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前列腺癌药物治疗的新进展

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[摘 要] 前列腺癌(prostate cancer，PCa)是男性泌尿系统常见恶性肿瘤，我国PCa发病率低于欧美等发达国家，但呈逐年增长的趋势。PCa正严重影响着我国男性患者的健康。近年来随着对PCa发病机制的深入认识，许多新药应用于临床并改善了PCa的预后。

[关键词] 前列腺癌；药物治疗；化疗；放疗；免疫治疗；信号通路抑制剂；整合素抑制剂

New progress in drug therapy for prostate cancer

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Abstract Prostate cancer is common malignant tumors of the male urinary system. It is the most common malignant tumor in men in developed countries. The incidence of prostate cancer in China is lower than that in developed countries such as Europe and America, but it is increasing year by year. Prostate cancer is seriously affecting the health of male patients in China. In recent years, with the understanding of the pathogenesis of prostate cancer, many new drugs have appeared in the clinic and improved the prognosis of prostate cancer.

Keywords prostate cancer; drug therapy; chemotherapy; radiotherapy; immunotherapy; signaling pathway inhibitors; integrin inhibitors

前列腺癌(prostate cancer，PCa)位居全球男性恶性肿瘤的第二位，是发达国家男性中最常见的癌症，据估计2012年有110万新发病例[1]。我国PCa发病率低于欧美国家，但近年来发病率呈明显增长趋势，据统计1998至2008年我国男性PCa的发病率每年平均增长比例为12.07%，PCa正成为严重影响我国男性健康的恶性泌尿系肿瘤[2]。近年来，许多新型药物，如最新批准的雄激素合成抑制剂醋酸阿比特龙，雄激素受体(androgen receptor，AR)拮抗剂恩杂鲁胺，放射性药物镭-223氯化物，sipuleucel-T免疫疗法药物和多西他赛、卡巴他赛等化学治疗药物改善了PCa的预后。

1 雄激素合成抑制剂

醋酸阿比特龙是一种合理设计的孕烯醇酮结构小分子口服药，通过不可逆地抑制细胞色素P450 C17 (CYP-l7)的羟化酶和裂解酶活性选择性、高亲和性，持续阻止雄性激素的合成[3-5]。醋酸阿比特龙不仅抑制前列腺雄激素的合成，同时睾丸和肾上腺雄性激素的分泌也被抑制，从而起到抑制PCa细胞生长的目的[6-7]。因此FDA批准在化学

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治疗前后对转移性去势抵抗性前列腺癌(metastasis castration-resistant prostate cancer，mCRPC)患者使用醋酸阿比特龙[8]。在COU-AA-301的研究[9]中，797名患者被随机分配接受醋酸阿比特龙加泼尼松(阿比特龙组)和398名接受安慰剂加泼尼松(安慰剂组)，中位随访时间为20.2个月，阿比特龙组的中位总生存期(median overall survival，mOS)长于安慰剂组，PSA进展的中位时间延长了1.9个月。最终分析证实：醋酸阿比特龙显著延长了mCRPC患者的总体存活期。Clarke等[10]通过一项随机、双盲、安慰剂对照的II期临床试验证实：与单用阿比特龙相比，奥拉帕尼联合阿比特龙为mCRPC患者提供临床疗效益处。接受奥拉帕尼和阿比特龙的患者比单独使用阿比特龙的患者出现更严重的不良反应，但奥拉帕尼和阿比特龙的组合可能为广泛的mCRPC患者提供额外的临床益处。其他CYP17A1抑制剂如orteronel和galeterone正在进行临床研究评估[11]。

2 AR 抵抗剂

恩杂鲁胺是新型AR拮抗剂，它直接与AR结合，抑制雄激素与受体结合，抑制AR核转位及AR介导的DNA结合[12]。它改善高风险非转移性去势抵抗性前列腺癌(non-metastasis castration-resistant prostate cancer，nmCRPC)患者的无转移生存期(metastasis-free survival，MFS)[12]。恩杂鲁胺分别于2012年和2014年获得FDA批准用于mCRPC治疗[13]。在一项随机恩杂鲁胺的II期试验中，既往未接受过化疗的nmCRPC患者，恩杂鲁胺治疗延长了无进展生存期[14]。Hussain等[15]进行了一项双盲、随机、安慰剂对照的III期临床试验，结果表明恩杂鲁胺组中位无转移生存期为36.6个月，安慰剂组为14.7个月，中位随访时间分别为18.5个月和15.1个月。与安慰剂相比，恩杂鲁胺治疗导致影像学进展或死亡的风险降低71%。恩杂鲁胺组的总病死率低于安慰剂组[恩杂鲁胺组933例患者中有103例(11%)，安慰剂组468例中有62例(13%)死亡]。然而恩杂鲁胺与安慰剂治疗比较，更频繁出现疲劳、腹泻、潮热、肌肉骨骼痛、头痛、高血压、癫痫发作。恩杂鲁胺已被批准联合其他药物如醋酸阿比特龙，多西他赛或镭-22二氯化物用于早期或晚期PCa[16]。

3 化疗药物

多种化学治疗药物被批准用于PCa的治疗。多西他赛和卡巴他赛通过抑制微管蛋白解聚，从而阻止有丝分裂，最终导致细胞死亡[17]。此外，已经提出了多西他赛和卡巴他赛具有的AR抑制特性，与其预防微管依赖性核转运有关[18]。多西他赛和卡巴他赛分别于2004年和2010年获得FDA批准用于mCRPC治疗[19-20]。对多西他赛在激素敏感的PCa和雄激素剥夺治疗(androgen deprivation therapy，ADT)进行评估。Morgans等[21]研究发现：ADT联合多西他赛与单用ADT相比，mOS显著改善，但常发生化疗的不良反应如中性粒细胞减少症的血液学毒性。米托蒽醌是一种拓扑异构酶抑制剂，与多西他赛相比，PCa患者的生存获益有限，但有一些症状缓解[22]。米托蒽醌与卡巴他赛联合使用可在mCRPC患者中延长药物作用时间[23]。然而，米托蒽醌的使用受到不良反应的限制[24]。

4 免疫治疗

Sipuleucel-T于2010年获得批准治疗mCRPC[25]。在III期临床研究中，sipuleucel-T组的mOS比安慰剂组长4.1个月。与安慰剂组相比，sipuleucel-T组的死亡风险降低了22%。此外，还促进了3年生存率(sipuleucel-T组为31.7%，安慰剂组为23.0%)。但是，未发现无进展生存期有所改善。Sipuleucel-T的主要不良反应包括寒战、发烧和头痛[26]。然而，高成本和复杂的程序限制了sipuleucel-T的使用[27-28]。

Ipilimumab是一种单克隆抗体，可抑制CTLA-4并增强抗肿瘤免疫力，CTLA-4是T细胞检查点受体，负调节T细胞活化，在肿瘤进展中发挥重要作用，CTLA-4为免疫治疗提供了新的靶点，首次使用ipilimumab的研究显示：在针对PCa患者的早期临床评估中得到了一些有希望的结果，在少数病例中观察到完全缓解[29]，但无法确定整体生存率的改善[30]。有两项临床试验[31-32]正在研究抗PD-1抗体，并且已经报道了转移性PCa患者的持久反应。关于抗PD-L1抗体，atezolizumab，durvalumab和avelumab正在进行用于治疗转移性PCa的早期临床研究[32]。

5 放射性药物

近年来，放射性药物已被用于治疗多种恶性肿瘤，并获得多项FDA批准。镭-223氯化物是静脉内施用的靶向α疗法。镭-223氯化物含有α发射核素，可与骨矿物羟基磷灰石形成复合物[33]。在PCa

异种移植模型中进行的体内实验表明：镭-223氯化物沉积在新形成的肿瘤内骨基质中，它通过诱导难以修复的双链DNA断裂，对邻近的肿瘤细胞、破骨细胞和促进疾病的成骨细胞具有细胞毒性作用，从而破坏肿瘤微环境细胞和成骨细胞之间的正反馈回路[34]。根据III期临床试验(ALSYMPCA)的分析，921例患有骨转移的CRPC患者接受镭-223与安慰剂组相比mOS显著改善。在12周时，镭-223组中16%的患者和6%的安慰剂组患者血液的PSA水平降低大于30%。此外，镭-223组患者死亡风险比安慰剂组低30%。与安慰剂组相比，镭-223组的第一次症状性骨骼事件的发生也延后。所有结果均证实镭-223在治疗骨转移CRPC方面具有良好的效果，并且不良反应较少[35]。

Lutetium-177是一种新型放射性药物，目前正在治疗mCRPC中研究。它发射β粒子以及伽马射线，其传播距离比α粒子更远，但携带的能量更少。对患有mCRPC的男性进行的无对照II期临床研究，接受Lutetium-177治疗的47名患者PSA下降了59.6%[36]。此外，该药物对可逆性骨髓抑制具有良好的耐受性。另外，临床I期剂量递增研究实验将Lutetium-177与多西紫杉醇联合用于患有mCRPC的男性(NCT00916123)。目前，正在进行男性mCRPC患者无对照II期研究(NCT03042312)。

6 其他药物

整合素是由α和β亚基组成的跨膜蛋白受体，其将细胞附着于细胞外基质或结合由其他细胞分泌的配体[37-38]。整合素在PCa中调节细胞黏附和迁移，促进细胞内运输，导致细胞增殖，细胞侵袭，肿瘤生长，新血管生成和转移[39-40]。*D*-松醇是一种整合素抑制剂，*D*-松醇在PC3和DU145雄激素非依赖性PCa细胞系中以非细胞毒性浓度抑制细胞迁移和侵袭[41-42]。此外，已显示*D*-松醇降低$\alpha_v\beta_3$整合素mRNA表达，导致转移的抑制[41]。*D*-松醇通过两条重要途径下调$\alpha_v\beta_3$整合素的表达。首先，其抑制FAK/c-Src激酶磷酸化途径，以剂量依赖性方式在细胞运动和侵袭中起重要作用[41,43]；其次，*D*-松醇降低NF-κB信号转导途径中的p65磷酸化，该途径调节细胞迁移和转移[41]。

Abituzumab是一种单克隆抗体，用于靶向整合素α_v亚基[43]。Abituzumab的作用机制是基于α_v整合素胞外结构域的识别，抑制配体与α_v异二聚体的结合，抑制细胞间相互作用、细胞与ECM的相互作用、细胞侵袭和细胞信号转导进而抑制PCa转移，而不与整联蛋白家族的其他成员交叉反应[43]。在骨转移的PCa患者中进行abituzumabI期临床试验的结果显示其具有潜在的抗肿瘤活性[40]。这些发现提供了未来研究的基础，以验证该药物控制整合素介导的PCa进展并开发额外的α_v整联蛋白抑制剂来治疗这种恶性肿瘤。

7 结语

近年来，科学进展增加了可用于治疗PCa的药物种类，FDA批准多种新药用于治疗PCa，提高了PCa患者的生存率和生活质量，但治疗依然有局限性。随着对PCa发病机制了解的逐渐加深，多种抗癌机制的药物正处于研发中，当前整合素抑制剂正成为研究热点，相信在不久的将来，会有疗效更好的新药问世，用于PCa患者。

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