

本文引用:张贇,郭艳平,张向东. 丁苯酞静脉注射序贯口服治疗血管性认知障碍伴高同型半胱氨酸血症疗效观察[J]. 新乡医学院学报,2022,39(6):552-556. DOI:10.7683/xyxyxb.2022.06.011.

【临床研究】

丁苯酞静脉注射序贯口服治疗血管性认知障碍伴高同型半胱氨酸血症疗效观察

张 贇, 郭艳平, 张向东

(安阳市人民医院神经内科,河南 安阳 455000)

摘要: **目的** 探讨丁苯酞静脉注射序贯口服治疗血管性认知障碍(VCI)伴高同型半胱氨酸血症(HHcy)患者的临床疗效。**方法** 选择2019年5月至2020年5月安阳市人民医院收治的100例VCI伴HHcy患者为研究对象,根据治疗方法将患者分为观察组和对照组,每组50例。对照组患者给予常规药物治疗,包括口服阿司匹林肠溶片,每次100 mg,每日1次;口服马来酸依那普利片,每次20 mg,每日1次;口服阿托伐他汀钙片,每次20 mg,每日1次;连续治疗3个月。观察组患者在常规药物治疗基础上给予丁苯酞氯化钠注射液100 mL(含丁苯酞25 mg),静脉滴注,每日2次,连续治疗14 d后改为口服丁苯酞软胶囊0.2 g,每日3次,累计治疗3个月。治疗后2组患者随访6个月。分别于治疗前及治疗1、3个月和治疗后3、6个月,采用简易智力状态检查(MMSE)量表评估患者的智力状态;采用蒙特利尔认知评估(MoCA)量表评估患者的认知功能;采用日常生活能力量表(ADL)评估患者的日常生活能力。**结果** 对照组患者治疗3个月及治疗后3、6个月的MMSE评分显著高于治疗前($P < 0.05$);观察组患者治疗1、3个月及治疗后3、6个月的MMSE评分显著高于治疗前($P < 0.05$);治疗1、3个月及治疗后3、6个月,2组患者的MMSE评分均呈升高趋势,且观察组患者的MMSE评分显著高于对照组($P < 0.05$)。2组患者治疗3个月及治疗后3、6个月的MoCA评分显著高于治疗前($P < 0.05$);治疗1、3个月及治疗后3、6个月,2组患者的MoCA评分均呈升高趋势($P < 0.05$);治疗3个月及治疗后3、6个月,观察组患者的MoCA评分显著高于对照组($P < 0.05$)。2组患者治疗1、3个月及治疗后3、6个月的ADL评分均显著高于治疗前($P < 0.05$);治疗1、3个月及治疗后3、6个月,2组患者的ADL评分均呈升高趋势($P < 0.05$),且观察组患者的ADL评分显著高于对照组($P < 0.05$)。**结论** 常规药物联合丁苯酞静脉注射序贯口服治疗可有效改善VCI伴HHcy患者智力状态、认知功能,提高患者日常生活能力,临床疗效显著。

关键词: 血管性认知障碍;高同型半胱氨酸血症;丁苯酞;认知功能

中图分类号: R749.1 **文献标志码:** A **文章编号:** 1004-7239(2022)06-0552-05

Efficacy of butylphthalide intravenously and sequentially oral in the treatment of vascular cognitive impairment with hyperhomocysteinemia

ZHANG Yun, GUO Yanping, ZHANG Xiangdong

(Department of Neurology, Anyang People's Hospital, Anyang 455000, Henan Province, China)

Abstract: **Objective** To explore the clinical efficacy of butylphthalide intravenously and sequentially oral in the treatment of vascular cognitive impairment (VCI) with hyperhomocysteinemia(HHcy). **Methods** A total of 100 patients with VCI and HHcy admitted to the Anyang People's Hospital from May 2019 to May 2020 were selected as the research objects. According to treatment methods, the patients were divided into control group and observation group, with 50 cases in each group. The patients in the control group were given conventional drug therapy, included taking aspirin enteric-coated tablets orally, 100 mg each time, once a day; taking enalapril maleate tablets orally, 5 mg each time, once a day; taking atorvastatin calcium tablets orally, 20 mg each time, once a day; the treatment lasted for 3 months. On the basis of routine drug treatment, the patients in the observation group were given butylphthalide sodium chloride injection intravenously, 100 mL each time (containing 25 mg of butylphthalide), twice a day; after 14 days of continuous treatment, the patients were changed to take butylphthalide soft capsules orally, 0.2 g each time, 3 times a day, and the treatment lasted for 3 months. After treatment, the patients in the two groups were followed up for 6 months. Before treatment, after 1 and 3 months of treatment, at 3 and 6 months after treatment, the mental state of the patients was assessed by the mini-mental state examination (MMSE) scale; the cognitive

DOI:10.7683/xyxyxb.2022.06.011

收稿日期:2021-12-03

基金项目:河南省医学科技攻关计划项目(编号:LHGJ20200796)。

作者简介:张 贇(1978-),女,河南范县人,学士,副主任医师,研究方向:脑血管病、痴呆、癫痫、认知障碍。

function of the patients was evaluated by the montreal cognitive assessment (MoCA) scale; the ability of daily living of patients was evaluated by the activities of daily living scale (ADL). **Results** The MMSE scores of patients in the control group after 3 months of treatment and at 3,6 months after treatment were significantly higher than those before treatment ($P < 0.05$); the MMSE scores of patients in the observation group after 1,3 months of treatment and at 3,6 months after treatment were significantly higher than those before treatment ($P < 0.05$); after 1,3 months of treatment and at 3,6 months after treatment, the MMSE scores of patients in the two groups showed a significant upward trend, and the MMSE score of patients in the observation group was significantly higher than that in the control group ($P < 0.05$). The MoCA scores of patients in the two groups after 3 months of treatment and at 3,6 months after treatment were significantly higher than those before treatment ($P < 0.05$); after 1,3 months of treatment and at 3,6 months after treatment, the MoCA scores of patients in the two groups showed a significant upward trend; after 3 months of treatment and at 3,6 months after treatment, the MoCA score of patients in the observation group was significantly higher than that in the control group ($P < 0.05$). The ADL scores of patients in the two groups after 1,3 months of treatment and at 3,6 months after treatment were significantly higher than those before treatment ($P < 0.05$); after 1,3 months of treatment and at 3,6 months after treatment, the ADL scores of patients in the two groups showed a significant upward trend ($P < 0.05$), and the ADL score of patients in the observation group was significantly higher than that in the control group ($P < 0.05$). **Conclusion** Conventional drugs combined with butylphthalide intravenously and sequentially oral therapy can effectively improve the mental state, cognitive function and daily living ability of patients with VCI and HHcy, and the clinical effect is significant.

Key words: vascular cognitive impairment; hyperhomocysteinemia; butylphthalide; cognitive function

血管性认知功能障碍(vascular cognitive impairment, VCI)是由脑血管病引起的认知障碍综合征,临床主要表现为血管性痴呆,是影响中老年人健康及生活质量的主要原因之一^[1-2]。有研究发现,高同型半胱氨酸血症(hyperhomocysteinemia, HHcy)是缺血性脑血管疾病的独立危险因素,而VCI是缺血性脑血管疾病的常见并发症,多数缺血性脑血管病患者存在VCI伴HHcy^[3-4]。丁苯酞是改善非痴呆型VCI的药物,可逆转患者脑细胞线粒体膜流动性,降低再灌注诱发线粒体肿胀风险,同时可干预花生四烯酸代谢过程,改善患者神经缺损状态,进而发挥减轻脑缺血损伤作用^[5]。此外,丁苯酞对脑神经细胞、脑循环、血栓等均有良好改善作用^[6]。目前,应用常规药物治疗VCI伴HHcy患者单一症状改善明显,但对合并症状疗效不一。因此,关于VCI伴HHcy患者的临床治疗方法尚需研究。本研究旨在探讨丁苯酞静脉注射序贯口服治疗对VCI伴HHcy患者的临床疗效,以期为临床研究提供参考。

1 资料与方法

1.1 一般资料 选择2019年5月至2020年5月安阳市人民医院收治的100例VCI伴HHcy患者为研究对象。病例纳入标准:(1)符合《中国血管性认知障碍诊疗指导规范》^[7]中VCI相关诊断标准;(2)血浆同型半胱氨酸水平 $> 15 \mu\text{mol} \cdot \text{L}^{-1}$;(3)未系统性接受抗精神病药物治疗且可正常交流沟通者;

(4)患者全程配合治疗且完成相关量表评估。病例排除标准:(1)伴有帕金森综合征、癫痫等影响认知功能的神经系统疾病;(2)伴有双相情感障碍、抑郁症等严重精神系统疾病;(3)伴有肝肾功能病变、凝血功能异常等影响药物代谢类疾病;(4)对本研究涉及药物过敏者。根据治疗方法将患者分为对照组和观察组,每组50例。对照组:男28例,女22例;年龄48~73(60.15±10.07)岁;体质量43~76(55.26±8.46)kg。观察组:男30例,女20例;年龄47~72(61.24±10.10)岁;体质量42~75(54.96±8.53)kg。2组患者的性别、年龄、体质量比较差异无统计学意义($P > 0.05$),具有可比性。本研究经医院医学伦理委员会批准,患者及家属均知情同意。

1.2 治疗方法 对照组患者给予常规药物治疗,包括抗血小板治疗:阿司匹林肠溶片(石药集团欧意药业有限公司,国药准字H13023635),口服,每次100mg,每日1次;降压治疗:马来酸依那普利片(上海现代制药股份有限公司,国药准字H31021938)12.5mg,口服,每日1次;降脂治疗:阿托伐他汀钙片(大连辉瑞制药有限公司,国药准字J20120049)20mg,口服,每日1次,连续治疗3个月。观察组患者在常规药物治疗基础上给予丁苯酞氯化钠注射液(石药集团恩必普药业有限公司,国药准字H20100041)100mL(含丁苯酞25mg),静脉滴注,每日2次,2次用药间隔需 ≥ 6 h,滴速每分钟不超过40滴,连续治疗14d后改为丁苯酞软胶囊(石药集团

恩必普药业有限公司,国药准字 H20050299)0.2 g,口服,每日3次,饭前口服,累计治疗3个月。2组患者均随访6个月。

1.3 观察指标 (1)智力状态:分别于治疗前、治疗1、3个月及治疗后3、6个月,采用简易智力状态检查(mini-mental state examination, MMSE)^[8]量表评估患者的智力状态。MMSE量表包括定向力、记忆力、注意力和计算力、回忆能力、语言能力5项,总分30分。总分 ≥ 27 分为正常;21分 \leq 总分 < 27 分为轻度痴呆;10分 \leq 总分 < 21 分为中度痴呆;总分 < 10 分为重度痴呆。(2)认知功能:分别于治疗前、治疗1、3个月及治疗后3、6个月,采用蒙特利尔认知评估(montreal cognitive assessment, MoCA)量表^[9]评估患者的认知功能。MoCA量表包括视功能与执行功能、命名、记忆、语言、延迟回忆、定向力6项,总分30分。总分 ≥ 26 分为正常,总分 < 26 分为存在认知功能障碍,分值越高表示患者认知功能障碍程度越低。(3)日常生活能力:分别于治疗前、治疗1、3个月及治疗后3、6个月,采用日常生活能力(activities of daily living scale, ADL)^[10]量表评估患者的日常生活能力。ADL包括步行、个人卫生、大

小便控制、衣着等10个项目,总分100分。ADL评分越高表示日常生活能力越强。

1.4 统计学处理 应用SPSS 24.0软件进行数据统计与分析。计量资料以均数 \pm 标准差($\bar{x} \pm s$)表示,2组间比较采用独立样本 t 检验,治疗后组内不同时间点的计量资料比较采用重复测量数据的方差分析,进一步两两比较采用最小显著性差异法- t 检验; $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 2组患者MMSE评分比较 结果见表1。对照组患者治疗1个月与治疗前的MMSE评分比较差异无统计学意义($P > 0.05$)。对照组患者治疗3个月及治疗后3、6个月的MMSE评分显著高于治疗前,差异有统计学意义($P < 0.05$)。观察组患者治疗1、3个月及治疗后3、6个月的MMSE评分显著高于治疗前,差异有统计学意义($P < 0.05$)。治疗前,2组患者的MMSE评分比较差异无统计学意义($P > 0.05$)。治疗1、3个月及治疗后3、6个月,2组患者的MMSE评分均呈升高趋势($P < 0.05$);观察组患者的MMSE评分显著高于对照组,差异有统计学意义($P < 0.05$)。

表1 2组患者MMSE评分比较

Tab.1 Comparison of MMSE score of patients between the two groups ($\bar{x} \pm s$)

组别	n	MMSE 评分				
		治疗前	治疗1个月	治疗3个月	治疗后3个月	治疗后6个月
对照组	50	22.94 \pm 1.07	23.13 \pm 0.85	24.05 \pm 1.16 ^a	24.67 \pm 0.72 ^a	25.41 \pm 0.82 ^a
观察组	50	22.86 \pm 1.05	23.58 \pm 0.93 ^a	25.07 \pm 1.25 ^a	26.41 \pm 0.86 ^a	27.46 \pm 0.97 ^a
t		0.377	2.526	4.229	10.970	11.413
P		>0.05	<0.05	<0.05	<0.05	<0.05

注:与治疗前比较^a $P < 0.05$;治疗后: $F_{组间} = 15.247, P < 0.05$; $F_{组间} = 6.371, P < 0.05$; $F_{交互} = 10.359, P < 0.05$ 。

2.2 2组患者MoCA评分比较 结果见表2。治疗前及治疗1个月时,2组患者的MoCA评分比较差异无统计学意义($P > 0.05$)。2组患者治疗1个月的MoCA评分与治疗前比较差异无统计学意义($P > 0.05$)。2组患者治疗3个月及治疗后3、6个月

的MoCA评分显著高于治疗前,差异有统计学意义($P < 0.05$)。治疗1、3个月及治疗后3、6个月,2组患者的MoCA评分均呈升高趋势($P < 0.05$)。治疗3个月及治疗后3、6个月,观察组患者的MoCA评分显著高于对照组,差异有统计学意义($P < 0.05$)。

表2 2组患者MoCA评分比较

Tab.2 Comparison of MoCA score of patients between the two groups ($\bar{x} \pm s$)

组别	n	MoCA 评分				
		治疗前	治疗1个月	治疗3个月	治疗后3个月	治疗后6个月
对照组	50	16.24 \pm 2.07	16.95 \pm 2.10	19.47 \pm 1.77 ^a	22.31 \pm 1.42 ^a	24.16 \pm 1.03 ^a
观察组	50	16.30 \pm 2.11	17.06 \pm 2.14	21.48 \pm 1.60 ^a	24.34 \pm 1.13 ^a	27.04 \pm 0.96 ^a
t		0.144	0.259	5.757	7.910	14.463
P		>0.05	>0.05	<0.05	<0.05	<0.05

注:与治疗前比较^a $P < 0.05$;治疗后: $F_{组间} = 9.457, P < 0.05$; $F_{时间} = 6.317, P < 0.05$; $F_{交互} = 11.387, P < 0.05$ 。

2.3 2组患者ADL评分比较 结果见表3。2组患者治疗1、3个月及治疗后3、6个月的ADL评分均显著高于治疗前,差异有统计学意义($P < 0.05$)。治疗1、3个月及治疗后3、6个月,2组患者的ADL

评分均呈升高趋势($P < 0.05$)。治疗前2组患者的ADL评分比较差异无统计学意义($P > 0.05$)。治疗1、3个月及治疗后3、6个月,观察组患者的ADL评分显著高于对照组,差异有统计学意义($P < 0.05$)。

表3 2组患者 ADL 评分比较

Tab.3 Comparison of ADL score of patients between the two groups

($\bar{x} \pm s$)

组别	n	ADL 评分				
		治疗前	治疗1个月	治疗3个月	治疗后3个月	治疗后6个月
对照组	50	63.24 ± 4.24	69.47 ± 5.24 ^a	73.44 ± 4.16 ^a	79.61 ± 3.92 ^a	84.15 ± 3.26 ^a
观察组	50	63.30 ± 4.27	72.31 ± 5.07 ^a	80.17 ± 3.96 ^a	86.27 ± 2.33 ^a	91.04 ± 1.07 ^a
t		0.071	2.754	8.286	10.327	14.199
P		>0.05	<0.05	<0.05	<0.05	<0.05

注:与治疗前比较^a $P < 0.05$; 治疗后: $F_{\text{组间}} = 20.154, P < 0.05$; $F_{\text{时间}} = 17.392, P < 0.05$; $F_{\text{交互}} = 23.401, P < 0.05$ 。

3 讨论

VCI 是缺血性脑血管疾病引起痴呆的主要形式,多发性腔隙性病变、大面积梗死病灶、脑动脉粥样硬化等均可引起 VCI 病理改变。有研究显示,缺血性脑血管疾病发生后患者认知功能损害发生率约为 37%,且每次卒中后的局部病灶易使认知功能损伤程度呈阶梯样加重^[11]。同型半胱氨酸存在于血浆中,是甲硫氨酸的代谢产物,参与肝脏、肾脏代谢等多种病理过程,其水平与脑卒中发生风险呈正相关^[12-13]。HHcy 是 VCI 常见并发症之一,易加重 VCI 患者头晕、头痛、言语功能障碍等症状的严重程度。

阿司匹林等抗血小板聚集类药物可改善 VCI 患者脑部血液循环,降压降脂类药物可促进 VCI 患者侧支循环的建立^[14]。但 VCI 伴 HHcy 患者常有心悸、头晕等症状,日常生活能力欠佳,常规药物治疗对患者日常生活能力及认知功能的改善作用较为轻微。丁苯酞可通过提高脑血管内皮一氧化氮、前列腺素 I₂ 水平降低细胞内钙浓度,抑制氧自由基,减少氧化应激反应,促进脑部血液循环,改善患者认知功能^[15]。本研究结果发现,治疗 1、3 个月及治疗后 3、6 个月,2 组患者的 MMSE 评分均呈升高趋势,且观察组患者的 MMSE 评分显著高于对照组,说明常规药物联合丁苯酞可显著改善 VCI 伴 HHcy 患者的智力状态,与 MARCO-CONTELLES 等^[16] 研究结果一致。这可能是由于丁苯酞可保护血管结构完整,对血管管径恢复有促进作用,同时可增加缺血区周围微血管数量及血流量,进而缓解 VCI 伴 HHcy 患者脑部缺血而引起的智力障碍,达到治疗目的。

本研究结果发现,治疗 1、3 个月及治疗后 3、6 个月,2 组患者的 MoCA 评分均呈升高趋势;且治疗 3 个月及治疗后 3、6 个月,观察组患者的 MoCA 评分显著高于对照组,说明常规药物联合丁苯酞可显著改善 VCI 伴 HHcy 患者的认知功能。丁苯酞通过保护内皮细胞的结构和完整性,促进末端小静脉间通路正常运行,进而使血液及组织细胞进行充分物质交换,缓解血管痉挛、降低缺血性脑组织损伤严重

程度^[17]。VCI 伴 HHcy 患者临床有不同程度痴呆、幻觉、假性延髓麻痹等症状且情绪不稳定,从而导致日常生活能力呈现不同程度下降。本研究结果发现,治疗 1、3 个月及治疗后 3、6 个月,2 组患者的 ADL 评分均呈升高趋势,且观察组患者的 ADL 评分显著高于对照组,说明常规药物联合丁苯酞可显著提高 VCI 伴 HHcy 患者的日常生活能力,对患者预后积极意义。

综上所述,常规药物联合丁苯酞静脉注射序贯口服治疗可有效改善 VCI 伴 HHcy 患者智力状态、认知功能,提高日常生活能力,临床疗效显著。但因本研究选择样本量有限,相关结论仍需大样本多中心临床试验进一步佐证。

参考文献:

- [1] CZAKÓ C, KOVÁCS T, UNGVARI Z, et al. Retinal biomarkers for alzheimer's disease and vascular cognitive impairment and dementia (vcid): implication for early diagnosis and prognosis[J]. *Geroscience*, 2020, 42(6): 1499-1525.
- [2] MEGURO K, DODGE H H. Vascular mild cognitive impairment: identifying disease in community-dwelling older adults, reducing risk factors, and providing support, the osaki-tajiri and kurihara Projects[J]. *J Alzheimers Dis*, 2019, 70(1): 293-302.
- [3] 赵永红,张鸿儒. 同型半胱氨酸与老年患者血管性认知功能障碍的临床研究[J]. *中国药物与临床*, 2020, 20(19): 3232-3234.
ZHAO Y H, ZHANG H R. A clinical study on homocysteine and vascular cognitive dysfunction in elderly patients[J]. *Chin Remed Clin*, 2020, 20(19): 3232-3234.
- [4] CHIANG C P, CHANG J Y, WANG Y P, et al. Atrophic glossitis: etiology, serum autoantibodies, anemia, hematinic deficiencies, hyperhomocysteinemia, and management[J]. *J Formos Med Assoc*, 2020, 119(4): 774-780.
- [5] 罗志秀,刘正芳,曾晓云,等. 老年无症状性颈动脉狭窄患者认知障碍影响因素分析及联合丁苯酞治疗效果研究[J]. *中华老年心脑血管病杂志*, 2020, 22(7): 729-733.
LUO Z X, LIU Z F, ZENG X Y, et al. Analysis of influencing factors of cognitive impairment in elderly patients with asymptomatic carotid stenosis and study on the effect of combined butylphthalide treatment[J]. *Chin J Geriatr Heart Brain Vessel Dis*, 2020, 22(7): 729-733.

- [6] 周黎,项予良,郭昭婷,等. 银杏内酯注射液对比丁苯酞注射液治疗大动脉粥样硬化性缺血性脑卒中的最小成本分析[J]. 中国药房,2020,31(18):2235-2239.
ZHOU L, XIANG Y L, GUO Z T, *et al.* Minimal cost analysis of ginkgolide injection versus butylphthalide injection in the treatment of large atherosclerotic ischemic stroke [J]. *China Pharmacy*, 2020, 31(18): 2235-2239.
- [7] 国家卫生计生委脑卒中防治工程委员会, 脑卒中防治系列指导规范编审委员会. 2016 中国血管性认知障碍诊疗指导规范 [J]. 心脑血管病防治, 2017, 17(1): 3-6.
NATIONAL HEALTH AND FAMILY PLANNING COMMISSION STROKE PREVENTION AND CONTROL ENGINEERING COMMITTEE, STROKE PREVENTION AND CONTROL SERIES GUIDELINES EDITING AND REVIEW COMMITTEE. 2016 guidelines for diagnosis and treatment of vascular cognitive impairment in China [J]. *Prev Treatment Cardio Cerebrov Dis*, 2017, 17(1): 3-6.
- [8] MYRBERG K, HYDÉN L C, SAMUELSSON C. The mini-mental state examination (MMSE) from a language perspective; an analysis of test interaction [J]. *Clin Linguist Phon*, 2020, 34(7): 652-670.
- [9] RIBEIRO M, DURAND T, ROUSSEL M, *et al.* Sensitivity of the montreal cognitive assessment in screening for cognitive impairment in patients with newly diagnosed high-grade glioma [J]. *J Neurooncol*, 2020, 148(2): 335-342.
- [10] 王军英,段毅,赵平平,等. 丁苯酞氯化钠注射液联合经颅磁刺激对急性脑梗死后血管性认知功能障碍的影响及机制研究 [J]. 河北医药, 2020, 42(22): 3459-3461.
WANG J Y, DUAN Y, ZHAO P P, *et al.* Effects and mechanism of butylphthalide sodium chloride injection combined with transcranial magnetic stimulation on vascular cognitive dysfunction after acute cerebral infarction [J]. *Hebei Med J*, 2020, 42(22): 3459-3461.
- [11] KERKHOFS D, VAN HAGEN B T, MILANOVA I V, *et al.* Pharmacological depletion of microglia and perivascular macrophages prevents vascular cognitive impairment in ang II-induced hypertension [J]. *Theranostics*, 2020, 10(21): 9512-9527.
- [12] DUBCHENKO E A, IVANOV A V, BOIKO A N, *et al.* Hyperhomocysteinemia and endothelial dysfunction in patients with cerebral vascular and autoimmune diseases [J]. *Zh Nevrol Psikhiatr Im S S Korsakova*, 2019, 119(11): 133-138.
- [13] NGUYEN D H, CUNNINGHAM J T, SUMIEN N. Estrogen receptor involvement in vascular cognitive impairment and vascular dementia pathogenesis and treatment [J]. *Geroscience*, 2021, 43(1): 159-166.
- [14] RYAN J, STOREY E, MURRAY A M, *et al.* Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline [J]. *Neurology*, 2020, 95(3): 320-331.
- [15] NIU X L, JIANG X, XU G D, *et al.* DL-3-n-butylphthalide alleviates vascular cognitive impairment by regulating endoplasmic reticulum stress and the Shh/Ptch1 signaling-pathway in rats [J]. *J Cell Physiol*, 2019, 234(8): 12604-12614.
- [16] MARCO-CONTELLES J, ZHANG Y. From seeds of apium graveolens linn. to a cerebral ischemia medicine; the long journey of 3-n-butylphthalide [J]. *J Med Chem*, 2020, 63(21): 12485-12510.
- [17] UPPAKARA K, JAMORNWAN S, DUAN L X, *et al.* Novel α -lipoic acid/3-n-butylphthalide conjugate enhances protective effects against oxidative stress and 6-ohda induced neuronal damage [J]. *ACS Chem Neurosci*, 2020, 11(11): 1634-1642.

(本文编辑:郭 潇)

(上接第 551 页)

- [9] RADOLOVIC P, GREBIC D, MUSTAC E, *et al.* Heat shock protein gp96 and CD4⁺ and CD8⁺ T-lymphocytes expression as prognostic factors in various molecular types of invasive breast carcinoma [J]. *Neoplasma*, 2020, 67(2): 421-429.
- [10] ZHANG G Y, ZHANG K, LI C, *et al.* Serum proteomics identify potential biomarkers for nasopharyngeal carcinoma sensitivity to radiotherapy [J]. *Biosci Rep*, 2019, 39(5): BSR20190027.
- [11] KASID U, DRITSCHILO A. RAF antisense oligonucleotide as a tumor radiosensitizer [J]. *Oncogene*, 2003, 22(37): 5876-5884.
- [12] 李思维,郭翔,吕星,等. Raf-1 蛋白预测鼻咽癌放疗敏感性的价值 [J]. 实用医学杂志, 2012, 28(1): 80-83.
LI S W, GUO X, LYU X, *et al.* The value of Raf-1 protein in predicting the radiosensitivity of nasopharyngeal carcinoma [J]. *J Pract Med*, 2012, 28(1): 80-83.
- [13] LI Y S, LU T, HU G H. Gene sequencing and expression of Raf-1 in lymphatic metastasis of hypopharyngeal carcinoma [J]. *Cancer Biomark*, 2020, 28(2): 181-191.
- [14] 贾全凡,袁龙,刘冬梅,等. BIRC5、NEIL2 表达水平与鼻咽癌放疗敏感性的相关性 [J]. 热带医学杂志, 2018, 18(10): 1322-1325.
JIA Q F, YUAN L, LIU D M, *et al.* Correlation study between the expressions of BIRC5, NEIL2 and the radiotherapy sensitivity of nasopharynx cancer [J]. *J Trop Med*, 2018, 18(10): 1322-1325.
- [15] 高莉萍,何炜. Neil2 基因 rs8191670 位点多态性与非小细胞肺癌化疗敏感性之间的关系 [J]. 肿瘤, 2018, 38(5): 446-451, 459.
GAO L P, HE W. Neil2 gene rs8191670 polymorphism (T/C) is associated with chemotherapy sensitivity of non-small cell lung cancer [J]. *Tumor*, 2018, 38(5): 446-451, 459.
- [16] BUELGA C B, BAQUERO J M, VACLOVA T, *et al.* Genetic variation in the NEIL2 DNA glycosylase gene is associated with oxidative DNA damage in BRCA2 mutation carriers [J]. *Oncotarget*, 2017, 8(70): 114626-114636.

(本文编辑:徐自超)