

¹⁷⁷Lu-PSMA 放射性配体治疗在转移性去势抵抗性前列腺癌的应用初探

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[摘要] 目的:评估¹⁷⁷Lu-PSMA 放射性配体治疗在转移性去势抵抗性前列腺癌的安全性及初步疗效。方法:收集 2017—2020 年空军军医大学西京医院收治并接受¹⁷⁷Lu-PSMA 放射性配体治疗的转移性去势抵抗性前列腺癌患者,对其中 3 例典型患者的临床资料进行回顾性分析。结果:病例 1 确诊前列腺癌后,分别先后予以前列腺癌根治术、双侧睾丸切除术、放疗、转移灶切除+粒子植入术,PSA 有效控制 10 余年后持续上升,⁶⁸Ga-PSMA PET/CT 提示多发淋巴结及骨转移,行 2 个周期¹⁷⁷Lu-PSMA 放射性配体治疗后,PSA 由 2092 ng/mL 下降至 920 ng/mL,治疗前后血红蛋白、白细胞、肝肾功无明显变化。病例 2 术前行⁶⁸Ga-PSMA PET/CT 发现 2 处骨转移灶,新辅助内分泌治疗 6 个月后行前列腺癌根治术,术后 PSA 逐渐升高,影像学检查发现转移灶增加,行 3 个周期¹⁷⁷Lu-PSMA 放射性配体治疗,复查⁶⁸Ga-PSMA PET/CT 转移灶缩小,病灶活性明显降低。病例 3 为高危转移性前列腺癌,予以去势+新型内分泌治疗后,PSA 控制不佳,加用多西他赛化疗,2 年后复查发现肝转移,遂行 1 个周期¹⁷⁷Lu-PSMA 放射性配体治疗,PSA 水平明显下降。结论:¹⁷⁷Lu-PSMA 放射性配体治疗是针对转移性去势抵抗性前列腺癌的新型治疗模式,具有较好的临床前景,安全性良好。

[关键词] 前列腺特异性膜抗原;转移性去势抵抗性前列腺癌;¹⁷⁷Lu;放射性配体治疗

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Application of ¹⁷⁷Lu PSMA radioligand in the treatment of metastatic castration-resistant prostate cancer

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Abstract Objective: To evaluate the efficacy and safety of ¹⁷⁷Lu PSMA radioligand in the treatment of metastatic castration-resistant prostate cancer. **Methods:** The patients with metastatic castration-resistant prostate cancer treated with ¹⁷⁷Lu PSMA radioactive ligand in Xijing Hospital, Air Force Military Medical University from 2017 to 2020 were collected, and the clinical data of 3 typical patients were analyzed retrospectively. **Results:** Case 1 received radical prostatectomy, bilateral orchiectomy, radiotherapy, metastasis resection+brachytherapy. PSA continued to rise after more than 10 years of effective control. The ⁶⁸Ga-PSMA PET/CT showed multiple lymph nodes and bone metastasis. After 2 cycles of ¹⁷⁷Lu-PSMA radioactive ligand treatment, PSA decreased from 2092 ng/mL to 920 ng/mL. There was no significant change in hemoglobin, leukocytes, liver or kidney function. In case 2, two bone metastases were found on ⁶⁸Ga-PSMA PET/CT before operation. Radical prostatectomy was performed after 6 months of neoadjuvant endocrine therapy. PSA gradually increased after operation. Imaging examination found that the metastases increased. Three cycles of ¹⁷⁷Lu-PSMA radioactive ligand treatment were performed. The ⁶⁸Ga-PSMA PET/CT metastases decreased and the activity of the lesions decreased significantly. Case 3 was high-risk metastatic prostate cancer. After castration + new endocrine therapy, PSA control was poor. Docetaxel chemotherapy was added. Liver metastasis was found after two years. One cycle of ¹⁷⁷Lu-PSMA radioactive ligand treatment was carried out, and the PSA level decreased significantly. **Conclusion:** ¹⁷⁷Lu-PSMA radioligand therapy is a novel therapeutic model for metastatic castration-resistant prostate cancer, with high clinical

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cal promise and good safety.

Key words prostate-specific membrane antigen; metastatic castration-resistant prostate cancer; ¹⁷⁷lutetium; radioligand therapy

我国前列腺癌发病率增长迅速,且在初诊时多数患者已属中晚期^[1-2]。经过中位时间 18~24 个月的内分泌治疗,绝大部分患者最终会进展为转移性去势抵抗性前列腺癌(metastatic castration-resistant prostate cancer, mCRPC)^[3]。mCRPC 是临床治疗的难点,化疗、内分泌治疗、放疗、姑息性手术等对这一阶段疾病疗效有限^[4-5],患者将面临生活质量下降、生存期缩短的问题。近年来,围绕前列腺特异性膜抗原(prostate specific membrane antigen,PSMA)这一靶分子,开发了各种小分子 PSMA 配体与放射性核素进行偶联,提高了前列腺癌的精准确诊。¹⁷⁷Lu-PSMA-617 靶向放射性配体治疗(radioligand therapy, RLT)显示了较好的临床价值和前景^[6]。本中心回顾性分析接受¹⁷⁷Lu-PSMA RLT 治疗的 3 例患者,现报告如下。

1 临床资料

病例 1,72 岁,2006 年检查发现前列腺特异性抗原(prostate specific antigen,PSA)30 ng/mL,诊断为前列腺癌,遂行开放前列腺癌根治术,术后复查 PSA 较低。2010 年行双侧睾丸切除术及放射治疗,2016 年 1 月 PSA 持续升高至 500 ng/mL,胸腹部 CT 及骨扫描提示肿瘤多发骨转移,给予 3 个周期多西他赛化疗效果不佳,右侧盆腔包块持续增大,进行 MDT 后,行右侧盆腔肿块切除术+右侧盆腔残余肿块放射性粒子植入术,术后 PSA 维持稳定。2017 年 11 月 PSA 升至 2092 ng/mL,再次行 MDT 讨论,予以 2 个周期¹⁷⁷Lu-PSMA RLT。治疗前行⁶⁸Ga-PSMA PET/CT 检查,示全身多处淋巴结及骨转移(图 1)。治疗后 PSA 下降至 920 ng/mL,血红蛋白、白细胞、肝肾功能无明显变化。复查 SPECT/CT 显示右侧盆腔转移淋巴结明显缩小。

病例 2,65 岁,2016 年体检发现 PSA 164.2 ng/mL,前列腺穿刺活检病理示前列腺腺癌。遂行⁶⁸Ga-PSMA PET/CT 检查发现 2 处骨转移病灶,先行新辅助内分泌治疗,6 个月后行前列腺癌根治术,术后继续内分泌治疗,PSA 维持在较低水平。半年后 PSA 逐渐升高,复查⁶⁸Ga-PSMA PET/CT,发现 3 处骨转移灶(图 2a),行 MDT 讨论后,予以 3 个周期¹⁷⁷Lu-PSMA RLT。PSA 从 26.95 ng/mL 降至 3.67 ng/mL,复查⁶⁸Ga-PSMA PET/CT,3 处骨转移病灶无异常核素摄取(图 2b)。

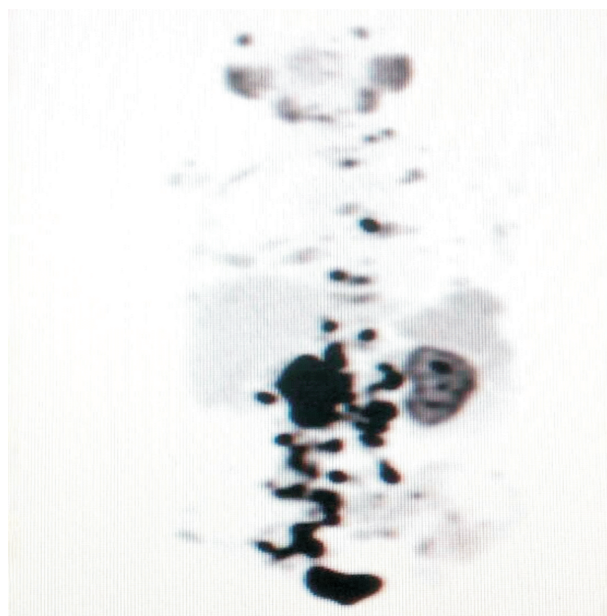
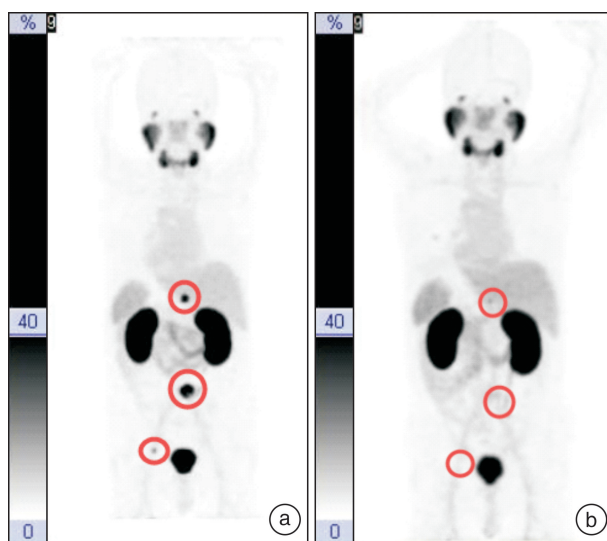


图 1 ⁶⁸Ga-PSMA PET/CT 显示



a: 治疗前 PSMA PET/CT; b: 治疗后 PSMA PET/CT。

图 2 ¹⁷⁷Lu-PSMA 治疗前后⁶⁸Ga-PSMA PET/CT 显像结果

病例 3,60 岁,2017 年体检发现 PSA 190.4 ng/mL,MRI 提示前列腺癌伴骨盆、双侧股骨颈多发转移瘤,双侧髂血管旁肿大淋巴结,骶骨前方异常信号。⁶⁸Ga-PSMA PET/CT 提示前列腺呈核素异常摄取,左侧精囊考虑转移性病变,腰 5 椎体水平右侧腰大肌内侧一枚淋巴结,脊柱多个椎体及附件、双侧肩胛骨、胸骨、双侧多个肋骨、骨盆呈核素摄取异常增高,考虑多发性转移。遂行前列腺穿刺活检,病理结果前列腺腺癌,Gleason 评分 5+5=10。给予比卡鲁胺+戈舍瑞林治疗,PSA 降至

2.87 ng/mL。半年后 PSA 逐渐升高,更换阿比特龙+泼尼松+戈舍瑞林治疗,同时行唑来膦酸预防骨相关事件,PSA 波动在 20~40 ng/mL 之间,行 MDT 讨论,联合多西他赛化疗 6 个周期,PSA 降至 1.51 ng/mL。2019 年 9 月 PSA 升至 73.59 ng/mL,再次联合多西他赛化疗 4 个周期,PSA 最低下降至 33.66 ng/mL。2019 年 12 月出现肉眼血尿,膀胱镜检查:膀胱颈口多发新生物,突向膀胱内。行经尿道膀胱颈口新生物电切术,术后血尿缓解,排尿通畅。2020 年 3 月行 CT 检查发现肝脏转移灶,PSA 升至 508 ng/mL,再次 MDT 讨论,予以 1 个周期¹⁷⁷Lu-PSMA RLT,PSA 降至 238.6 ng/mL,治疗后 24 h 复查 SPECT/CT:¹⁷⁷Lu-PSMA-617 在肿瘤病灶中高度摄取(图 3)。血液学及肝肾功指标在治疗后无明显变化。



a: 正面观;b: 背面观。

图 3 ¹⁷⁷Lu-PSMA RLT 后 24 h SPECT/CT 显像结果

2 讨论

PSMA 是一种前列腺癌细胞表面 II 型跨膜蛋白,在几乎所有前列腺癌高度表达(100~1000 倍)^[7]。在生理分布上,正常前列腺组织不表达或仅少量表达 PSMA,而在晚期和去势抵抗性前列腺癌中表达量进一步增加^[8-9];在结构功能上,PSMA 细胞外段部分可以结合抗体,细胞内段部分可以产生内化作用,将外段结合的物质内化进入细胞内。这就使得抗体携带的核素也进入细胞,在细胞内沉积,有利于后续进行显像诊断和治疗^[10-12]。放射性配体治疗的基本原理就是利用高亲和力的小分子配体与前列腺癌细胞特异性结合,将携带的放射性核素靶向运送到肿瘤部位,产生杀伤肿瘤作用。

PSMA 是⁶⁸Ga-PSMA-11 用于显像和¹⁷⁷Lu-PSMA-617 用于治疗共同分子基础,PSMA-617 表现出更高的亲和力和内化效率,动物实验显示,¹⁷⁷Lu-PSMA-617 标记肿瘤病灶具有更高的靶/本底比值^[13],因此是性能优良的 RLT 探针。

PSMA 单克隆抗体(J591)由于相对分子质量较大,血液清除慢,对肿瘤组织渗透性差,骨髓抑制的发生率较高^[14-15],限制了其在临床的推广应用。海德堡大学德国癌症中心于 2015 年最先开始实施¹⁷⁷Lu-PSMA 的 RLT^[16]。¹⁷⁷Lu-PSMA 的 RLT 具有血液清除快,对肿瘤渗透性强的特点,能够在肿瘤内高度滞留,在体内稳定性高,且不良反应小。¹⁷⁷Lu 作为治疗用放射性核素,具有以下特点^[17]:合适的半衰期,可达 6.65 d;发射 β 射线用于治疗,最大能量 496 keV,最大射程 1.5 mm^[18];释放的低能 γ 射线可满足 SPECT 显像需求;较高的体内稳定性。射线产生的“旁观效应”或“串烧效应”,可以对肿瘤周边血供不足或异种抗原细胞产生间接杀伤作用^[19]。

肿瘤对放射性核素的摄取程度是决定治疗有效性的关键因素。¹⁷⁷Lu 可以与 PSMA 高亲和力结合,从而被靶向运送到前列腺癌组织。Kratochwil 等^[18]研究表明¹⁷⁷Lu-PSMA-617 在前列腺癌细胞的平均摄取量是肾脏摄取量的 6~12 倍,体内生理性清除主要通过肾脏在 48 h 内完成。¹⁷⁷Lu-PSMA-617 治疗总的 PSA 反应率可达 90%,在 1 个周期治疗后 40% 的患者就出现良好反应^[6,20-21]。2018 年 Hofman 等^[22]评估了其在 30 例 mCRPC 患者治疗效果,纳入患者均为既往接受过化疗、阿比特龙或恩杂鲁胺的患者,57% 的患者 PSA 下降超过 50%,82% 患者出现淋巴结或内脏转移灶客观缓解,100% 的患者出现疼痛缓解。2020 年 Yadav 等^[23]报道了 90 例接受了¹⁷⁷Lu-PSMA-617 治疗的 mCRPC 患者,显示了良好的有效性和安全性,平均治疗 4 个周期,56% 的患者 PSA 下降,29% 的患者 PSA 下降超过 50%。国内研究显示在¹⁷⁷Lu-PSMA-617 治疗 11 例转移性前列腺癌患者中,9 例患者 PSA 下降,其中 2 例下降 > 30%,7 例下降 > 50%,且未见明显不良反应。在治疗前后,白细胞、血红蛋白、血小板无明显变化,未发现明显肾脏毒性^[24]。在目前的共识中,适宜进行¹⁷⁷Lu-PSMA RLT 临床治疗的患者应满足^[25]:① 现有治疗失败后 mCRPC,病情持续进展;② 通过 PSMA PET/CT 已经证实有 PSMA 表达的肿瘤和转移灶;③ 具有足够的骨髓储备,已经停止使骨髓抑制的治疗达 6 周以上;④ 血清肌酐水平低于正常上限的 2 倍,肝转氨酶水平低于正常上限的 5 倍;⑤ 无尿路梗阻。建议周期重复的 RLT 疗法,2 次治疗的间隔为 8 周^[26-27],其中每 4 周进行 1 次复查,主要复查

血细胞计数,肝肾功变化情况等,判断有无血液毒性以及监测 PSA 变化情况。在第 3 次治疗开始之前,复查⁶⁸Ga-PSMA PET/CT,评估疗效^[28]。

基于 PSMA 的一体化精准诊断和靶向治疗新模式将快速提高前列腺癌的诊疗水平^[29]。目前,国内外¹⁷⁷Lu-PSMA RLT 研究仍以单中心小样本报道为主,仅用于 mCRPC 终末期三线方案,缺乏大样本前瞻性的随机对照研究和早期干预数据。作为一种新的前列腺癌诊疗模式,以 PSMA 为靶点的多种放射性探针,有望改变 mCRPC 患者的诊疗现状。

利益冲突 所有作者均声明不存在利益冲突

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