.0
Bcr-abl	Dasatinib[25]	Global	28.1	2.8
	Nilotinib[25]	Global	7.1	0.5
CD20	Rituximab[26]	China	5.8	0
	Ofatumumab[27]	Global	12.2	1.3

2 分子靶向药物相关性腹泻的发病机制

在本世纪初, 曾有学者认为分子靶向药物相关性腹泻的发病机制与化疗相关性腹泻 (chemotherapy-induced diarrhea, CID) 相同[28]。CID常被用于描述肿瘤患者在使用5-氟尿嘧啶、卡培他滨和伊立替康等化疗药物时发生的腹泻, 普遍认为其发生机制遵循“5期模型”, 即化疗药物直接刺激结直肠黏膜而导致组织损伤, 或诱导机体产生活性氧, 通过激活核因子-κB (nuclear factor-κB, NF-κB) 诱导细胞产生大量促炎因子, 引起细胞凋亡和组织炎症, 再通过信号放大效应导致上皮细胞死亡, 使肠道通透性增加, 肠道黏膜屏障遭到破坏, 该过程通常伴随肠道菌群失调和致病菌增加[29,30]。但是一项组织病理学研究显示, 分子靶向药物相关性腹泻的病变部位通常是小肠, 而结直肠无明显改变, 两者的发病部位完全不同, 这一证据推翻了过去认为其发病机制相同的观点[31,32]。

小肠是拥有丰富上皮细胞的主要消化吸收器官, 而EGFR和VEGFR均在小肠上皮细胞中高表达。分别用厄洛替尼和吉非替尼给小鼠灌胃55天后, 发现小鼠肠壁组织存在炎症细胞浸润和小肠绒毛结构改变等

变化, 体外实验也证实EGFR-TKIs可造成细胞间紧密连接受损, 引发肠壁细胞凋亡, 该研究表明内质网应激可能是EGFR-TKIs造成小肠上皮细胞损伤的机制[33]。也有研究者认为分子靶向药物可能直接作用于小肠黏膜内皮细胞, 拮抗其表面的EGFR受体, 抑制小肠黏膜增殖, 使毛细血管网减少, 进而引发腹泻[34]。Bowen[35]认为EGFR-TKIs抑制小肠上皮细胞的信号转导, 造成小肠黏膜上皮细胞生长和修复能力下降, 使小肠黏膜萎缩, 从而导致腹泻, 相关分子机制见图1A。

另有研究表明, 由于恶性肿瘤患者的免疫力低下, 胃肠道功能较弱, 从而易发生肠道病原学微生物感染, 这可能是部分患者出现腹泻症状的主要原因[36,37]。一项临床研究表明, 在接受VEGFR-TKIs治疗的患者中, 与对照组相比, 服用多西环素组的腹泻发生率较低(85% *vs* 56%), 因此不能排除胃肠道感染导致分子靶向药物相关性腹泻的可能性[38]。

一项EGFR抑制剂拉帕替尼的临床前研究表明, 拉帕替尼诱导的腹泻大鼠模型的肠道菌群多样性显著降低[39]。应用16S rRNA测序分析20例接受VEGFR-TKIs治疗的肾癌患者的粪便细菌分布情况, 发现腹泻患者比未腹泻患者的肠道菌群组分中普雷沃氏菌分布较少, 拟杆菌属的含量较高, 而且双歧杆菌属的相对丰度较健康人偏低[40]。以上结果均提示, 肠道菌群紊乱可能与分子靶向药物相关性腹泻有关。

Loriot等[28]发现EGFR-TKIs相关性腹泻的临床表型包括分泌型腹泻, 这类腹泻是由于囊性纤维化跨膜电导调节因子的活性增高和氯离子通道被激活而引起的, 而EGFR对氯化物的分泌有抑制作用[41]。在此基础上, 提出小肠黏膜的EGFR信号通路调节因受到EGFR-TKIs的影响而减弱, 引起氯离子分泌增加, 进而引发分泌型腹泻的假说[42]。有研究者试图通过离体模型实验证明该假说, 结果表明EGFR-TKIs相关性腹泻的发病机制是小肠上皮细胞中的钾离子通道和氯离子通道被激活, 并证明通道阻断剂在腹泻大鼠模型中的功效[43]。但是, Bowen[44]使用拉帕替尼建立了腹泻小鼠模型, 发现小鼠血清中的氯离子含量没有发生明显变化, 故该理论目前尚缺乏有力证据, 需要进一步研究。2020年, 通过测量3个不同的肠上皮单层细胞中氯离子的传导性和黏膜的完整性, 证实了氯化物分泌和屏障功能障碍的增强可能是EGFR-TKIs相关性腹泻的机制[45], 相关分子机制见图1B。

由上述研究可知, 国内外多位学者认为分子靶向药物相关性腹泻是由多因素共同导致的, 涉及药物刺激小肠黏膜、离子转运失调、胃肠道感染、肠道菌群紊乱和胰腺外分泌功能障碍等多种可能机制, 其中药物刺激小肠黏膜和离子转运失调两种可能机制已有相关分子机制研究 (图1)。

随着分子靶向药物的不断更新, 除了以EGFR和VEGFR为靶点的药物外, 其他分子靶向药物的腹泻机制研究也在逐步开展。如以PI3K为靶点的抗肿瘤药物Taselisib, 多项III期临床试验表明其腹泻发生率较高[24,46,47], 一项临床前研究表明, PI3Kδ缺陷小鼠具有受损的免疫应答, 其特征是结肠巨噬细胞的Toll样受体信号增强和杀菌水平降低, 证实了腹泻的发生可能与该药物的PI3Kδ高选择性有关[48-50]。另一类以CDK4/6为靶点的药物是通过释放Rb蛋白抑制癌细胞增殖, 而胃肠道上皮细胞很容易受到这种抑制作用的影响, 但腹泻的产生不仅由于药物对胃肠道黏膜的直接刺激作

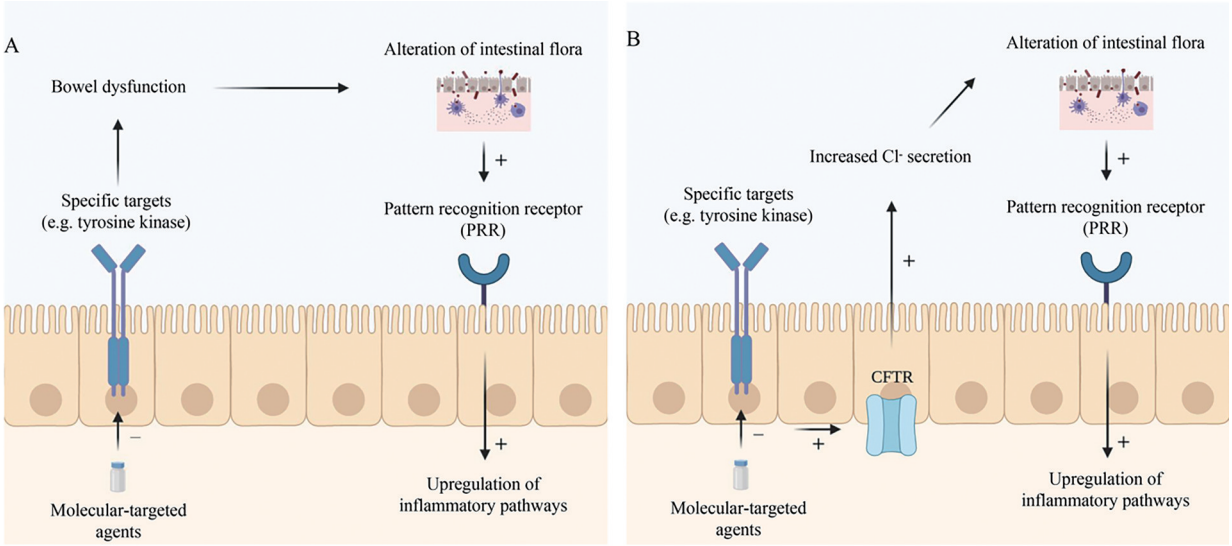

Figure 1 Proposed mechanisms of molecular-targeted agents. A: Direct inhibition driven alteration of intestinal flora; B: Increased chloride secretion driven alteration of intestinal flora

用, 还由于某些刷状缘酶的功能缺陷、细胞对损伤的反应紊乱以及与其他途径的相互作用[51,52]。

中医认为, 分子靶向药物相关性腹泻属于“泄泻”范畴, 虽然腹泻病位在肠, 但病机当以脾为主, 与肝、肾二脏密切相关。《EGFR-TKI不良反应管理专家共识》指出泄泻的发生与“药毒”和“体虚”有关, 或因久病而脾胃虚弱, 或因情志抑郁而肝郁乘脾, 或因日久而伤肾, 最终脾胃运化失常, 内生湿滞, 易感寒湿, 而致泄泻, 此为体虚之因; EGFR-TKI是攻伐之品, 属中医“药毒”的范畴, 易伤脾胃而致泄泻, 此为药毒之因。恶性肿瘤患者体质虚弱, 脏腑亏虚, 则正气益虚, 因此分子靶向药物相关性腹泻的中医病因多在脾虚与湿邪[53]。

3 分子靶向药物诱导的腹泻动物模型

3.1 腹泻动物模型的建立 研究人员可以根据实验需求对常见腹泻动物模型进行改造, 构建分子靶向药物诱导的腹泻动物模型。Secombe等[54]通过口服管饲法给予每只Wistar大鼠50 mg·kg^{-1}奈拉替尼, 连续给药14天, 每天记录大鼠的体重和腹泻严重程度, 使用免疫组织化学法检测细胞中caspase-3的凋亡情况, 通过多重细胞因子/趋化因子测定法测量炎症因子, 使用PCR和Western blot测量*ErbB*基因水平。Bowen等[55]每天以100、240或500 mg·kg^{-1}拉帕替尼对Wistar大鼠进行口服给药, 连续给药4周, 并在每周结束时评估其对胃肠道损伤的指标, 通过免疫组化和RT-PCR检测EGFR通路信号的标记, 并进行形态计量分析以评估黏膜结构的变化, 可以观察到电解质的改变、空肠中隐窝腔的延长、黏蛋白分泌的增加、EGFR和ErbB-2的蛋白表达下降以及细胞凋亡, 该模型深化了研究者对拉帕替尼引起腹泻的机制认识。Hare等[56]给雌性C57BL小鼠口服吉非替尼、胰高血糖素样肽-2 (glucagon-like peptide-2, GLP-2) 或两者联合给药, 连续给药10天后处死小鼠, 确定胃肠道的重量和长度, 并通过形态计量学方法分析组织学切片, 可以观察到吉非替尼组小鼠的肠壁明显萎缩, 小肠重量、绒毛高度和横截面积均降低, GLP-2组和联合给药组的小鼠肠重量显著增加, 所有的肠道形态参数均相当甚至有所提高, 小肠近端的变化最为明显, 从而证实可以通过GLP-2治疗来避免由EGFR-TKIs引起的腹泻。

3.2 腹泻模型的评价标准 以滤纸有无污迹为干便和稀便的区分标准, 根据粪便次数、稀便级和粪便直径判断动物的腹泻程度, 最后计算腹泻指数 (腹泻指数 = 稀便率×稀便级)。腹泻的4个等级: 0级无腹泻; 1级轻度腹泻 (粪便软, 未变形); 2级中度腹泻 (粪便松散, 伴有肛周染色); 3级重度腹泻 (水样粪便或黏液, 伴有双腿和腹部染色)。

切片经HE染色后, 在光学显微镜下观察肠壁有无下列病变, 进行病理学评分: ① 黏膜上皮细胞有无变性、坏死及其程度; 黏膜固有层有无充血、水肿和炎细胞浸润; ② 黏膜层或黏膜下层、肌层有无坏死; ③ 黏膜下层、肌层、浆膜层有无充血、水肿和炎细胞浸润。根据病变由轻变重的程度分别计分为1、2、3、4分, 无明显病变计为0分, 极轻病变计为0.5分。累加所有分数, 得出总分, 计算出每组动物的均分, 分值越高病变越严重。

其余相关评价指标: 动物体重、肠道敏感性、肠道酶活性等。

4 分子靶向药物相关性腹泻的治疗

4.1 分子靶向药物相关性腹泻的诊断 腹泻通常是指粪便含水量和大便次数异常增加, 在24 h内排出3次及以上的稀松或水样大便, 病程持续不超过14天。对于在分子靶向治疗前无腹泻而治疗后出现腹泻症状者, 或治疗前已有腹泻而治疗后腹泻症状显著加重者, 均应考虑分子靶向药物导致腹泻的可能性。由于神经内分泌肿瘤的类癌综合征、胃泌素瘤和血管活性肠肽瘤等疾病本身也可导致腹泻的发生[57,58], 因此在建立分子靶向药物相关性腹泻诊断时, 应尽可能排除其他原因导致的腹泻。在确诊为分子靶向药物相关性腹泻之后, 应先对腹泻的严重程度进行合理评估, 为后续治疗决策提供依据。根据美国国立癌症研究所 (NCI) 制定的不良事件通用术语评价标准5.0评价标准 (CTCAE 5.0)[59], 可将腹泻的严重程度分为5级: 1级是与基线相比, 大便次数增加, 每天 < 4次, 造瘘口排出物轻度增加; 2级是与基线相比, 大便次数增加, 每天4～6次, 造瘘口排出物中度增加, 并且借助于工具的日常生活活动受限; 3级是与基线相比, 大便次数增加, 每天≥7次, 造瘘口排出物重度增加, 自理性日常生活活动受限, 需要住院治疗; 4级是危及生命, 需要紧急治疗; 5级为死亡。在按照上述标准进行分级的同时, 也应当对下列内容进行评估[60]: ① 确认出现腹泻症状的时间及持续时间; ② 记录排便次数及排便性状; ③评估是否有发烧、晕眩、痉挛等症状, 以排除其他严重不良反应的影响; ④ 评估患者的饮食特点和用药依从性。

4.2 分子靶向药物相关性腹泻的预防 在进行分子靶向药物治疗前, 医生应告知患者及其家属治疗中可能出现的腹泻风险, 以便及时监测、早日诊断并采用适当的治疗方案; 收集患者在治疗开始前6周的大便信息, 以便更好评估腹泻的状况; 收集患者同时服用的其他药物情况, 以便评估药物对消化系统的潜在影响; 治疗期间应保持低脂高蛋白饮食, 少食多餐, 忌食用咖啡

因、酒精、奶制品、脂肪、纤维、橘子汁、葡萄汁以及辛辣食物[61]。

4.3 分子靶向药物相关性腹泻的处理措施 目前, 分子靶向药物相关性腹泻被认为属于药物刺激性腹泻, 但其严重程度一般低于3级, 无需停药治疗, 但是相关研究表明阿法替尼、伊马替尼、索拉非尼、卡瑞利珠单抗等部分靶向药物会引起剂量依赖性腹泻, 必要时可以通过调整药物剂量来降低腹泻的发生率和严重程度[19,62-64]。因此, 临床主要通过一般治疗、调整药物剂量和止泻药物治疗等对症治疗手段在一定程度上改善患者的腹泻症状, 具体处理措施可参见表2[61]。不过止泻药洛哌丁胺的治疗效果有限, 对于重度腹泻患者只能采取以低剂量重新开始分子靶向治疗和中断治疗等措施。

目前, 临床上尚无治疗分子靶向药物相关性腹泻的特效药物, 仍在沿用以往用于治疗化疗性相关腹泻的洛哌丁胺等药物。已有研究表明, 尼克酰胺类药物可通过抑制s-HBEGF/SIRT1 (s-heparin binding epidermal growth factor/sirtuin 1) 通路有效治疗索拉非尼相关性皮疹 (手足综合征), s-HBEGF作为EGFR的配体, 被认为是多种癌症的重要分子靶标。虽然腹泻的机制尚无定论, 但目前更倾向于小肠黏膜的EGFR信号通路调节因受到分子靶向药物的影响而减弱, 引起氯离子分泌增加, 导致分泌型腹泻, 因此尼克酰胺类药物可能用于分子靶向药物相关性腹泻的治疗, 值得进一步研究[65]。

除西药外, 分子靶向药物相关性腹泻的中医药研究也较为多见, 临床上经常根据实际情况辨证使用中药, 如脾胃虚弱者可选用参苓白术丸、香砂六君丸、理中丸等; 肝气乘脾者可选用逍遥丸合香砂六君丸; 肾阳虚衰者可选四神丸、桂附理中丸等[53]。有研究者采用参苓白术散颗粒联合吉非替尼/厄罗替尼治疗脾虚型晚期肺癌患者, 与对照组相比, 联合给药组的腹泻发生率显著降低 (70.0% *vs* 28.60%), 表明参苓白术散颗粒联合分子靶向药物可有效减轻腹泻症状, 且对免疫有正向调节作用[66]。在一项使用自拟扶正抑癌1号联合吉非替尼治疗中晚期肺癌的随机对照试验中, 对照组给予口服吉非替尼片治疗, 1天1次250 mg; 试验组在此基础上加用扶正抑癌1号, 每日1剂, 分3次服用, 3个月后分别按照RECIST标准和Karnofsky评分进行判定, 数据表明试验组肿瘤控制率优于对照组 (61.90% *vs* 55.00%), 证实扶正抑癌1号联合吉非替尼治疗中晚期肺癌的效果优于单用吉非替尼, 且具有增效减毒的作用[67]。以上报道均显示, 在口服分子靶向药物的同时配合使用中药可以有效降低腹泻的发生率, 同时调节胃肠道功能, 增进患者的食欲, 有效预防腹泻的发生, 有助于提升患者的生活质量并延长生存期, 但目前的研究均以临床观察及经验总结为主, 相关动物实验研究较少, 缺乏在动物模型中的客观评价及作用机制的研究[68]。

5 总结与展望

分子靶向药物具有低毒性、高特异性和不良反应较轻等优点, 在临床上应用广泛, 提高了肿瘤患者的生存质量和用药依从性, 但也存在亟待解决的问题: ① 1～2级腹泻发生率较高且患者的个体差异性较大, 研究者应当充分意识到分子靶向药物相关性腹泻的严重性和多样性, 注意用药细节, 为患者制定个体化治疗方案; ② 临床上不乏严重腹泻导致靶向药物治疗中断的案例, 研究者应当在治疗过程中严密监测不良反应, 及时发现并诊断, 采取对症处理的措施; ③ 分子靶向药物相关性腹泻的机制尚无定论, 该领域仍处于探索阶段, 尤其是一些近年来才问世的新型分子靶向药物, 相关腹泻机制研究更是寥寥无几, 应进一步研究其作用机制和危险因素, 从而确保临床合理安全用药, 使患者

Table 2 Management of diarrhea in patients treated with molecular-targeted drugs[61]

Grade	Management	Treatment
1−2	① Remove stool softeners and laxatives; drink 8−10 glasses of clear fluids daily; ② Change the diet modification; ③ Assess for dehydration and electrolyte imbalance. Consider intravenous fluids and electrolyte replacement	① Maintain dose level of molecular-targeted agents. Immediately start loperamide: 4 mg (2 tablets) followed by 2 mg (1 tablet) after each loose stool (up to 20 mg daily) until bowel movements cease for 12 h; ② If diarrhea does not improve after 48 h, temporarily discontinue molecular-targeted agents. Upon improvement to grade 1, restart molecular-targeted agents at a reduced dose (except gefitinib, which should be restarted at the original dose)
3−5	① Use stool cultures to rule out an infectious process. Use hospitalization to monitor the patient's progress; ② Apply aggressive intravenous fluid replacement for 24 h or more. Consider prophylactic antibiotics if the patient is also neutropenic	① The patient should be hospitalized; ② Temporarily discontinue molecular-targeted agents. Upon improvement to grade 1, restart molecular-targeted agents at a reduced dose (except gefitinib, which should be restarted at the original dose); ③ Permanently discontinue molecular-targeted agents if diarrhea does not return to grade 1 within 14 days despite treatment discontinuation and best supportive care; ④ Continue with loperamide (up to 20 mg daily); ⑤ If the patient is neutropenic, antibiotics should be given prophylactically

获得更好的生存益处, 实现精准医疗; ④ 中医药在防治分子靶向药物相关性腹泻方面展现出较好的临床效果和开发潜力, 应对其相关机制展开深入研究与探讨, 为临床制定标准治疗方案提供有力的理论依据。

作者贡献: 王施元负责文献检索、文章撰写及文稿修改; 王致红负责对文章内容提出修改意见; 李春雨负责文章撰写思路设计和文章修改; 李国辉负责综述选题并对文章内容提出指导性意见。全体作者都阅读并同意最终版本。

利益冲突: 所有作者均声明不存在利益冲突。

References

[1] Gerber DE. Targeted therapies: a new generation of cancer treatments [J]. Am Fam Physician, 2008, 77: 311-319.

[2] Liu QH, Lin LZ. The pharmacology and clinic of tumor molecular targeted drugs [J]. Clin Med J (临床药物治疗杂志), 2008, 6: 50-54.

[3] Hu HX, Wang XQ, Zhang H, et al. The mechanism of action and clinical research progress of molecular targeted anti-tumor drugs [J]. Acta Pharm Sin (药学学报), 2015, 50: 1232-1239.

[4] Li XL, Tang XL, Li YP, et al. Efficacy and safety of EGFR-TKIs *versus* chemotherapy as the first line treatment for patients with advanced non-small cell lung cancer: a systematic review [J]. Chin J Evid Based Med (中国循证医学杂志), 2016, 16: 191-199.

[5] National Health Commission of the People's Republic of China. Guiding principles for the clinical application of new anti-tumor drugs (2019 edition) [J]. J Multidiscip Cancer Manag (肿瘤综合治疗电子杂志), 2020, 6: 16-47.

[6] Czito BG, Willett CG, Bendell JC, et al. Increased toxicity with gefitinib, capecitabine, and radiation therapy in pancreatic and rectal cancer: phase I trial results [J]. J Clin Oncol, 2006, 24: 656-662.

[7] Messersmith WA, Laheru DA, Senzer NN, et al. Phase I trial of irinotecan, infusonal 5-fluorouracil, and leucovorin (FOLFIRI) with erlotinib (OSI-774): early termination due to increased toxicities [J]. Clin Cancer Res, 2004, 10: 6522-6527.

[8] Barron F, de la Torre-Vallejo M, Luna-Palencia RL, et al. The safety of afatinib for the treatment of non-small cell lung cancer [J]. Expert Opin Drug Saf, 2016, 15: 1563-1572.

[9] Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer [J]. Lung Cancer, 2015, 88: 74-79.

[10] Hopkins AM, Nguyen AM, Karapetis CS, et al. Risk factors for severe diarrhea with an afatinib treatment of non-small cell lung cancer: a pooled analysis of clinical trials [J]. Cancers (Basel), 2018, 10: 384.

[11] Tai XJ, Ma HF. Lenvatinib in the treatment of severe diarrhea caused by thyroid cancer [J]. Chin J Hosp Pharm (中国医院药学杂志), 2020, 40: 2004-2005.

[12] Wu YL, Cheng Y, Zhou X, et al. Dacomitinib *versus* gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial [J]. Lancet Oncol, 2017, 18: 1454-1466.

[13] Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab *versus* placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer [J]. J Clin Oncol, 2017, 35: 40-47.

[14] Ott PA, Piha-paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal [J]. Ann Oncol, 2017, 28: 1036-1041.

[15] Huang J, Xu J, Chen Y, et al. Camrelizumab *versus* investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study [J]. Lancet Oncol, 2020, 21: 832-842.

[16] Wang Y, Wang H, Jiang Y, et al. A randomized phase III study of combining erlotinib with bevacizumab and panitumumab *versus* erlotinib alone as second-line therapy for Chinese patients with non-small-cell lung cancer [J]. Biomed Pharmacother, 2017, 89: 875-879.

[17] Scagliotti G, von Pawel J, Novello S, et al. Phase III multinational, randomized, double-blind, placebo-controlled study of tivantinib (ARQ 197) plus erlotinib *versus* erlotinib alone in previously treated patients with locally advanced or metastatic nonsquamous non-small-cell lung cancer [J]. J Clin Oncol, 2015, 33: 2667-2674.

[18] Shi YK, Wang L, Han BH, et al. First-line icotinib *versus* cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study [J]. Ann Oncol, 2017, 28: 2443-2450.

[19] Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations [J]. J Clin Oncol, 2013, 31: 3327-3334.

[20] Wu YL, Zhou C, Hu CP, et al. Afatinib *versus* cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial [J]. Lancet Oncol, 2014, 15: 213-222.

[21] Akamatsu H, Katakami N, Okamoto I, et al. Osimertinib in Japanese patients with EGFR T790M mutation-positive advanced non-small-cell lung cancer: AURA3 trial [J]. Cancer Sci, 2018, 109: 1930-1938.

[22] Yamashita T, Kudo M, Ikeda K, et al. REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the

treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset [J]. J Gastroenterol, 2020, 55: 113-122.

[23] Odogwu L, Mathieu L, Blumenthal G, et al. FDA approval summary: dabrafenib and trametinib for the treatment of metastatic non-small cell lung cancers harboring BRAF V600E mutations [J]. Oncologist, 2018, 23: 740-745.

[24] Baselga J, Dent SF, Cortes J, et al. Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) *v* FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): primary analysis from SANDPIPER [J]. J Clin Oncol, 2018, 36: LBA1006.

[25] Mohanavelu P, Mutnick M, Mehra N, et al. Meta-analysis of gastrointestinal adverse events from tyrosine kinase inhibitors for chronic myeloid leukemia [J]. Cancers (Basel), 2021, 13: 1643.

[26] Huang X, Qiu L, Jin J, et al. Ibrutinib *versus* rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study [J]. Cancer Med, 2018, 7: 1043-1055.

[27] Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib *vs* ofatumumab in relapsed and refractory CLL/SLL [J]. Blood, 2018, 132: 2446-2455.

[28] Loriot Y, Perlemuter G, Malka D, et al. Drug insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy [J]. Nat Clin Pract Oncol, 2008, 5: 268-278.

[29] Bowen J, Al-Dasooqi N, Bossi P, et al. The pathogenesis of mucositis: updated perspectives and emerging targets [J]. Support Care Cancer, 2019, 27: 4023-4033.

[30] Sonis ST. New thoughts on the initiation of mucositis [J]. Oral Dis, 2010, 16: 597-600.

[31] Janjigian YY. Lapatinib in gastric cancer: what is the LOGiCal next step? [J]. J Clin Oncol, 2016, 34: 401-403.

[32] Ramlau R, Thomas M, Novello S, et al. Phase I study of lapatinib and pemetrexed in the second-line treatment of advanced or metastatic non-small-cell lung cancer with assessment of circulating cell free thymidylate synthase RNA as a potential biomarker [J]. Clin Lung Cancer, 2015, 16: 348-357.

[33] Hu LN. Intestinal Epithelial Injury Induced by Molecular Targeted Drug EGFR Tyrosine Kinase Inhibitor and Its Mechanism (分子靶向药物EGFR酪氨酸激酶抑制剂诱导的肠上皮损伤及其机制) [D]. Jiangsu: Nanjing University, 2012.

[34] Uribe JM, Keely SJ, Traynor-Kaplan AE, et al. Phosphatidylinositol 3-kinase mediates the inhibitory effect of epidermal growth factor on calcium-dependent chloride secretion [J]. J Biol Chem, 1996, 271: 26588-26595.

[35] Bowen JM. Mechanisms of TKI-induced diarrhea in cancer patients [J]. Curr Opin Support Palliat Care, 2013, 7: 162-167.

[36] Xue Y, Wang QQ. Research progress of intestinal flora and malignant tumors [J]. J Pract Oncol (实用肿瘤杂志), 2016, 31: 9-13.

[37] Wang M, Johnson S. Enteric infections [J]. Cancer Treat Res, 2014, 161: 237-251.

[38] Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer [J]. J Clin Oncol, 2010, 28: 1351-1357.

[39] Mayo BJ, Secombe KR, Wignall AD, et al. The GLP-2 analogue elsiglutide reduces diarrhoea caused by the tyrosine kinase inhibitor lapatinib in rats [J]. Cancer Chemother Pharmacol, 2020, 85: 793-803.

[40] Pal SK, Li SM, Wu X, et al. Stool bacteriomic profiling in patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor-tyrosine kinase inhibitors [J]. Clin Cancer Res, 2015, 21: 5286-5293.

[41] Thiagarajah JR, Donowitz M, Verkman AS. Secretory diarrhoea: mechanisms and emerging therapies [J]. Nat Rev Gastroenterol Hepatol, 2015, 12: 446-457.

[42] Van Sebille YZ, Gibson RJ, Wardill HR, et al. ErbB small molecule tyrosine kinase inhibitor (TKI) induced diarrhoea: chloride secretion as a mechanistic hypothesis [J]. Cancer Treat Rev, 2015, 41: 646-652.

[43] Duan T, Cil O, Thiagarajah JR, et al. Intestinal epithelial potassium channels and CFTR chloride channels activated in ErbB tyrosine kinase inhibitor diarrhea [J]. JCI Insight, 2019, 4: e126444.

[44] Bowen JM. Development of the rat model of lapatinib-induced diarrhoea [J]. Scientifica (Cairo), 2014, 2014: 194185.

[45] Kim Y, Quach A, Das S, et al. Potentiation of calcium-activated chloride secretion and barrier dysfunction may underlie EGF receptor tyrosine kinase inhibitor-induced diarrhea [J]. Physiol Rep, 2020, 8: e14490.

[46] Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant *versus* placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial [J]. Lancet Oncol, 2017, 18: 904-916.

[47] Di Leo A, Johnston S, Lee KS, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial [J]. Lancet Oncol, 2018, 19: 87-100.

[48] Okkenhaug K, Graupera M, Vanhaesebroeck B. Targeting PI3K in cancer: impact on tumor cells, their protective stroma, angiogenesis, and immunotherapy [J]. Cancer Discov, 2016, 6: 1090-1105.

[49] Curigliano G, Shah RR. Safety and tolerability of phosphatidylinositol-3-kinase (PI3K) inhibitors in oncology [J]. Drug Saf, 2019, 42: 247-262.

[50] Uno JK, Rao KN, Matsuoka K, et al. Altered macrophage function contributes to colitis in mice defective in the phos-

phoinositide-3 kinase subunit p110δ [J]. Gastroenterology, 2010, 139: 1642-1653.

[51] Ko TC, Pan F, Sheng H, et al. Cyclin D3 is essential for intestinal epithelial cell proliferation [J]. World J Surg, 2002, 26: 812-818.

[52] Wei L, Leibowitz BJ, Wang X, et al. Inhibition of CDK4/6 protects against radiation-induced intestinal injury in mice [J]. J Clin Invest, 2016, 126: 4076-4087.

[53] Hu J, Lin LZ, Luo XQ, et al. EGFR-TKI ADR management Chinese expert consensus [J]. Chin J Lung Cancer (中国肺癌杂志), 2019, 22: 57-81.

[54] Secombe KR, Ball IA, Shirren J, et al. Targeting neratinib-induced diarrhea with budesonide and colesevelam in a rat model [J]. Cancer Chemother Pharmacol, 2019, 83: 531-543.

[55] Bowen JM, Mayo BJ, Plews E, et al. Determining the mechanisms of lapatinib-induced diarrhoea using a rat model [J]. Cancer Chemother Pharmacol, 2014, 74: 617-627.

[56] Hare KJ, Hartmann B, Kissow H, et al. The intestinotrophic peptide, GLP-2, counteracts intestinal atrophy in mice induced by the epidermal growth factor receptor inhibitor, gefitinib [J]. Clin Cancer Res, 2007, 13: 5170-5175.

[57] Anthony LB. Practical guide to supportive care of patients with functional neuroendocrine tumors [J]. Semin Oncol, 2013, 40: 45-55.

[58] Sheng WQ. Advances and pathological diagnostic standard of gastroenteropancreatic neuroendocrine neoplasms [J]. Chin J Cancer (中国癌症杂志), 2013, 23: 401-407.

[59] Common terminology criteria for adverse events (CTCAE) version 5.0 [EB/OL]. U. S: NCI, 2017 [2021-03-20]. https://ctep.cancer. gov/protocoldevelopment/electronic_applications/ctc. htm #ctc_50.

[60] Yang JC, Reguart N, Barinoff J, et al. Diarrhea associated with afatinib: an oral ErbB family blocker [J]. Expert Rev Anticancer Ther, 2013, 13: 729-736.

[61] Califano R, Tariq N, Compton S, et al. Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK [J]. Drugs, 2015, 75: 1335-1348.

[62] Escudier B, Szczylik C, Eisen T, et al. Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC) [J]. J Clin Oncol, 2005, 23: LBA4510.

[63] Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma [J]. JAMA, 2006, 295: 2516-2524.

[64] Shibayama H, Teshima T, Choi I, et al. Phase I study of ibrutinib in Japanese patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma [J]. J Clin Exp Hematop, 2019, 59: 179-186.

[65] Luo PH, Yan H, Chen XQ, et al. s-HBEGF/SIRT1 circuit-dictated crosstalk between vascular endothelial cells and keratinocytes mediates sorafenib-induced hand-foot skin reaction that can be reversed by nicotinamide [J]. Cell Res, 2020, 30: 779-793.

[66] Zhang XW, Shao Y, Zhang XX, et al. Clinical study of Shenling-baizhu granule combined with gefitinib/erlotinib in the treatment of advanced non-small cell lung cancer with spleen-qi deficiency [J]. J New Chin Med (新中医), 2014, 46: 127-129.

[67] Sun JF, Guo H, Zeng Z, et al. Clinical study of Fuzheng Yiai No. 1 prescription combined with EGFR-TKIs gefitinib in the treatment of advanced lung adenosquamous cell carcinoma [J]. Lishizhen Med Mater Med Res (时珍国医国药), 2019, 30: 396-399.

[68] Deng B, Jia LQ, Deng C, et al. Research progression of traditional Chinese medicine for target agents related adverse events [J]. Chin Arch Tradit Chin Med (中华中医药学刊), 2018, 36: 1580-1583.