

doi: 10.13241/j.cnki.pmb.2018.22.016

中药通窍活血汤联合脑蛋白水解物对老年痴呆患者日常生活能力和血清 Hcy、CRP、FA 水平的影响 *

王 翔¹ 曹荣耀¹ 王 然¹ 赵 丽² 刘海丽¹

(1 辽宁中医药大学附属第四医院脑病科 辽宁 沈阳 110101; 2 沈阳市中医院医学科 辽宁 沈阳 110004)

摘要 目的:探讨中药通窍活血汤联合脑蛋白水解物对老年痴呆日常生活能力和血清同型半胱氨酸(Hcy)、C 反应蛋白(CRP)、叶酸(FA)水平的影响。**方法:**选择 2014 年 1 月~2016 年 12 月在我院脑病科神经内科进行诊治的 79 例老年痴呆患者,随机分为对照组 40 例和观察组 39 例。对照组静脉滴注脑蛋白水解物治疗,每次 60 mg,每天 2 次;观察组联合口服中药通窍活血汤治疗,每天服用 1 剂,早晚分 2 次温服,每次 200 mL。分别于治疗前后采用简易精神状态检查量表(MMSE)对患者的精神状态进行评估,比较两组的临床治疗有效率,治疗前后的日常生活能力情况以及血清 Hcy、CRP、FA 水平的变化,比较两组在治疗期间不良反应的发生情况。**结果:**观察组的有效率为 92.31%(36/39),明显高于对照组的 72.50%(29/40) ($P<0.05$)。两组治疗后的日常生活能力 BI、MMSE 评分、血清 FA 水平均较治疗前明显升高($P<0.05$),且观察组明显高于对照组($P<0.05$)。两组治疗后的血清 Hcy、CRP 水平均较治疗前明显降低($P<0.05$),且观察组明显低于对照组($P<0.05$)。两组不良反应的发生情况间比较无显著差异($P>0.05$)。**结论:**中药通窍活血汤联合脑蛋白水解物对老年痴呆患者具有较为显著的临床效果,安全可靠,可提高其日常生活能力,改善精神状态以及血清 Hcy、CRP、FA 水平。

关键词:通窍活血汤;脑蛋白水解物;老年痴呆;日常生活能力;同型半胱氨酸;C 反应蛋白;叶酸

中图分类号:R749.16 文献标识码:A 文章编号:1673-6273(2018)22-4273-04

Effect of Tongqiaohuoxue Decoction Combined with Brain Protein Hydrolysate on the Ability of Daily Life and Serum Hcy, CRP and FA Levels of Senile Patients with Dementia*

WANG Xiang¹, CAO Rong-yao¹, WANG Ran¹, ZHAO Li², LIU Hai-li¹

(1 Encephalopathy Department, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning, 110101, China;

2 Medical Department, Traditional Chinese Medicine Hospital of Shenyang City, Shenyang, Liaoning, 110004, China)

ABSTRACT Objective: To investigate the clinical effect of Tongqiaohuoxue decoction combined with brain protein hydrolysate on the ability of daily life and serum Hcy, CRP and FA levels of senile patients with dementia. **Methods:** 79 cases of senile patients with dementia who were treated in our hospital from January 2014 to December 2016 were selected and randomly divided into two groups. The control group was treated with intravenous infusion of brain protein hydrolysate, 60 mg each time, 2 times a day. The observation group was combined with Tongqiaohuoxue decoction treatment. The mental state of patients was evaluated by mini mental state examination (MMSE) before and after treatment. The clinical effective rate, daily living ability and serum Hcy, CRP and FA levels of the two groups were compared before and after treatment. The incidence of adverse reactions in the two groups was compared between the two groups. **Results:** After treatment, the effective rate of observation group was 92.31%(36/39), which was significantly higher than that of the control group [72.50%(29/40)] ($P<0.05$); the BI score of daily living ability, score, mental state MMSE score and serum FA level of both groups were significantly increased ($P<0.05$), which were significantly higher in the observation group than those of the control group ($P<0.05$); while the levels of serum Hcy and CRP of both groups were significantly decreased ($P<0.05$), which were significantly lower in the observation group ($P<0.05$). There was no significant difference in the adverse reactions between the two groups ($P>0.05$). **Conclusions:** Tongqiaohuoxue decoction combined with brain protein hydrolysate had more significant clinical effect on the senile dementia patients with high safety, it could improve the ability of daily life, mental state and serum Hcy, CRP, FA levels.

Key words: Tongqiaohuoxue Decoction; Cerebrolysin; Senile dementia; Ability of daily life; Hcy; CRP; FA

Chinese Library Classification(CLC): R749.16 **Document code:** A

Article ID: 1673-6273(2018)22-4273-04

* 基金项目:辽宁省自然科学基金项目(2014020058)

作者简介:王翔(1983-),女,硕士,主治医师,研究方向:神经内科方面,E-mail: wangxiang_1983@papmedline.cn

(收稿日期:2018-01-28 接受日期:2018-02-24)

前言

老年痴呆是由于大脑功能障碍而引发持续性及获得性智能减退的一组临床症候群^[1-2],初期的临床症状主要包括记忆力减退、判断能力下降、人格改变以及行为改变等,随着病情的逐渐加重,患者甚至会出现大小便失禁、生活无法自理、肢体僵直等症状,造成患者社会生活、独立生活以及工作能力出现显著减退甚至丧失^[3-5]。目前,临床治疗老年痴呆主要通过改善并调节脑神经元、脑细胞的代谢功能,提高病变区的脑细胞功能,使患者的各项临床症状得以改善,从而增强患者的认知能力、记忆力和智能^[6,7]。西医治疗老年痴呆的效果往往不佳,中医由于从整体出发采取辨证论治,在治疗此病方面具有独特的优势。

通窍活血汤在临床治疗脑梗死中发挥着较为显著的治疗效果,其具有醒脑开窍、活血化瘀之功效^[8-10]。关于通窍活血汤治疗老年痴呆的研究报道较为少见。鉴于此,本研究将中药通窍活血汤与脑蛋白水解物联合使用,探讨其对老年痴呆日常生活能力和血清 Hcy、CRP、FA 水平的影响,现将具体结果报道如下。

1 资料与方法

1.1 一般资料

选择 2014 年 1 月~2016 年 12 月在我院脑病科神经内科进行诊治的 79 例老年痴呆患者,均符合相关的诊断标准^[9],排除过敏体质患者,患有较为严重的躯体疾病患者,近 3 个月内服用过精神类药物的患者,有精神疾病史患者,合并有其他类型的痴呆患者,随机分为两组。观察组 39 例,男 20 例,女 19 例;年龄 65~83 岁,平均 (70.39 ± 5.21) 岁;病程 1~7 年,平均 (3.24 ± 0.57) 年;其中,痴呆程度:轻度痴呆期 24 例,中度痴呆期 15 例。对照组 40 例,男 21 例,女 19 例;年龄 65~84 岁,平均 (69.52 ± 4.39) 岁;病程 1~6 年,平均 (3.17 ± 0.46) 年;其中,痴呆程度:轻度痴呆期 26 例,中度痴呆期 14 例。所有患者均签署知情同意书。两组的基线资料比较差异均无统计学意义,具有可比性($P>0.05$)。

1.2 治疗方法

对照组单独给予脑蛋白水解物治疗,即静脉滴注脑蛋白水解物(批号:国药准字 H13024089,生产厂家:河北智同生物制药有限公司,规格:2 mL),每次 60 mg,每天 2 次。观察组联合口服中药通窍活血汤,药物组成包括如下:黄酒 250 g,生姜 9 g,红花 9 g,老葱 6 g,桃仁 6 g,川芎 3 g,赤芍药 3 g,麝香(冲) 0.15 g,大枣 5 枚。常规加水煎煮,每天服用 1 剂,早晚分 2 次温服,每次 200 mL。两组均治疗 1 个月。

1.3 观察指标

分别于治疗前后采用 MMSE^[11]对患者的精神状态进行评估,MMSE 量表主要包括记忆力、定向力、注意力、语言能力和回忆力者五个方面,满分值是 30 分,评分值越高则说明患者的精神状态越佳。

比较两组的临床治疗效果,疗效标准^[12]:① 显效:经过治疗后,患者的 MMSE 量表评分值与满分即 30 分接近;② 有效:经过治疗后,患者的 MMSE 量表评分值与治疗前相比升高 15%~40%;③ 无效:经过治疗后,患者的 MMSE 量表评分值与治疗前相比无显著差异。

比较两组治疗前后的日常生活能力情况,分别在于治疗前后使用常生活能力评定量表(BI)^[9]对患者的日常生活能力进行评估,主要包括进出厕所、进食、平地行走、修饰、穿衣、大便控制、床椅转移、小便控制和上下楼梯十个方面。满分值是 100 分,评分值越高则说明患者的日常生活能力越好。

分别于治疗前后采集两组患者 3 mL 空腹肘静脉血,使用贝克曼 AU480 全自动生化分析仪,采用电化学发光免疫法检测血清 FA 水平,采用电化学发光法检测血清 Hcy、CRP 水平。

1.4 统计学分析

采用 SPSS15.00 软件进行统计学分析,计量资料以 $\bar{x} \pm s$ 表示,组间和组内对比用方差分析和 t 检验,组间率的比较用 χ^2 检验,以 $P<0.05$ 表明差异有统计学意义。

2 结果

2.1 两组临床疗效的对比

观察组的有效率为 92.31%(36/39),明显高于对照组的 [72.50%(29/40)]($P<0.05$),见表 1。

表 1 两组临床疗效对比[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	n	Excellent	Valid	Invalid	Effective rate
Control group	40	15(37.50)	14(35.00)	11(27.50)	72.50
Observation group	39	21(53.85)	15(38.46)	3(7.69)	92.31*

Note: Compared with the control group, * $P<0.05$.

2.2 两组治疗前后日常生活能力 BI 评分的对比

两组治疗后的日常生活能力 BI 评分均较治疗前明显升高($P<0.05$),且观察组明显高于对照组($P<0.05$),见表 2。

2.3 两组治疗前后精神状态 MMSE 评分的对比

两组治疗后的精神状态 MMSE 评分均较治疗前明显升高($P<0.05$),且观察组明显高于对照组($P<0.05$),见表 3。

2.4 两组治疗前后血清 Hcy、CRP、FA 水平的对比

两组治疗后的血清 FA 水平均较治疗前明显升高 ($P<$

0.05),血清 Hcy、CRP 水平均明显较治疗前降低($P<0.05$),且观察组血清 FA 水平明显高于对照组,血清 Hcy、CRP 水平显著低于对照组($P<0.05$),见表 4。

2.5 两组不良反应的发生情况比较

对照组在治疗期间出现 1 例胸闷不适、1 例呕吐、1 例过敏症状,观察组出现 1 例头痛、1 例胃肠道不适症状,均未经特殊处理,2-5 d 后症状消失。两组不良反应的发生情况间比较无显著差异($P=0.665$)。

表 2 两组治疗前后日常生活能力 BI 评分的对比($\bar{x} \pm s$, 分)Table 2 Comparison of the BI scores of daily living ability between two groups before and after treatment($\bar{x} \pm s$, scores)

Groups	n	Before treatment	After treatment
Control group	40	47.51± 8.24	59.87± 9.93 [#]
Observation group	39	47.39± 8.62	69.26± 10.31 ^{*#}

Note: compared with the control group, ^{*} $P < 0.05$; compared with before treatment, [#] $P < 0.05$.

表 3 两组治疗前后精神状态 MMSE 评分的对比($\bar{x} \pm s$, 分)Table 3 Comparison of the MMSE scores of mental state between two groups before and after treatment($\bar{x} \pm s$, scores)

Groups	n	Before treatment	After treatment
Control group	40	8.57± 2.25	19.07± 3.52 [#]
Observation group	39	8.24± 2.44	25.65± 3.73 ^{*#}

Note: compared with the control group, ^{*} $P < 0.05$; compared with before treatment, [#] $P < 0.05$.

表 4 两组治疗前后血清 Hcy、CRP、FA 水平的对比($\bar{x} \pm s$)Table 4 Comparison of the serum Hcy, CRP, FA levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Time	Hcy ($\mu\text{mol/L}$)	CRP(mg/mL)	FA(ng/mL)
Control group	40	Before treatment	19.23± 6.54	5.79± 3.21	6.35± 3.17
		After treatment	16.45± 5.39 [#]	4.23± 2.25 [#]	8.13± 2.13 [#]
Observation group	39	Before treatment	19.75± 7.08	5.83± 3.47	6.24± 3.08
		After treatment	10.28± 3.72 ^{*#}	2.03± 1.94 ^{*#}	12.25± 3.27 ^{*#}

Note: compared with the control group, ^{*} $P < 0.05$; compared with before treatment, [#] $P < 0.05$.

3 讨论

老年痴呆是一种临床上常见的老年神经退行性疾病,具有起病慢、病程长的特点^[13,14],其临床表现主要为不同程度的语言能力、记忆能力、视空间能力以及认知能力的减退,患者通常出现行为、情感和人格方面异常,病情严重者甚至生活无法自理,对老年患者的生活质量造成严重的不良影响^[15-17]。老年痴呆的发生是由于负责传递各个神经元之间信息的神经递质水平低于正常值,不能正常进行信息的传递,进而引发记忆功能和认知功能障碍,大脑功能出现全面的衰退^[18-20]。目前,临床上对于老年痴呆尚无特效的治疗药物和治疗方法,西医主要采取营养神经以及雌激素替代法治疗老年痴呆,但是病程较长,使得患者的治疗依从性较差,治疗效果往往并不理想^[21-23]。

祖国传统医学认为老年痴呆属于“呆病”、“健忘”范畴,其发病机制主要为气、精、血亏损不足,造成脑失所养、髓海失充和火、风、痰、瘀诸邪内阻,脏腑失调,清窍受蒙,上扰清窍,累及脑窍,神明失用而致。现代药理学研究表明通窍活血汤具有改善微循环障碍、降低血液黏滞度、扩张血管、抑制血小板聚集以及缓解脑血管痉挛等作用^[24-26]。通窍活血汤中,红花具有散瘀止痛、活血通经之功效,生姜具有止呕、发散、止咳之功效,桃仁具有润肠通便,活血祛瘀,止咳平喘之功效,川芎具有祛风燥湿,行气开郁,麝香(冲)具有保护缺血缺氧的脑组织之功效,活血止痛之功效,赤芍药具有改善脑缺血损伤之功效,大枣具有补血、滋阴补阳之功效^[27,28]。本研究结果显示观察组的有效率为92.31%,明显高于对照组,提示中药通窍活血汤联合脑蛋白水解物对老年痴呆患者的临床效果明显优于单独使用西药脑蛋

白水解物。有研究^[29]对老年痴呆患者采用通窍活血汤治疗,治疗有效率由70.83%提高到87.50%,与本研究结果相一致。

Hcy作为独立的心血管危险因素,是糖尿病、吸烟和高血脂之外的又一危险因素^[30]。由于炎症反应在动脉粥样硬化的形成以及发展过程中发挥着极为重要的作用,而CRP作为一种急性炎症反应蛋白,其与脑血管病的发生、发展以及预后紧密相关。FA是一种降低血浆Hcy水平最基本而且最有效的药物^[31]。本研究结果显示两组治疗后的血清FA水平、日常生活能力BI评分、精神状态MMSE评分均明显升高,血清Hcy、CRP水平均明显降低,且观察组更为明显,提示中药通窍活血汤联合脑蛋白水解物可以缓解老年痴呆患者的炎症状态,促进认知功能的恢复,提高其日常生活能力,改善精神状态。脑蛋白水解物可以有效改善老年痴呆患者的认知功能、记忆功能以及智力。通窍活血汤具有活血化瘀、补肝益肾、醒脑开窍之功效。二者联合使用可以发挥协同作用,效果显著。在不良反应的发生情况方面,本研究结果显示,对照组出现1例胸闷不适、1例呕吐、1例过敏症状,观察组出现1例头痛、1例胃肠道不适症状,均未经特殊处理,2-5d后症状消失,且两组不良反应的发生情况间比较无显著差异,以上结果说明中药通窍活血汤联合脑蛋白水解物治疗老年痴呆患者是安全可靠的。

综上所述,中药通窍活血汤联合脑蛋白水解物对老年痴呆患者具有较为显著的临床效果,安全可靠,可提高其日常生活能力,改善精神状态以及血清Hcy、CRP、FA水平。

参考文献(References)

- [1] Shoyama M, Ukai S, Shinosaki K. Evaluation of regional cerebral blood flow in patient with atypical senile dementia with asymmetrical

- calcification[J]. *Psychogeriatrics*, 2015, 15(4): 272-276
- [2] Engelhardt E, Gomes M M. Alzheimer's 100th anniversary of death and his contribution to a better understanding of Senile dementia[J]. *Arquivos de neuro-psiquiatria*, 2015, 73(2): 159-162
- [3] Armstrong R A. Survival in the pre-senile dementia frontotemporal lobar degeneration with TDP-43 proteinopathy: effects of genetic, demographic and neuropathological variables [J]. *Folia Neuropathologica*, 2016, 54(2): 137-148
- [4] Takizawa C, Thompson P L, Van W A, et al. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America[J]. *Journal of Alzheimers Disease* Jad, 2015, 43(4): 1271-1284
- [5] Miguel Y J M, Jiménez G R, Hernández B V, et al. Hospital Admissions in People With Alzheimer's Disease or Senile Dementia According to Type 2 Diabetes Status: An Observational 10-Year Study [J]. *American Journal of Alzheimers Disease & Other Dementias*, 2017, 1(116): 1533317517726389
- [6] Bi D Y, Liu Q, Chen Y X, et al. Therapeutic observation on electroacupuncture at Zusanli (ST 36) and Fenglong (ST 40) for senile dementia [J]. *Journal of Acupuncture & Tuina Science*, 2016, 14(6): 386-390
- [7] Abraham R, Vuyyuru A B, Fernandes J, et al. Characterization of topiramate: an antiepileptic in conditions of senile dementia [J]. *Alzheimers & Dementia*, 2017, 13(7): P1132
- [8] Ragy M M, Kamal N N. Linking senile dementia to type 2 diabetes: role of oxidative stress markers, C-reactive protein and tumor necrosis factor- α [J]. *Neurological Research*, 2017, 39(7): 587-595
- [9] Lee C, Shen Y C. Aripiprazole Improves Psychotic, Cognitive, and Motor Symptoms in a Patient With Lewy Body Dementia [J]. *Journal of Clinical Psychopharmacology*, 2017, 37(5): 628-630
- [10] Kenawy S, Hegazy R, Hassan A, et al. Involvement of insulin resistance in D-galactose-induced age-related dementia in rats: Protective role of metformin and saxagliptin [J]. *Plos One*, 2017, 12(8): e0183565
- [11] Lankelma J M, Nieuwdorp M, de Vos W M, et al. The gut microbiota in internal medicine: implications for health and disease [J]. *Netherlands Journal of Medicine*, 2015, 73(2): 61-68
- [12] Yuan Y, Li L H, Huang Y J, et al. Tiapride is more effective and causes fewer adverse effects than risperidone in the treatment of senile dementia[J]. *European Review for Medical & Pharmacological Sciences*, 2016, 20(14): 3119-3122
- [13] Verkhatsky A, Marutle A, Rodríguez-Arellano J J, et al. Glial Asthenia and Functional Paralysis: A New Perspective on Neurodegeneration and Alzheimer's Disease [J]. *Neuroscientist A Review Journal Bringing Neurobiology Neurology & Psychiatry*, 2015, 21(5): 552-568
- [14] Niikura T, Hashimoto Y, Tajima H, et al. A tripartite motif protein TRIM11 binds and destabilizes Humanin, a neuroprotective peptide against Alzheimer's disease-relevant insults [J]. *European Journal of Neuroscience*, 2015, 17(6): 1150-1158
- [15] Young J E, Boulangerweill J, Williams D A, et al. Elucidating Molecular Phenotypes Caused by the SORL1 Alzheimer's Disease Genetic Risk Factor Using Human Induced Pluripotent Stem Cells[J]. *Cell Stem Cell*, 2015, 16(4): 373-385
- [16] Crisancholacroix V, Wrobel J, Cantegreilkallen I, et al. A Web-Based Psychoeducational Program for Informal Caregivers of Patients With Alzheimer's Disease: A Pilot Randomized Controlled Trial[J]. *Journal of Medical Internet Research*, 2015, 17(5): e117
- [17] Zhang Y, Wang S, Phillips P, et al. Detection of Alzheimer's disease and mild cognitive impairment based on structural volumetric MR images using 3D-DWT and WTA-KSVM trained by PSOTVAC[J]. *Biomedical Signal Processing & Control*, 2015, 21(5): 58-73
- [18] Weinstock M, Goren T, Youdim M B H. Development of a novel neuroprotective drug (TV3326) for the treatment of Alzheimer's disease, with cholinesterase and monoamine oxidase inhibitory activities[J]. *Drug Development Research*, 2015, 50(3-4): 216-222
- [19] Murray M E, Lowe V J, Graff-Radford N R, et al. Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum [J]. *Brain Journal of Neurology*, 2015, 138(5): 1370-1381
- [20] Kurz A F, Erkinjuntti T, Small G W, et al. Long-term safety and cognitive effects of galantamine in the treatment of probable vascular dementia or Alzheimer's disease with cerebrovascular disease [J]. *European Journal of Neurology*, 2015, 10(6): 633-640
- [21] Pietrzak R H, Lim Y Y, Ames D, et al. Trajectories of memory decline in preclinical Alzheimer's disease: results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of ageing [J]. *Neurobiology of Aging*, 2015, 36(3): 1231-1238
- [22] Zhang Y, Dong Z, Phillips P, et al. Detection of subjects and brain regions related to Alzheimer's disease using 3D MRI scans based on eigenbrain and machine learning [J]. *Frontiers in Computational Neuroscience*, 2015, 9(9): 66
- [23] Goldberg T E, Harvey P D, Wesnes K A, et al. Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials [J]. *Alzheimers & Dementia Diagnosis Assessment & Disease Monitoring*, 2015, 1(1): 103-111
- [24] Chao-Liang G E, Wang X M, Fei-Long L I, et al. Activity of Tongqiao Huoxue Decoction on the Memory and Learning Ability and Fluorescence Intensity of Intracellular Calcium Concentration of Hippocampal Neurons of Vascular Dementia Rats [J]. *Chinese Pharmaceutical Journal*, 2015, 50(8): 671-675
- [25] Cai M D, Sun-Mi C, Yang E J. The Effects of Bee Venom Acupuncture on the Central Nervous System and Muscle in an Animal hSOD1G93 A Mutant[J]. *Toxins*, 2015, 7(3): 846-858
- [26] Sayyahmelli M, Ghorbanihaghjo A, Alizadeh M, et al. The Effect of High Dose Folic Acid throughout Pregnancy on Homocysteine (Hcy) Concentration and Pre-Eclampsia: A Randomized Clinical Trial [J]. *Plos One*, 2016, 11(5): e0154400
- [27] Cai C, Xiao R, Halm-Lutterodt N V, et al. Association of MTHFR, SLC19A1 Genetic Polymorphism, Serum Folate, Vitamin B12 and Hcy Status with Cognitive Functions in Chinese Adults [J]. *Nutrients*, 2016, 8(10): 665
- [28] Sayyahmelli M, Ghorbanihaghjo A, Alizadeh M, et al. The Effect of High Dose Folic Acid throughout Pregnancy on Homocysteine (Hcy) Concentration and Pre-Eclampsia: A Randomized Clinical Trial [J]. *Plos One*, 2016, 11(5): e0154400

2375-2385

- [13] Kirchheiner K, Pötter R, Tanderup K, et al. Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study [J]. *International Journal of Radiation Oncology Biology Physics*, 2016, 94(5): 1088-1098
- [14] De Kok I M, Van Rosmalen J, Van Ballegooijen M. Authors' reply re: Cost effectiveness of cervical cancer screening: cytology versus human papillomavirus DNA testing [J]. *BJOG An International Journal of Obstetrics & Gynaecology*, 2016, 123(8): 1401
- [15] Trudeau E, Regn R, Robinson W, et al. Overall Survival of Women with Locally Advanced Cervical Cancer (STAGE IIB-IVA) is Adversely Affected by Treatment Delays Measureable in Days [J]. *Gynecologic Oncology*, 2016, 143(1): 198-198
- [16] Rodriguez S, Otal A, Richart J, et al. Interstitial Brachytherapy in Locally Advanced Cervical Cancer: From MUPIT to Full Compatible MRI Mixed Intracavitary/Interstitial Template. 10 Years of Experience [J]. *Brachytherapy*, 2016, 15(1): S119-S119
- [17] Ramlov A, Pedersen E M, Røhl L, et al. Risk Factors for Pelvic Insufficiency Fractures in Locally Advanced Cervical Cancer Following Intensity Modulated Radiation Therapy [J]. *International Journal of Radiation Oncology Biology Physics*, 2017, 97(5): 1032
- [18] Petitnicolas C, Azaïs H, Ghesquière L, et al. Morbidity of Staging Inframesenteric Para-aortic Lymphadenectomy in Locally Advanced Cervical Cancer Compared With Infrarenal Lymphadenectomy [J]. *International Journal of Gynecological Cancer Official Journal of the International Gynecological Cancer Society*, 2017, 27(3): 575
- [19] Chagari C, Mazon R, Dunant A, et al. Impact of primary para-aortic lymphadenectomy on distant failure in locally advanced cervical cancer patients treated in the era of image-guided adaptive brachytherapy [J]. *Clinical & Experimental Metastasis*, 2016, 33(8): 1-11
- [20] Pereira E, Cooper H H, Zelaya P G, et al. Concurrent chemoradiation versus radiotherapy alone for the treatment of locally advanced cervical cancer in a low-resource setting [J]. *Gynecologic Oncology Reports*, 2017, 19(C): 50-52
- [21] Rivera A, Mehta K J, Yaparalvi R, et al. Outcomes of Locally Advanced Cervical Cancer Patients Following the Use of the Hybrid Intracavitary and Interstitial Utrecht Tandem and Ovoids Applicator in an Outpatient Setting [J]. *Brachytherapy*, 2017, 16(3): S60
- [22] Yang Z, Chen D, Zhang J, et al. The efficacy and safety of neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer: A randomized multicenter study [J]. *Gynecologic Oncology*, 2016, 141(2): 231-239
- [23] Vici P, Buglioni S, Sergi D, et al. DNA Damage and Repair Biomarkers in Cervical Cancer Patients Treated with Neoadjuvant Chemotherapy: An Exploratory Analysis [J]. *Plos One*, 2016, 11(3): e0149872
- [24] Yao Y Y, Wang Y, Wang J L, et al. Outcomes of fertility and pregnancy in patients with early-stage cervical cancer after undergoing neoadjuvant chemotherapy [J]. *European Journal of Gynaecological Oncology*, 2016, 37(1): 109
- [25] Jin Z, Xiong L, Huang K, et al. Young Cervical Cancer Patients May Be More Responsive than Older Patients to Neoadjuvant Chemotherapy Followed by Radical Surgery [J]. *Plos One*, 2016, 11(2): e0149534
- [26] Minig L, Zanagnolo V, Cárdenas-Rebollo J M, et al. Feasibility of robotic radical hysterectomy after neoadjuvant chemotherapy in women with locally advanced cervical cancer [J]. *European Journal of Surgical Oncology*, 2016, 42(9): 1372-1377
- [27] Park H S, Lim S M, Cho A, et al. Pharmacogenetic analysis of advanced non-small-cell lung cancer patients treated with first-line paclitaxel and carboplatin chemotherapy [J]. *Pharmacogenetics & Genomics*, 2016, 26(3): 116
- [28] Chiorean E G, Hoff D D V, Reni M, et al. CA19-9 decrease at 8 weeks as a predictor of overall survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer [J]. *Annals of Oncology*, 2016, 27(4): 654-660
- [29] Wang H, Zhu L, Lu W, et al. Clinicopathological risk factors for recurrence after neoadjuvant chemotherapy and radical hysterectomy in cervical cancer [J]. *World Journal of Surgical Oncology*, 2013, 11(1): 301
- [30] Chen H, Liang C, Zhang L, et al. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study [J]. *Gynecol Oncol*, 2008, 110(3): 308-315

(上接第 4276 页)

- [29] Jr W K, Shamim A A, Mehra S, et al. Effect of maternal multiple micronutrient vs iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: the Jivita-3 randomized trial [J]. *Jama*, 2016, 312(24): 2649-2658
- [30] Hodgetts V, Morris R, Francis A, et al. Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis [J]. *BJOG An International Journal of Obstetrics & Gynaecology*, 2015, 122(4): 478-490
- [31] Geddes J R, Gardiner A, Rendell J, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 × 2 factorial randomised trial [J]. *Lancet Psychiatry*, 2015, 3(1): 31-39