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Analysis of the Efficacy of Apatinib in the Treatment of Brain Metastases of Lung Adenocarcinoma

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Abstract

Lung cancer is one of the world's most common and most malignant tumors. The lethality rate of which is the highest in all types of malignant tumors. The five-year survival rate of it is less than 20%, non-small cell lung cancer accounting for more than 70% of all cases and being diagnosed in the locally advanced stage. The 5-year survival rate of NSCLC is less than 6%. Patients can get relief and survival benefit by chemotherapy. Most patients will get PD in 2 or 3 months after the last chemotherapy, especially for those with negative genetic testing showing dismal efficacy to the application of molecular targeted drugs. Study found that neovascularization provide oxygen and nutrition for the growth of the tumor, to promote its growth. Anti-angiogenic drugs can inhibit tumor from progressing and metastasis by inhibiting angiogenesis. And the vascular epidermal growth factor (VEGF) can activate the downstream pathway to stimulate the proliferation of vessel endothelium via binding vascular epidermal growth factor receptor (VEGFR), thus leading to the growth of tumor. Paclitaxel mesylate is a small molecular anti-angiogenesis inhibitor. It can inhibit solid tumor growth factor tyrosine kinase receptor. Acid apatinib shows excellent efficacy and good tolerance for the advanced NSCLC whose multi-line treatment has been failed. This paper reports a case of apatinib mesylate as a fourth-line drug treatment in patients with advanced non-squamous NSCLC brain metastases.

Keywords

Apatinib, Non-Small-Cell Lung Cancer, Advanced Lung Cancer

甲磺酸阿帕替尼治疗一例肺腺癌脑转移患者的疗效分析

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摘　要

肺癌是世界上最常见也是恶性程度最高的恶性肿瘤之一，其致死率高居各类恶性肿瘤之首，五年生存率不足20%，其中非小细胞肺癌占其中70%以上，发现时多为晚期，非小细胞肺癌的5年生存率不足6%，患者可以通过选择放化疗得到疾病缓解和生存获益，仍有大部分患者会在末次化疗后的2到3个月内再次出现疾病的进展，特别是对于基因检测阴性的患者，对针对应用此类基因的靶向药物疗效不佳，研究发现新生血管为肿瘤生长提供氧和营养，促进肿瘤的生长，而血管内皮生长因子(VEGF)能激活下游通路刺激血管通过结合血管内皮细胞增生的表皮生长因子受体(VEGFR)，从而导致肿瘤的生长，抗血管生成药物通过抑制抑制血管生成能够抑制肿瘤发生发展和转移，甲磺酸阿帕替尼属于小分子抗血管生成抑制剂，作用于血管表皮生长因子酪氨酸激酶受体，通过抗血管生成来抑制实体肿瘤生长，甲磺酸阿帕替尼对于多线治疗失败的的非小细胞肺癌晚期治疗优确切的疗效，具有较好的耐受性。本文报道1例甲磺酸阿帕替尼作为四线药物治疗晚期非鳞NSCLC脑转移患者。

关键词

甲磺酸阿帕替尼，非鳞非小细胞肺癌，晚期肺癌

1. 病例概况

患者刘 xx，男，55 岁，吸烟 40 余年，每天 20 支以上。患者 2014 年 1 月因“头晕、头痛 2 个月”入院，于天坛医院完善相关检查发现左枕叶占位性病变、左肺上叶占位，而后行“左枕叶占位切除术”，术后病理示：肺腺癌脑转移。EGFR 基因检测：未见突变；EML4-ALK 融合基因为阴性；KRAS 为野生型。2014 年 3 月 14 日、2014 年 4 月 4 日行一线培美曲塞(900 mg d1) + 顺铂(130 mg 分 d1-3)化疗 2 周期。2014 年 3 月 25 日至 4 月 29 日行全脑放疗 20 次，Dt40Gy/20f。局部加量 5 次，Dt10Gy/5f。此后患者分别于 2014 年 3 月在我院，2014 年 5 月在 304 医院行细胞免疫治疗 2 疗程。2014 年 7 月疗效评价 PR。2014 年 7 月 29 日、8 月 20 日、9 月 18 日、10 月 11 日行一线第 3~6 周期培美曲塞(1000 mg d1)联合顺铂(130 mg 分 d1-2)化疗；4 周期后疗效评价维持 PR。2015 年 9 月复查胸部 CT 提示左肺上叶病灶较前增大，并出现颈部淋巴结转移，考虑疾病进展。于 2015 年 9 月 24 日开始行紫杉醇(330 mg d1)联合卡铂(600 mg d1)方案二线治疗化疗 6 周期，疗效评价 PR。2016 年 4 月复查提示疾病进展，三线治疗 2016-04-23 开始行吉西他滨(1900 mg，d1、d8)联合洛铂(60 mg，d1)方案 2 周期，疗效评价 PD，并出现多发颅内转移。四线治疗于 2016 年 7 月 2 日开始给予甲磺酸阿帕替尼 0.25 g 口服 2/日、替莫唑胺 100 mg 1/日口服治疗。2016 年 10 月 18 日复查肺部病灶稳定，颅内病灶较前稍增大，疗效评价 SD，4 线治疗有效目前 PFS4 个月(图 1~13)。期间多次建议靶病灶放疗，患者拒绝。

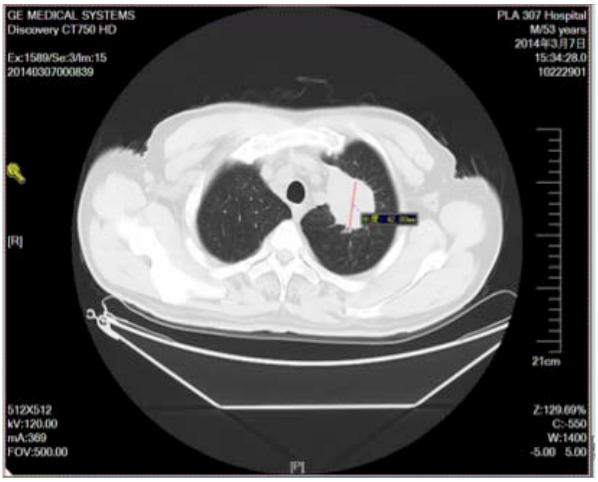

Figure 1. Before treatment
图 1. 未治疗前

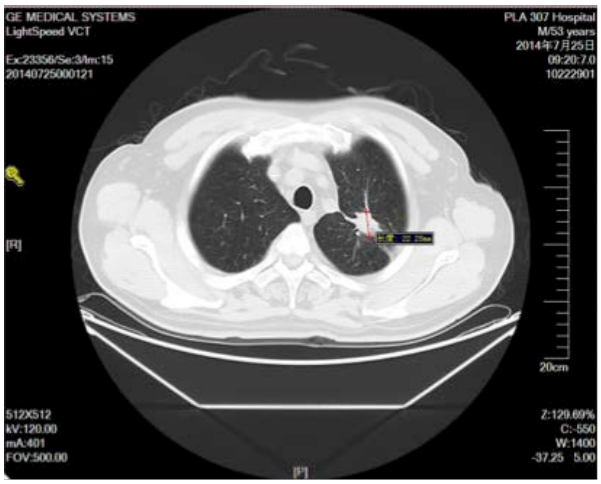

Figure 2. Line 4 cycle
图 2. 一线 4 周期

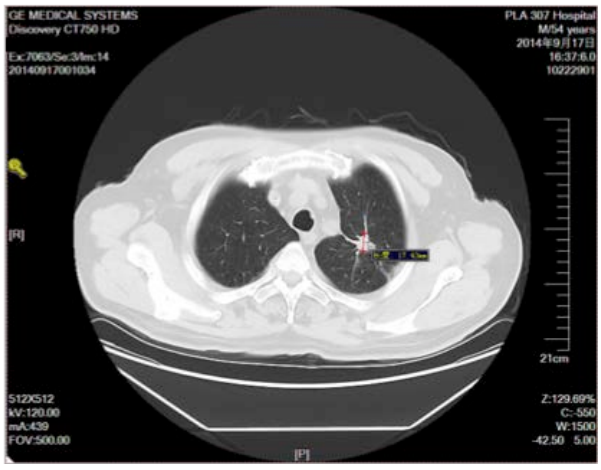

Figure 3. Line 6 cycle
图 3. 一线 6 周期

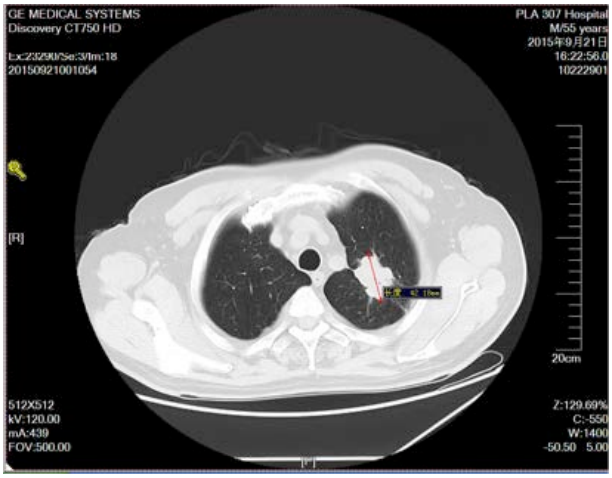

Figure 4. Disease development in September 2015
图 4. 2015 年 9 月疾病进展

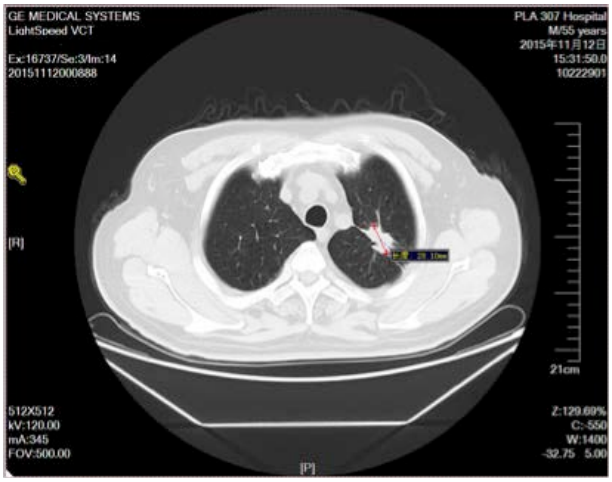

Figure 5. Second-line treatment
图 5. 二线治疗 2 周期图

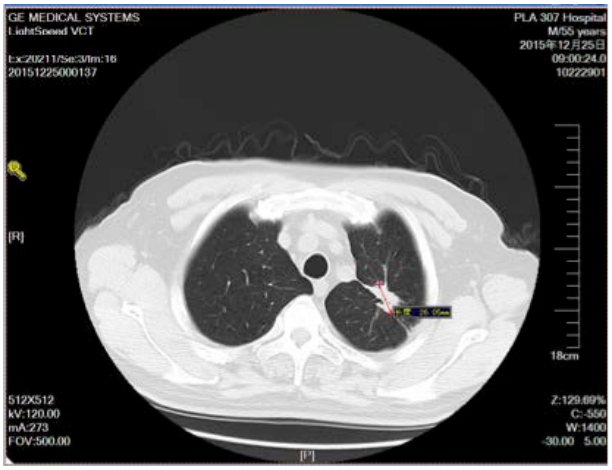

Figure 6. Second-line treatment for 4 cycles
图 6. 二线治疗 4 周期

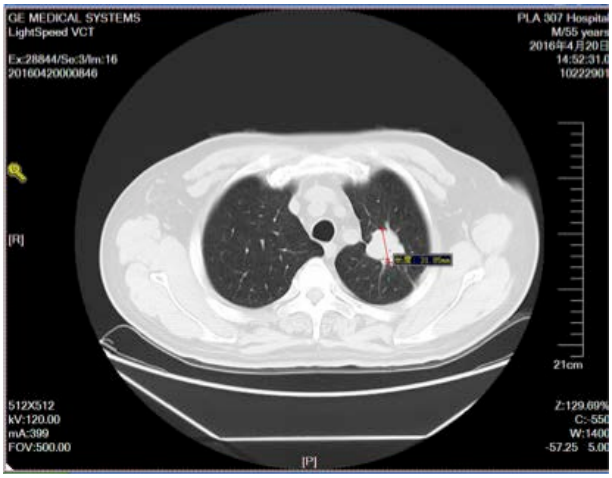

Figure 7. Review of disease progression in December 2015
图 7. 2015 年 12 月复查疾病进展

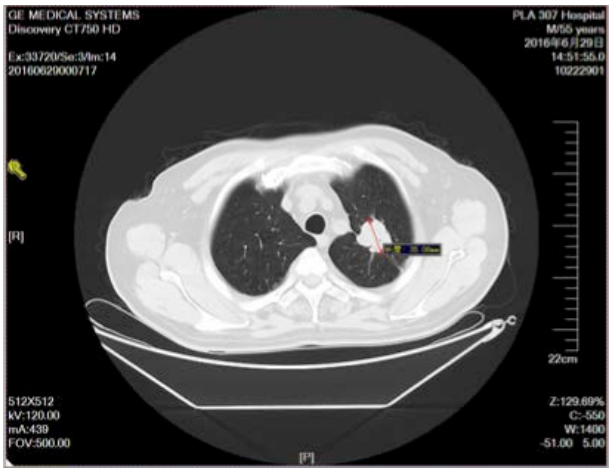

Figure 8. After three cycles of chemotherapy
图 8. 三线化疗 2 周期后

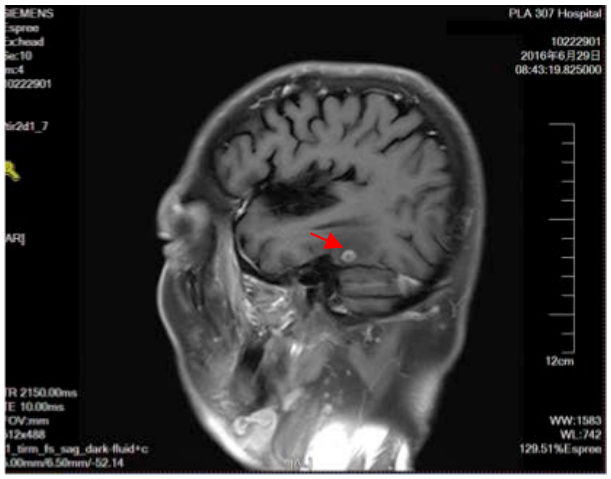

Figure 9. Appears intracranial multiple metastases
图 9. 出现颅内多发转移瘤

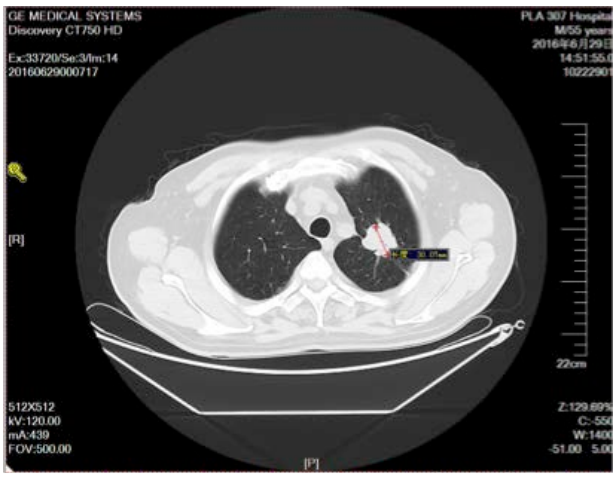

Figure 10. Oral treatment after oral administration
图 10. 口服艾坦治疗 1 月后

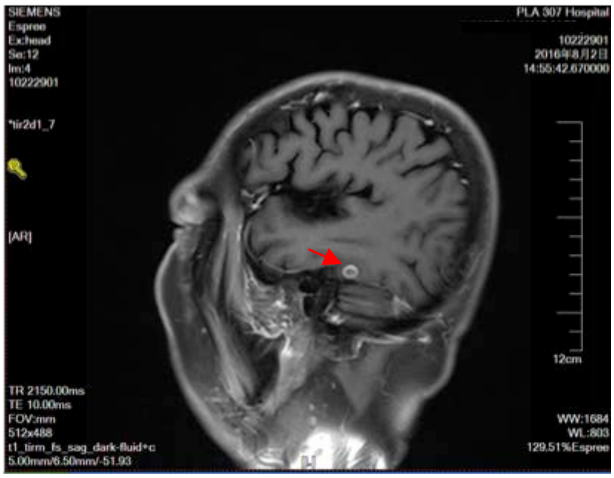

Figure 11. Intracranial multiple metastases
图 11. 颅内多发转移瘤

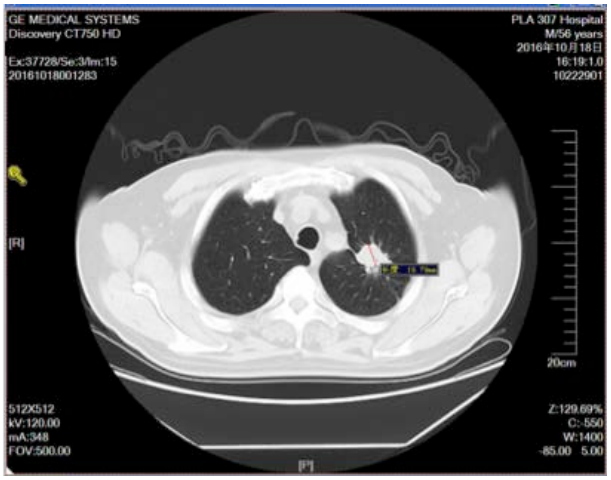

Figure 12. Oral administration of apatinit for 4 months
图 12. 口服阿帕替尼治疗 4 月

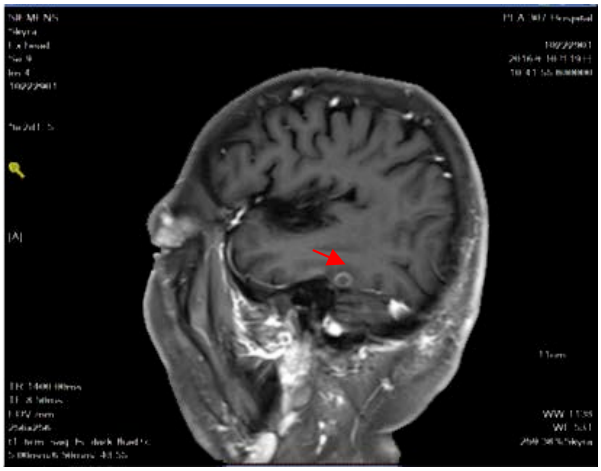

Figure 13. Intracranial tumor slightly increased lung tumor stability
图 13. 颅内肿瘤略增大肺部肿瘤稳定

2. 讨论

该患者为三线治疗后疾病进展的非小细胞肺癌，经过四线给予口服甲磺酸阿帕替尼治疗之后，疾病处于稳定状态，左肺上叶靶病灶曾多次建议患者做局部治疗患者及家属表示拒绝，如果适当局部靶病灶治疗介入可能疗效更好。甲磺酸阿帕替尼是我国自主研发生产的多靶点小分子抗血管生成药物，其作用靶点主要为 VEGFR-2，也可作用于一类受体酪氨酸激酶，包括 c-kit、RET 和 c-src，VEGF-2 通过激活丝裂原活化蛋白激酶(MAPK)信号通路从而促进血管内皮细胞增殖。甲磺酸阿帕替尼阻断 VEGFR-2，从而降低 MAPK 的活化，抑制血管内皮细胞的增殖。从而起到抗血管生成的作用，抑制肿瘤的生长，在治疗晚期非鳞非小细胞肺癌的二期临床研究中，甲磺酸阿帕替尼显示出诸多优点，疗效显著，使中位 PFS 延长 2.8 个月，优于索拉非尼的 1.4 个月，ORR 和 DCR 均高于索拉非尼，常见的不良反应为高血压、蛋白尿、手足综合症等，血液学毒性较低，与高度的靶点选择性相关，出血发生率较低(9.9%)，主要为咯血及便血；目前，我们期待临床 3 期的研究结果，总体上，甲磺酸阿帕替尼具有较好的安全性及有效性[1]-[12]。

3. 总结

甲磺酸阿帕替尼作为我国具有自主产权的抗血管生成靶向药物，在多种晚期肿瘤治疗中产生了良好的疗效，比如胃癌、乳腺癌、骨肉瘤等疾病，近年来在化疗失败的晚期非鳞非小细胞肺癌的治疗中也是取得了良好的治疗效果。以甲磺酸阿帕替尼为代表的抗血管生成药物在肺癌中的研究虽然取得了一定的进步，但仍旧面临巨大的挑战，仍需通过大量的实验数据研究来明确抗血管生成药物治疗肺癌的机制，探索更有价值的标志物，从而提高患者的疗效，延长患者的生存时间。通过此例病例，根据患者疗效证明，甲磺酸阿帕替尼对于多线治疗失败的非鳞非小细胞肺癌的治疗有较好的疗效，使得我们在以后应用抗血管生成药物治疗肺癌增加了信心，期待甲磺酸阿帕替尼更多的临床治疗新进展，为肿瘤患者的治疗带来新的希望。

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