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雄激素去势治疗联合多西他赛对晚期前列腺癌患者血清 hk2、miR-221 及 NF-κB 水平的影响 *

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摘要 目的：研究雄激素去势治疗联合多西他赛对晚期前列腺癌患者血清人激肽释放酶（hk2）、微核糖核酸 -221（miR-221）及核转录因子 -κB（NF-κB）水平的影响。**方法：**选择我院 2014 年 9 月 ~2016 年 1 月收治的 80 例晚期前列腺癌患者为研究对象，依据随机数字表法分为对照组和实验组，各 40 例。对照组采用单纯雄激素去势治疗，实验组采用雄激素去势治疗联合多西他赛，对比两组临床疗效，治疗前后血清前列腺抗原（PSA），hk2、miR-221 及 NF-κB 水平，生活质量，不良反应和生存情况。**结果：**治疗后，实验组总有效率显著高于对照组，差异有统计学意义（*P*<0.05）。治疗后，两组血清 PSA、hk2、miR-221 及 NF-κB 水平水平均显著低于治疗前，实验组以上指标明显低于对照组（*P*<0.05）。治疗后，实验组机体状况及生活状况较对照组高（*P*<0.05）；两组家庭状况、情感状况、与医师关系及前列腺癌特异性生活质量评分比较差异无统计学意义（*P*>0.05）。治疗后，实验组机体状况及生活状况较对照组高（*P*<0.05）；两组家庭状况、情感状况、与医师关系及前列腺癌特异性生活质量评分比较无统计学差异（*P*>0.05）。两组 1 年生存情况比较差异无统计学意义（*P*>0.05）；实验组 2 年生存例数多于对照组（*P*<0.05）。**结论：**雄激素去势治疗联合多西他赛能够降低血清 hk2、miR-221、NF-κB 水平，改善患者生活质量及生存情况。

关键词：晚期前列腺癌；雄激素去势治疗；多西他赛；人激肽释放酶；微核糖核酸 -221；核转录因子 -κB
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Effects of Androgen Castration Combined with Docetaxel on Serum Levels of hk2, miR-221 and NF-κB in Patients with Advanced Prostate Cancer*

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ABSTRACT Objective: To study the effect of androgen castration combined with docetaxel on serum levels of human kallikrein (hk2), microribonucleic acid -221 (miR-221) and nuclear transcription factor-κB (NF-κB) in patients with advanced prostate cancer. **Methods:** 80 patients with advanced prostate cancer treated in our hospital from September 2014 to January 2016 were selected as the research objects, and were divided into control group and experimental group according to random number table method, with 40 cases in each group. The control group was treated with androgen castration alone, while the experimental group was treated with androgen castration combined with docetaxel. The clinical efficacy, serum prostate antigen (PSA), levels of hk2, miR-221 and NF-κB, quality of life, adverse reactions and living conditions were compared between the two groups before and after treatment. **Results:** After treatment, the total effective rate of the experimental group was significantly higher than that of the control group (*P*<0.05). After treatment, the levels of serum PSA, hk2, miR-221 and NF-κB in the two groups were significantly lower than those before treatment, and the above indexes in the experimental group were significantly lower than those in the control group (*P*<0.05). After treatment, the physical and living conditions of the experimental group were higher than those of the control group (*P*<0.05). There was no significant difference in family status, emotional status, relationship with doctors and prostate cancer specific quality of life score between the two groups (*P*>0.05). After treatment, the physical and living conditions of the experimental group were higher than those of the control group (*P*<0.05). There was no significant difference in family status, emotional status, relationship with doctors and prostate cancer specific quality of life score between the two groups (*P*>0.05). There was no significant difference in one-year survival between the two groups (*P*>0.05). The number of 2-year survival cases in the experimental group was more than that in the control group (*P*<0.05). **Conclusion:** Androgen castration combined with docetaxel can reduce the levels of serum hk2, miR-221 and NF-κB, and improve the quality of life and survival of patients.

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前言

前列腺癌发病较隐匿，大部分患者就诊时已处于晚期，预后不甚理想[1]。相关研究表明[2]，机体雄激素浓度过高可能是导致前列腺癌的危险因素之一。雄激素去势治疗为晚期前列腺癌的姑息性治疗方法，能够去除或阻断雄激素对前列腺肿瘤细胞的作用，抑制肿瘤细胞的生长[3]。但有研究报道[4]，晚期前列腺癌经单纯雄激素去势治疗后有一定复发率。化疗为此类患者的另一主要治疗方式，能够控制患者症状，延长其生存时间。多西他赛能够利于微管蛋白聚合，抑制癌细胞有丝分裂及增殖[5]。目前研究已证实[6]，多西他赛在内分泌抵抗性前列腺癌中能够得到生存获益。近年来有研究指出[7]，多种血清标志物在前列腺癌诊断及病情评价中有重要作用，人激肽释放酶 2（Human kallikrein 2, hk2）的氨基酸序列与前列腺抗原有较高的相似性，孕激素与雄激素能够上调 hk2 于前列腺上皮细胞中的表达。又有研究发现[8]，癌症患者尿液、血液中微核糖核酸表达谱有一定变化，微核糖核酸 -221(MicroRNA -221, miR-221)可在前列腺癌中异常表达，是监测此类疾病预后的良好标志物。核转录因子 -κB（Nuclear transcription factor-κ B, NF-κB）为机体重要的核转录因子，其生物学活性较广泛，Liu VWS 等 [9] 研究发现，NF-κB 在前列腺癌发生中有重要作用。本研究中目的在于探讨雄激素去势治疗联合多西他赛对晚期前列腺癌患者血清 hk2、miR-221 及 NF-κB 水平的影响。

1 资料与方法

1.1 一般资料

80 例晚期前列腺癌患者入选标准[10]：经血清 PSA、直肠指检、B 超、胸片及直肠前列腺穿刺活检病理学明确诊断为前列腺癌，既往未经治疗的转移性前列腺癌；TNM 分期Ⅳ期；预计生存期在 3 个月以上；卡氏功能状态评分≥ 70 分；年龄 53~74 岁。排除标准：严重心肺功能障碍；血液系统异常。80 例患者依据随机数字表法分为对照组和实验组，每组 40 例，对照组年龄（63.85±3.06）岁；鳞癌 8 例，腺癌 32 例。实验组年龄（62.64±3.53）岁；鳞癌 11 例，腺癌 29 例。两组基线资料比较无统计学差异（P>0.05）。

1.2 方法

对照组采用雄激素去势治疗，每次口服比卡鲁胺片 50 mg，每天 1 次；皮下注射醋酸亮丙瑞林微球，每 4 周 1 次，每周期 28d，持续治疗至疾病进展。实验组采用雄激素去势治疗联合多西他赛治疗，雄激素去势治疗方法同对照组，多西他赛每周期第 1d 静脉滴注 75 mg/m^2，每周期 21d，共 6 个周期。所有患者治疗期间均进行常规副反应防治处理，于治疗结束时评估疗效，统计药物副反应。

1.3 观察指标

1.3.1 **临床疗效** 病灶完全消失，且维持时间在 1 个月以上为完全缓解；病灶缩小大于 50%，未产生新病灶，且维持时间在 1 个月以上为部分缓解；病灶缩小在 50%以内或增大在 25%以内，无新病灶发生，维持时间在 1 个月以上为稳定；有新病灶发生或病灶增加大于 20%为进展。完全缓解、部分缓解记稳定均判定为总有效[10]。

1.3.2 **血液指标** 于治疗前及结束时采集患者空腹静脉血，用电化学发光分析仪测定血清前列腺抗原（Prostate antigen, PSA）水平。用酶联买棉衣法测定血清 hk2、NF-κB 水平，用实时荧光定量 RT-PCR 技术测定 miR-221 水平，以 $N=2^{-\Delta\Delta ct}$ 计算相对表达量。

1.3.3 **生活质量** 于治疗前及结束时通过前列腺癌治疗功能评价（Functional assessmentof cancer therapy, FACT-P）量表进行，包含 6 个模块，分数和机体健康状态呈正比[11]。

1.3.4 **随访** 通过电话回访、回院复诊等方式对患者进行为期 2 年随访，记录患者随访期间的死亡情况。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包，计量资料用（$\bar{x}\pm s$）表示，选用 t 检验，计数资料用 [例（%）] 表示，用 χ^2 检验比较，用 Log-rank 检验分析并比较生存情况，P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床疗效分析

实验组总有效率高于对照组（P<0.05），见表 1。

2.2 两组血清 PSA 分析

治疗后，实验组血清 PSA 水平低于对照组（P<0.05），见表 2。

2.3 两组血清 hk2、miR-221 及 NF-κB 水平分析

治疗后，实验组血清 hk2、miR-221 及 NF-κB 水平低于对照组（P<0.05），见表 3。

表 1 两组临床疗效分析（例，%）

Table 1 Analysis of clinical efficacy of the two groups (n, %)

Groups	n	Complete response	Some relief	Stable	Progress	Total effective rate
Control group	40	0(0.00)	13(32.50)	15(37.50)	12(30.00)	28(70.00)
Experimental group	40	0(0.00)	23(57.50)	13(32.50)	4(10.00)	36(90.00)$^{\triangle}$

Note: VS control group, $^{\triangle}$ P<0.05.

表 2 两组血清 PSA 分析($\bar{x}\pm s$,分)

Table 2 Analysis of serum PSA of the two groups ($\bar{x}\pm s$, points)

Groups	n	Time	PSA(ngg/mL)
Control group	40	Before treatment	56.02±6.94
		After treatment	14.23±2.01▲
Experimental group	40	Before treatment	54.98±7.83
		After treatment	10.75±1.42▲△

Note: VS control group, △ P<0.05; VS before treatment,▲P<0.05.

表 3 两组血清 hk2、miR-221 及 NF-κB 水平分析($\bar{x}\pm s$)

Table 3 Analysis of Serum HK2, miR-221 and NF- B levels of the two groups ($\bar{x}\pm s$)

Groups	n	Time	hk2(ng/L)	miR-221	NF-κB(μg/L)
Control group	40	Before treatment	79.04±8.51	0.59±0.06	18.03±2.27
		After treatment	35.08±4.26▲	0.35±0.04▲	12.94±1.39▲
Experimental group	40	Before treatment	77.93±9.04	0.57±0.08	17.65±2.53
		After treatment	27.17±3.03▲△	0.29±0.03▲△	10.28±1.02▲△

Note: VS control group, △ P<0.05; VS before treatment,▲P<0.05.

表 4 两组生活质量评分分析($\bar{x}\pm s$,分)

Table 4 Analysis of quality of Life score of the two groups ($\bar{x}\pm s$)

Groups	n	Time	Body condition	Living conditions	Family situation	Case status	Relationship with physician	Prostate cancer is specific for quality of life
Control group	40	Before treatment	10.85±1.26	7.19±0.89	12.33±1.25	6.49±0.75	6.78±0.84	67.88±7.42
		After treatment	16.02±2.57▲	13.27±1.42▲	12.41±1.16	6.60±0.72	6.83±0.80	68.39±8.05
Experimental group	40	Before treatment	10.36±1.24	7.24±0.81	12.06±1.42	6.36±0.81	6.57±0.87	66.94±8.92
		After treatment	19.75±2.89▲△	15.93±2.25▲△	12.55±1.13	6.51±0.84	6.71±0.74	68.01±7.95

Note: VS control group, △ P<0.05; VS before treatment,▲P<0.05.

2.4 两组生活质量评分分析

治疗后，实验组机体状况及生活状况较对照组高(P<0.05)；两组家庭状况、情感状况、与医师关系及前列腺癌特异性生活质量评分比较无统计学差异(P>0.05)，见表 4。

3 讨论

近年来，随着血 PAS 检测的不断推广，前列腺癌的发生率呈增加趋势，其病程相对较长，早期缺乏特异性表现，目前临床上大部分前列腺癌初诊时已处于晚期，错过根治术手术治愈时机[12]。内分泌治疗是晚期前列腺癌的首选方法，雌激素类药物的心血管毒性明显，能够多种并发症，有一定局限性[13]。有关研究报道[14]，前列腺为雄激素依赖器官，肾上腺肌睾丸能够生成雄激素，并在前列腺细胞内转化为双氢睾酮，从而和雄激素受体结合，参与前列腺癌细胞的生长发育。大部分前列腺癌存在雄激素依赖性，并表明前列腺癌细胞缺乏雄激素刺激时可发生凋亡。雄激素去势治疗仍是目前晚期前列腺癌的主要治疗方案，目前以比卡鲁胺联合亮丙瑞林较为常用，其可降低机体雄激素含量，抑制前列腺肿瘤细胞生长[15]。比卡鲁胺是雄激素去势治疗前列腺癌的代表药物，能够与雄性激素受体竞争性结合，影响雄激素对前列腺细胞的作用，且可促进细胞凋亡[16,17]。亮丙瑞林属促性腺激素类药物，可抑制垂体 - 性腺系统功能，用药初期雄激素能够出现短暂性上升，之后垂体反应性下降，导致雄激素、雌激素分泌受到抑制，从而对前列腺癌起到治疗作用。但雄激素去势治疗抑制雄激素的同时能够增加睾丸对睾酮的分泌，从而影响疗效。有研究认为[18]，晚期前列腺癌无法通过雄激素去势治疗得到彻底治愈。Blessing AM 等[19]研究也表明，大部分晚期前列腺癌患者可从激素依赖性转换为非雄激素依赖性。

紫杉烷为经典的细胞毒药物，有较高的抗肿瘤活性。多西他赛为紫杉烷的衍生物，目前研究认为，多西他赛为前列腺癌的主要化疗药物，其能够结合微管蛋白，抑制肿瘤细胞分裂，促进肿瘤细胞凋亡[20,21]。药理研究报道[22]，多西他赛较紫衫烷在机体内存留的时间较长，抗肿瘤活性较强，其具有一定的靶向性。近年来有研究表明[23]，多西他赛联合内分泌治疗能够提高前列腺癌患者的效果。本研究结果显示，多西他赛联合雄激素去势治疗组总有效率较单纯雄激素去势治疗组高，表明在雄激素去势治疗基础上联合多西他赛对前列腺癌患者治疗上有积极作用，更能促进病灶的缩小，可能原因为两种药物能够通过不同药物途径起到协同作用，从而提高疗效。PSA 为临床评价前列腺癌疗效及预测复发的可靠指标，PSA 有器官特异性，机体正

常状态下血清中 PSA 的含量较低，前列腺癌能够刺激 PSA 表达[24,25]。本研究中，多西他赛联合雄激素去势治疗后血清 PSA 水平相对较低，进一步证实二者联合作用的效果。

前列腺癌的发生发展是涉及多个细胞因子的复杂过程，hk2 为前列腺癌的新型标志物，其主要在前列腺中产生，能够分布在机体精液、血液中。雄激素与其受体结合后能够诱导 hk2 表达，临床通过检测 hk2 含量能够增加前列腺癌诊断的敏感度[26]。hk2 可刺激 uPA 的单链形式，降解细胞外基质，参与肿瘤的侵袭及转移。另外 hk2 又可促进类胰岛素样生长因子 -I 的表达，参与癌变前列腺细胞的有丝分裂和抗凋亡反应，增加前列腺癌的发生风险[27]。等[28]通过研究报道，前列腺癌患者血液中 hk2 水平较良性前列腺增生患者高，并表明 hk2 浓度和前列腺癌疾病分期有良好相关性。近年来，miRNA 在肿瘤发生发展中的作用已得到临床研究证实，多个研究指出 miRNA 对细胞的自身稳定及发育起到重要作用[29,30]。miR-221 为前列腺癌最常见的癌基因，可诱导癌细胞增殖、迁移及侵袭，Kobayashi M 等[31]研究显示，前列腺癌患者血液中 miR-221 浓度较健康对照组显著上调。既往研究已报道[32]，miR-221 一方面能够参与肿瘤细胞的侵袭及转移，另一方面又可影响癌细胞对放化疗的敏感性。又有研究发现 [33]，肿瘤微环境中的相关细胞能够刺激 NF-κB 表达，NF-κB 属信号转导枢纽，能够连接机体多个传导通路，从而影响其他因子的转录及翻译，参与机体细胞增殖、肿瘤发生发展等病理、生理反应中基因的调控。一项研究指出[34]，药物抑制 NF-κB 表达，能够影响前列腺癌中血管的新生，抑制癌细胞凋亡及侵袭力，导致大量癌细胞凋亡。前列腺癌中 NF-κB 的表达明显上调，其活化和核转位可增加抗凋亡蛋白的转录、翻译，参与癌症细胞的增殖及凋亡。Studencka-Turski M 等研究表明 [35]，NF-κB 的表达和血管内皮生成因子（Vascular endothelial growth factor, VEGF）有直接关联，NF-κB 能够促进 VEGF 表达，增加淋巴管和中细胞的接触面积，诱导肿瘤的淋巴转移。NF-κB 高表达能够刺激前列腺细胞增殖、转化及恶变，NF-κB 高表达的前列腺癌患者的预后相对较差。本研究结果显示，多西他赛联合雄激素去势治疗后 hk2、miR-221、NF-κB 含量相对较低，可能原因为两种药物联合作用能缩小瘤负荷，从而改善肿瘤微环境，下调 hk2、miR-221、NF-κB 表达。

生活质量能够准确反映癌症患者的临床疗效及康复状态，本研究中，联合治疗组治疗后机体状况及生活状况改善更为明显。安全性分析显示，多西他赛组有部分患者发生胃肠道及骨髓抑制反应，经及时对症处理后均得到明显改善，患者能够耐受治疗。Wallis CJD 等[36]研究报道，多西他赛联合雄激素去势治疗能够降低晚期前列腺癌的死亡风险，并改善患者无进展生存期。一项 Meta 研究分析也表明[37]，在雄激素去势治疗基础上联合多西他赛能够提高晚期前列腺癌患者的 1 年生存率。本研究结果也显示，雄激素去势治疗联合多西他赛能够改善晚期前列腺癌患者生存情况。

综上所述，雄激素去势治疗联合多西他赛能够降低血清 hk2、miR-221、NF-κB 水平，有助于改善患者生活质量。

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