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吉西他滨热化疗治疗肝癌的临床效果及对血清 MGMT 水平的影响 *

王 宏[1] 夏永寿[2] 加 静[3] 张 燕[1] 王 瑛[4△]

(1 空军军医大学唐都医院肿瘤科 陕西 西安 710038;2 西安市长安医院血液科 陕西 西安 710016;
3 西安医学院第二附属医院肿瘤内科 陕西 西安 710038;4 空军军医大学唐都医院呼吸科 陕西 西安 710038)

摘要 目的: 探讨吉西他滨热化疗治疗肝癌的临床效果及对血清 O6- 甲基鸟嘌呤 DNA 甲基转移酶(O6-methylguanine-DNA methyltransferase,MGMT)水平的影响。**方法:**选取 2014 年 2 月 -2017 年 4 月在我院诊治的 59 例肝癌患者,根据治疗方法的方法不同分为观察组 30 例、对照组 29 例,对照组给予常规化疗,化疗观察 3 个周期;观察组在对照组化疗的基础上给予吉西他滨热灌注化疗,比较两组的临床疗效、不良反应的发生情况、生存情况及治疗前后血清 MGMT 表达的变化情况。**结果:**观察组患者的热灌注化疗均成功进行,治疗前后患者的体温、呼吸频率、心率、血压等对比无显著差异(*P>0.05*)。治疗后,观察组总有效率是 66.7%,显著高于对照组(31.0%) (*P<0.05*)。两组治疗期间的毒性反应发生率间无显著差异(*P>0.05*)。两组治疗后血清 MGMT 表达都较治疗前显著降低(*P<0.05*),且观察组的血清 MGMT 表达明显比对照组低(*P<0.05*)。随访至 2017 年 11 月 30 日,观察组的疾病进展时间(Time to Progression,TTP)、生存时间(overall survival,OS)分别为 8.11± 2.19 个月和 14.29± 1.87 个月,都显著高于对照组的 6.22± 1.82 个月和 11.48± 2.19 个月(*P<0.05*)。**结论:**吉西他滨热化疗治疗肝癌可提高疗效,延长患者的生存时间,且不增加毒副反应,可能与其有效降低患者血清 MGMT 表达有关。

关键词:吉西他滨;热化疗;肝癌;毒副反应;DNA 甲基转移酶

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Clinical Efficacy of Gemcitabine Thermal Chemotherapy in the Treatment of Liver Cancer and Effect on the Serum MGMT Level*

WANG Hong[1], XIA Yong-shou[2], JIA Jing[3], ZHANG Yan[1], WANG Ying[4△]

*(1 Department of Oncology, Tangdu Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710038, China;
2 Department of Hematology, Chang'an Hospital of Xi'an City, Xi'an, Shaanxi, 710016, China;
3 Department of Medical Oncology, The Second Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi, 710038, China;
4 Department of Pneumology, Tangdu Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710038, China)*

ABSTRACT Objective: To explore the clinical efficacy of gemcitabine thermal chemotherapy in the treatment of liver cancer and effect on the serum O6-methylguanine DNA methyltransferase (MGMT) level. **Methods:** 59 cases of liver cancer patients in our hospital from February 2014 to April 2017 were selected as the research object. All the cases were divided into the observation group (30 cases) and the control group (29 cases) according to the methods of treatment. The control group was given conventional chemotherapy for 3 cycles and the observation group was given gemcitabine thermo perfusion chemotherapy based on the control group. The clinical efficacy, incidence of adverse reactions, survival and changes of serum MGMT expression before and after treatment were compared between the two groups. **Results:** The thermo perfusion chemotherapy was successfully performed in the observation group. There was no significant difference in the body temperature, respiratory rate, heart rate and blood pressure between two groups before and after treatment (*P>0.05*). The total effective rate of observation group and control group after treatment were 66.7% and 31% respectively, which was significantly higher in the observation group than that of the control group (*P<0.05*). There was no significant difference in the incidence of digestive tract reaction, blood system reaction, skin reaction and neurotoxic reaction between the two groups (*P>0.05*). After treatment, the serum MGMT levels of both groups were lower than those before treatment (*P<0.05*), which was also significantly lower in the observation group than that in the control group (*P<0.05*). Following up to November 30, 2017, the time to progression and overall survival in the observation group were 8.11± 2.19 months and 14.29± 1.87 months, respectively, which were significantly higher than those in the control group (6.22± 1.82 months and 11.48± 2.19 months)(*P<0.05*). **Conclusions:** Gemcitabine chemotherapy can improve the curative effect, prolong the survival time with high safety in the treatment of liver cancer, which may be related to effective reduction of serum MGMT level.

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作者简介:王宏(1971-),男,本科,副主任医师,研究方向:肿瘤内科治疗,E-mail: wanghong_1971@medhos2017.com

△ 通讯作者:王瑛(1978-),女,本科,主治医师,研究方向:肿瘤内科治疗,E-mail: wangying_1978@medhos2017.com

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前言

原发性肝细胞癌(Hepatocel lular carcinoma,HCC)是最常见的恶性肿瘤之一,具有起病隐匿、转移复发率高、恶性程度高、进展速度快、预后差等特点[1,2]。流行病学调查显示超过 75%的肝癌病例发生在亚太地区,大部分与乙肝相关。我国肝癌的新增病例和死亡人数均占世界首位,且发病数和死亡数当前呈现明显上升的趋势[3,4]。

手术切除是肝癌唯一有可能根治的治疗方法,但受限于远处转移、肝硬化、肿瘤直接侵犯静脉等因素的影响,很多肝癌患者不存在手术治疗指征,且有 2/3 可能发生复发和 / 或转移[5,6]。热灌注化疗(thermal perfusion chemotherapy)是向患者腹腔内持续、恒温充盈灌注液,其中含有大量化疗药物,维持一定时间,此方法可防止残留亚临床病灶、肿瘤复发 [7]。基础研究发现,40-45℃的高温对肿瘤细胞能产生致死效应, 对于杀灭腹腔内微小癌转移灶、游离肿瘤细胞是有效的;另外热疗与化疗可协同发挥作用,化疗药物在加温条件下,抗肿瘤作用明显增加[8-10]。

吉西他滨(GEM)是嘧啶核苷类抗肿瘤药物,能造成 DNA 双链断裂,抑制 DNA 的合成,进而引起肿瘤细胞死亡,主要应用于治疗非小细胞肺癌、胰腺癌等[11-12],在肝癌中的应用还无详细报道。MGMT 可修复 DNA 烷基化损伤,降低肿瘤细胞对化疗药物的耐药性[13]。因此,本研究主要探讨了吉西他滨热化疗治疗肝癌的临床效果及对 MGMT 的影响,现报道如下。

1 资料与方法

1.1 研究对象

选取 2014 年 2 月 -2017 年 4 月在我院诊治的 59 例肝癌患者,根据治疗方法的方法不同分为观察组 30 例、对照组 29 例。纳入标准:经病理组织学确诊;卡氏(Karnofsky)评分 70-90 分;预计生存期 >3 个月。排除标准:妊娠期、哺乳期妇女;有生育要求;严重的中枢神经系统病变者;脑转移者,严重心肾功能不全者;存在其他来源的肿瘤患者;精神疾病患者。两组一般资料比较差异不显著(*P>0.05*)。见表 1。该研究已通过医院伦理委员会批准。

表 1 两组一般资料对比(例, %)

Table 1 Comparison of the general information between two groups (n, %)

Groups	Cases(n)	Pathological stage (Ⅰ/Ⅱ/Ⅲ)	Gender (male/female)	Age(years)	BIM(kg/m^2)	Differentiated degree (low/middle/high)
Observation group	30	11/13/6	18/12	66.43± 2.56	23.87± 2.14	15/10/5
Control group	29	12/12/5	16/13	65.98± 3.14	23.11± 1.93	13/11/5
P		>0.05	>0.05	>0.05	>0.05	>0.05

1.2 治疗方法

对照组:给予常规化疗,化疗方案为吉西他滨 + 奥沙利铂方案,均以 21d 为 1 周期,吉西他滨 100 mg/m^2,iv drip 30 min,d1、8;奥沙利铂 30 mg/m^2,iv drip d1 或 d2,化疗观察 3 个周期。观察组: 在对照组化疗的基础上给予吉西他滨热灌注化疗,化疗药物在肝脏膈面、脾窝、盆腔留置硅胶导管作引流并进行固定,每个化疗周期 1 次。安装循环管路于灌注机上,并安装相应测温装置, 灌注袋内加入 2000 mL 生理盐水、200 mg 吉西他滨,启动循环泵、加热系统,化疗液稳定于 38℃即可将引流连接到体外循环管路,灌注速度设置为 500 mL/min,逐步升温后控制到 43℃,维持 60 min,关闭循环管路并解除与引流管的连接,负压引流。

1.3 观察指标

(1)灌注参数:所有患者在灌注过程都进行心电监护,记录患者灌注前后体温、心率、收缩压、舒张压、呼吸频率等指标。(2)疗效标准:依疗效评价标准(RECIST,Response Evaluation Criteria in Solid Tumors)进行评定,部分缓解,基线病灶长径总和缩小超过 30%;完全缓解,肿瘤病灶均消失;疾病进展,基线病灶长径总和增加超多 20%或出现新病灶;稳定,基线病灶总长径和有缩小,未达到疾病进展。(3)毒副反应:按美国国立癌症研究所抗癌药物常见不良反应评价标准进行分级, 分为 0-Ⅳ度,分度越高,毒副反应越严重。(4)MGMT 检测:治疗前后采集患者的清晨空腹静脉血 5 mL,离心后在 -70℃储存,采用酶联免疫法检测 MGMT 含量。(5)远期疗效:观察并比较两组疾病进展时间(Time to Progression,TTP)、生存时间(overall survival,OS),OS 指治疗开始至死亡 / 末次随访的时长,TTP 为从此方案化疗第一天起至 PD 的时间。

1.4 统计学分析

用 SPSS20.00 对数据进行统计学分析,计量资料以($\bar{x}\pm s$)表示,计数数据采用%表示,用 Kaplan-Meier 法分析生存期,对比方法包括 t 检验、卡方 x^2 分析与 Log-rank 检验,以 *P<0.05* 为差异有统计学意义。

2 结果

2.2 热灌注化疗的可行性

观察组患者的热灌注化疗均成功进行,治疗前后患者的体温、呼吸频率、心率、血压等对比无显著差异(*P>0.05*),见表 2。

2.2 两组总有效率的对比

治疗后, 观察组与对照组的总有效率分别为 66.7%和 31.0%,观察组显著高于对照组(*P<0.05*),见表 3。

表 2 观察组患者热灌注化疗前后生命体征指标的变化 (n=30, $\bar{x}\pm s$)

Table 2 Changes of vital signs of observation group before and after chemohyperthermia(n=30, $\bar{x}\pm s$)

Items	Before treatment	After treatment	*P*
Temperature(℃)	36.66± 0.82	37.10± 0.65	>0.05
Respiratory rate(times/min)	124.59± 18.49	126.30± 14.11	>0.05
Heart rate(times/min)	78.82± 6.78	79.65± 5.33	>0.05
Systolic pressure (mmHg)	124.99± 16.72	126.02± 14.10	>0.05
Diastolic pressure(mmHg)	79.20± 8.19	80.01± 7.82	>0.05

表 3 两组治疗后总有效率对比(例, %)

Table 3 Comparison of the total effective rate between two groups(n, %)

Groups	Cases(n)	Complete remission	Partial response	Stable disease	Progression disease	Total effective rate
Observation group	30	10	10	6	4	66.7%
Control group	29	4	5	12	8	31.0%
P						<0.05

2.3 两组毒副反应发生情况的对比

两组治疗期间的消化道反应、血液系统反应、皮肤反应、神经毒性反应的发生率对比差异均无统计学意义(*P>0.05*),见表 4。

表 4 两组治疗期间毒副反应发生情况的对比(例)

Table 4 Comparison of the incidence of toxic?and?side?effect?between two groups(n)

Groups	Cases(n)	Gastrointestinal reaction (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	Blood system reaction (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	Skin reaction(Ⅰ/Ⅱ/Ⅲ/Ⅳ)	Peripheral nerve toxic reaction (Ⅰ/Ⅱ/Ⅲ/Ⅳ)
Observation group	30	4/3/1/1	3/4/4/2	5/4/4/2	2/2/1/0
Control group	29	9/5/2/0	6/8/6/4	8/9/7/4	6/4/2/1
P		>0.05	>0.05	>0.05	>0.05

2.4 两组治疗前后血清 MGMT 变化的对比

治疗后，两组的血清 MGMT 表达均显著低于治疗前（*P<0.05*），且观察组的血清 MGMT 表达明显显著低于对照组（*P<0.05*),见表 5。

表 5 两组治疗前后血清 MGMT 表达的对比($\bar{x}\pm s$)

Table 5 Comparison of the expression of serum MGMT between two groups before and after treatment($\bar{x}\pm s$)

Groups	Cases(n)	Before treatment	After treatment	*P*
Observation group	30	16.30± 2.13	2.29± 1.34	<0.05
Control group	29	16.09± 4.30	6.30± 2.09	<0.05
P		>0.05	<0.05	

2.5 两组生存情况的对比

随访至 2017 年 11 月 30 日，观察组的 TTP 与 OS 分别为 8.11± 2.19 个月和 14.29± 1.87 个月，都显著长于对照组的 6.22± 1.82 个月和 11.48± 2.19 个月(*P<0.05*)。

3 讨论

肝癌是全世界最常见的恶性肿瘤之一,致残率与病死率均较高[14]。由于早期缺乏特异性症状,大多数患者确诊时已为中晚期,失去了手术治疗指征。化疗的应用可延长患者的生存时间,提高生活质量,但是传统静脉化疗很难清除腹腔内游离癌细胞及微小癌灶,极有可能造成癌症复发、转移,严重影响晚期肝癌的预后[15,16]。

热灌注化疗是一种辅助治疗手段,在治疗恶性肿瘤中可有效杀灭腹腔内微小癌转移灶、游离肿瘤细胞,安全、有效且操作简单[17]。腹腔灌注化疗也属于高选择性局部化疗,药物主要经门静脉循环入肝,经肝脏代谢后进入体循环,提高了腹腔内抗癌药的浓度,对经门静脉转移入肝脏的癌栓和癌细胞有较强的杀灭作用,延长了药物与肿瘤细胞的接触时间[18,19]。本研究显示观察组患者的热灌注化疗均成功进行，治疗前后患者的体温、呼吸频率、心率、血压等对比无显著差异,而两组治疗期间的消

化道反应、血液系统反应、肝肾功能损害、神经毒性反应等对比差异无统计学意义，表明热灌注化疗的应用具有很好的可行性与安全性。相关研究表明腹腔内化疗药物能够作用于门脉系统及肝实质中的微小转移灶，可减轻化疗药物引起的不良反应[20,21]。

目前，治疗肝癌的首选方法是手术，但由于肝癌的早期诊断率低，多数肝癌患者需要进行化疗治疗[22]。肝癌的传统化疗存在疗效不高与耐药性等缺点[23]。热灌注化疗可消除癌症术后亚临床病灶、癌转移病灶，可提高晚期肝癌的 5 年生存率[24]。从机制上分析，热疗的高温能对癌细胞造成杀伤作用，也可进一步增强化疗药物对肿瘤细胞的杀伤作用。吉西他滨具有抗瘤谱广、无毒性反应叠加、作用机制独特、与其他化疗药物无交叉耐药等特点；其服用后容易穿透细胞膜，被细胞充分摄取，可抑制细胞 DNA 的合成，也破坏 DNA 的双链[25]。本研究显示观察组治疗后总有效率是 66.7%，显著高于对照组 (31.0%)。随访至 2017 年 11 月 30 日，观察组的 TTP 与 OS 分别为 8.11± 2.19 个月和 14.29± 1.87 个月，都显著高于对照组的 6.22± 1.82 个月和 11.48± 2.19 个月，表明吉西他滨热化疗的应用能提高治疗疗效，延长患者的生存时间。热灌注与化疗药物的协和应用能提高化疗药物的穿透力与敏感性，杀伤常温低浓度化疗所不能杀伤的肿瘤细胞[26]。相关研究也表明化疗联合热灌注处理能够增加癌细胞对化疗的敏感性，在一定程度上克服耐药性，增加细胞内药物的浓度，从而提高治疗效果[27]。

MGMT 是重要的肿瘤修复基因，可对 DNA 序列相关损伤进行修复[28]。有报道显示 MGMT 的表达与肝癌患者生存时间、化疗有效率密切相关，表达较低的患者以上指标更优，50%以上的肝癌患者具有较高的 MGMT 表达[29]。本研究显示观察组治疗后的血清 MGMT 表达明显比对照组低。从机制上分析，热灌注治疗热可以增强肝癌细胞对化疗的敏感性，增加肿瘤细胞对化疗药物的摄取，扩张肿瘤组织血管并增加血管及肿瘤细胞通透性，促进药物诱导肝癌细胞凋亡，也有利于降低 MGMT 表达[30]。

总之，吉西他滨热化疗治疗肝癌可提高疗效，延长患者的生存时间，且不增加毒副反应，可能与其有效降低患者血清 MGMT 表达有关。

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