

· 论 著 ·

尼莫司汀配合全脑放疗治疗 35 例肺癌多发性 脑转移的临床观察

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【摘要】背景与目的: 肺癌脑转移的临床预后较差, 本研究观察尼莫司汀配合放疗治疗肺癌多发性脑转移的疗效及不良反应。方法: 35 例肺癌多发脑转移患者, 放疗后使用尼莫司汀单药化疗。全脑放疗为 DT1.8~2Gy/次, 5 次/周, 总剂量 36~40Gy。尼莫司汀化疗平均剂量 125mg/次, 每 4~6 周重复, 所有患者使用 2~3 次。治疗期间注意血常规及肝肾功能变化情况, 并给予脱水、支持对症治疗。在放疗结束后 3 个月复查脑 MRI, 观察肿瘤大小, 并统计 1 年生存情况。结果: 所有病例在治疗期间无颅内、外病灶进展病例, 28 例伴有神经症状者均得到缓解。放疗结束后 3 个月单纯颅内病灶评价: 其中 CR 5 例, PR 26 例, SD 4 例, PD 0 例。颅内病灶有效率(CR+PR)为 88.6% (31/35)。一年生存率为 45.7% (16/35), 中位生存期 9.3 个月。不良反应主要是脑充血水肿以及尼莫司汀化疗反应, 多为 I、II 度, 无 IV 度不良反应。结论: 尼莫司汀配合放疗治疗肺癌多发性脑转移的疗效好, 不良反应轻, 远期效果尚需进一步观察。

关键词: 肺癌; 脑转移; 尼莫司汀; 放疗

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Clinical Observation of ACNU Combined with Whole Brain Radiotherapy for Brain Metastases from Lung Cancer

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【ABSTRACT】 BACKGROUND & OBJECTIVE: The prognosis of patient with brain metastases from lung cancer is poor. In this study, we evaluated the efficacy and toxic side effect of ACNU combined with whole brain radiotherapy for brain metastases from lung cancer. **METHODS:** Thirty-five patients with brain metastases from lung cancer received whole brain radiotherapy with a dosage ranging from 36 to 40Gy in 20 fractions over 4 weeks. ACNU was administrated after the radiotherapy. The average dose of ACNU is 125mg per cycle with 4-6 weeks a cycle for 2-3 cycles. Hemogram and liver/renal function were regularly monitored. MRI was evaluated 3 months after radiation. **RESULTS:** No progressive disease was observed in this group of patients. Neurological symptoms in twenty-eight patients were relieved. Complete response (CR) was achieved in 5 cases, partial response (PR) in 26 cases and stable disease in 4 cases respectively. The objective response rate (CR + PR) was 88.6% (31/35). The 1-year survival rate

was 45.7% (16/35) and the median overall survival was 9.3 months. Common toxicities were brain edema and ACNU-related toxicity.

CONCLUSION: ACNU combined with radiotherapy is well tolerated and has activity

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against brain metastases from lung cancer.

KEY WORDS: Lung Cancer; Brain Metastasis; Nimustine; Radiotherapy

肺癌脑转移在临床上很常见,一般预后不佳,中位生存期约 3 个月。因为有血脑屏障的存在,普通化疗药物一般难以进入脑内,治疗以放疗为主。尼莫司汀(ACNU)是亚硝脲类抗脑瘤药物,可以穿透血脑屏障。湖北省肿瘤医院放疗科从 2005 年 9 月至 2006 年 10 月共计使用尼莫司汀配合放疗治疗 35 例肺癌多发性脑转移病例。

1 资料与方法

1.1 一般资料

患者中男性 23 例,女性 12 例,年龄 38~70 岁,中位年龄 52 岁。肺部原发灶均经过病理证实,其中鳞癌 14 例,腺癌 11 例,小细胞癌 10 例。所有病例预计生存期大于 3 个月。脑部转移病灶经 MRI 诊断,均为多发灶,13 例有两处病灶,其余 22 例为 3 个及 3 个以上病灶。伴有神经症状者 28 例,无神经症状者 7 例。神经症状分别包括头痛、运动障碍、意识模糊等。有 18 例同时伴有颅外转移,分别是骨转移 10 例,肾上腺转移 5 例,肺内转移 2 例,骨转移合并肾上腺转移 2 例。脑部病灶大小:以 MRI 作标准最大直径 0.5~6cm,其中最大直径大于 3cm 患者有 21 例,小于 3cm 有 14 例。颅外病变的治疗:有 16 例曾接受过治疗,其中曾行手术治疗肺部原发病灶 5 例,均为完全切除;放化综合治疗 7 例,单纯化疗 3 例,单纯放疗 1 例。

1.2 全脑放疗方法

放疗采用水解塑料固定头部,在模拟定位机下制定靶区,靶区下界为基底线,用加速器 6MV 高能 X 线放疗。分次剂量为 DT1.8~2Gy/次,5 次/周,总剂量 36~40Gy。放疗同时使用甘露醇、高渗糖、地塞米松等减轻颅内水肿。

1.3 尼莫司汀(ACNU)使用方法

尼莫司汀在放疗开始后一周使用,均采用上海三共制药公司生产(商品名宁得朗)。ACNU2~3mg/kg,2~6h 内静脉滴注完毕。在 ACNU 使用之前 125ml 甘露醇快速静脉滴注,以打开血脑屏障。化疗前常规使用 5-HT₃ 受体拮抗剂药物止吐预处理。化疗 4~6 周一次,使用前均需查血常规、肝肾功能等。有 18 例化疗 2 周期,14 例使用 3 周期,3 例

使用 4 周期。

2 结果

2.1 疗效

患者均能够耐受治疗,在治疗期间无死亡病例。所有病例在治疗期间无颅内、外病灶进展病例。28 例伴有神经症状者症状均得到不同程度缓解。放疗结束后 3 个月单纯颅内病灶评价:以头部 MRI 影像学为标准,其中 CR 5 例,PR 26 例,SD 4 例,PD 0 例。其中 CR 5 例中 4 例为小细胞癌,另外 1 例为鳞癌,最大直径均小于 3cm;SD 3 例为腺癌,且病灶直径均大于 3cm。所有患者颅内病灶治疗有效率(CR+PR)为 88.6%(31/35)。一年生存率为 45.7%(16/35),中位生存期 9.3 个月。至今尚有 13 例生存,死亡 22 例。死于脑部病灶复发 6 例,死于颅外肿瘤病变 14 例,其它非肿瘤原因 2 例。

2.2 不良反应

骨髓抑制 I 度 9 例,II 度 3 例,III 度 2 例,无 IV 度骨髓抑制。其中出现 III 度骨髓抑制 2 例者为使用尼莫司汀化疗 3 周期以上病例。骨髓抑制一般发生在化疗第 2~3 周之后,以白细胞及血小板下降最明显,红细胞及血红蛋白变化不大。对骨髓抑制大于 II 度者用粒细胞集落刺激因子和/或升血小板药物如 TPO 等相应支持治疗后血常规恢复正常。有 5 例出现胃肠道反应,表现为恶心呕吐、食欲下降。胃肠道反应 I 度 4 例,II 度 1 例,无 III 度及 IV 度胃肠道不良反应。在治疗期间所有病例均出现了不同程度颅脑充血水肿,予以脱水治疗后均得到缓解。35 例患者均有不同程度脱发,尤以放疗区域为重,放疗区域外脱发不明显。有 1 例在使用尼莫司汀后第二天出现过敏反应(皮疹),抗过敏治疗后好转。无脑疝、癫痫、肝肾功能损伤等不良反应病例,无放射性脑损伤病例。

3 讨论

肺癌是脑转移瘤最常见的原发肿瘤,约占各种恶性肿瘤的 40%,同时约有 30%肺癌患者会发生脑转移^[1]。肺癌一旦发生脑转移时,则预后很差。脑转移瘤的自然生存时间约为 1 个月,使用糖皮质激素

素及脱水对症治疗的生存时间约为 2 个月。目前脑转移的主要治疗手段是放疗,放疗平均生存期是 6 个月,部分可望延长至 6 个月以上。但放疗有剂量限制,一般全脑放疗 DT 30~40Gy^[2],剂量较低对于病灶只有姑息治疗效果,不能达到根治。现在对于如何提高放疗的疗效有不同的方法。单个病灶可以予以手术切除,也可以局部适形放疗加量或伽玛刀治疗。对于多个转移病灶手术及适形放疗方法存在较大的限制,而脑转移有 70% 以上是多发病灶^[3],所以手术治疗脑转移开展并不广泛。由于有血脑屏障的存在,许多化疗药物都不能进入颅内,所以常规化疗对于脑转移效果有限。目前有人认为发生脑转移后血脑屏障已经遭到破坏,很多化疗药物可以穿透血脑屏障^[4]。但对于普通化疗药物是否能够提高脑转移患者生存率尚存在较大争议。何汉平等^[5]报道配合顺铂等药物化疗可以提高生存时间,分析主要原因是提高对颅外病灶的控制。

尼莫司汀是一种新型亚硝基类抗肿瘤药物,是通过抑制 DNA 分子合成而控制癌细胞。给药后迅速分布全身,进入体内可变成脂溶性物质而通过血脑屏障,脑组织分布也很好^[6]。资料表明,不同期别的肿瘤细胞对放疗的敏感性是不同的,M 期和 G₂ 期的细胞对放疗更敏感,尼莫司汀可以使肿瘤细胞集中在 M 期和 G₂ 期,增加了放疗的敏感性,更延长了患者的生存期,提高了患者生活质量。有报道全脑放疗可促进化疗药物通过血脑屏障^[7],所以尼莫司汀一般在放疗开始后使用,可增加药物疗效。使用时首先静脉输入 20% 甘露醇 50ml 加上地塞米松 5mg,以打开血脑屏障,将溶解后的 ACNU 注入 5% 葡萄糖注射液 500ml 中,于 2~6 小时内静脉滴注完毕,以便于使颅脑中此药物浓度进一步提高。用 ACNU 联合化疗治疗脑转移报道多见^[8],但是单药配合放疗尚不多见。尼莫司汀本身具有较好的抗肿瘤作用,配合放疗可以增加疗效。本组尼莫司汀配合放疗治疗 35 例肺癌脑转移,近期有效率达 88.6% (31/35); 其中完全缓解率为 11.4% (4/35),均是肿瘤最大径小于 3cm 者。肿瘤体积越小,对放化疗越敏感、疗效越好;而肿瘤体积大则需要更高的放疗剂量。本组病例患者一年生存率 45.7%,中位生存期达 9.3 月。与 Furuse 等曾报道一组放疗联合化疗的病例,中位生存时间 9.7 个月,1 年生存率 40% 的结果类似^[9]。高于张湘衡等报道的单纯放疗

中位生存时间 6.5 个月^[10],及 Wronsi 等报告的单纯放疗中位生存期 6 个月^[11]。本组死于颅脑病变 6 例,占死亡病例的 27.3%,而明显低于 Patchell 等所报道单纯全脑放疗野内复发而死亡的 50%^[12]。说明尼莫司汀配合全脑放疗可以提高转移灶的控制率。

本组病例不良反应以骨髓抑制和胃肠道反应为主。骨髓抑制以白细胞及血小板下降为主,血红蛋白也有所下降。但仅为 I、II 级。骨髓抑制主要发生在化疗后第 3、4 周,予以相应治疗后基本恢复正常。该治疗方案应用止吐药物后,胃肠道反应较轻,主要为 I、II 级,联合放疗后并没有明显加重胃肠道反应。在放疗过程中所有病例均出现了不同程度颅脑充血水肿,但都比较轻微,予以脱水治疗后均得到缓解。用尼莫司汀单药配合放疗较联合用药不良反应小,而且使用方便(4~6 周一次),患者耐受性好。

尼莫司汀配合放疗治疗肺癌脑转移有效、安全,其远期生存尚须进一步观察。

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国外文摘

Endoscopic options in children: experience with 134 procedures

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OBJECT: There are frequent applications for endoscopy in neurosurgery. However, endoscopic surgery in children has peculiar characteristics and is associated with different rates of success. In this study, the authors report on their experience with 134 consecutive endoscopy procedures performed in 126 patients <18 years of age. **METHODS:** Between April 1993 and October 2007, 134 endoscopic procedures were performed in 126 children. Indications for surgery included brain tumors in 48 children, cystic lesions in 24, aqueductal stenosis in 23, various malformations in 20, hemorrhage and infarction in 6, and isolated ventricles in 5 children. In this long-term followup study, data were analyzed with respect to clinical and radiological success rates, as well as shunt dependence both in relation to lesion origin, and to the type of endoscopic procedure performed (endoscopic third ventriculostomy [ETV], septostomy, aqueductoplasty, or cystocisternostomy). Finally, the influence of patient age on the success rate was evaluated. **RESULTS:** In 114 patients, restoration of CSF circulation was the goal of endoscopy, but in 2 patients only ventriculostomy was performed followed by ventriculoperitoneal shunt placement. In 12 of 114 patients, tumor biopsy sampling or resection was performed simultaneously with shunt placement. In another 12 patients, only endoscopic tumor resection without CSF circulation restoration was done. The follow-up period ranged from 1 to 6 years. Thirteen tumor biopsies, 7 partial tumor resections, and 4 endoscopically complete tumor resections were performed. An intraoperative switch to microsurgery was made in 2 patients because of recurrent hemorrhage and an overly time-consuming endoscopic surgery. Cerebrospinal fluid circulation was successfully restored in 81 (72) of 112 patients, with the use of endoscopy in the setting of tumor-related hydrocephalus providing the best results (86 success rate). However, of the various endoscopic procedures, cyst openings (cystocisternostomy, cystoventriculostomy, and ventriculocystocisternostomy) provided the best results—superior even to ETV—with a success rate of 77 and no complications. In contrast, endoscopic aqueductoplasty had a high failure and complication rate. Patients <6 months old who underwent ETV, septostomy, or aqueductoplasty had poor results and became more frequently shunt dependent than older children. **CONCLUSIONS:** Overall, endoscopy can be considered safe and effective in children. Based on the authors' data, acute hydrocephalus cases such as those caused by tumors are the best candidates for endoscopic CSF flow restoration. Interestingly, cyst openings to the ventricles or cisterns were the most successful endoscopic techniques with the lowest complication rate. Aqueductoplasty should be reserved for selected cases. Finally, the success rate of endoscopic techniques remains poor in infants <6 months of age; this was not only true of ETV, but also other techniques such as septostomy and aqueductoplasty.