

微管蛋白抑制剂在前列腺癌中的应用进展[△]

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摘要 前列腺癌进入转移性去势抵抗阶段后, 临床治疗面临重要挑战。微管蛋白抑制剂因其独特的作用机制, 已成为转移性去势抵抗性前列腺癌治疗的一线药物。其中, 紫杉烷类微管蛋白抑制剂(如多西他赛和卡巴他赛)因明确的生存获益被列为标准治疗方案, 而其他类微管蛋白抑制剂(如长春新碱、秋水仙碱)因毒性较大应用受限。目前, 临床主要采用基于多西他赛的三联疗法、联用免疫检查点抑制剂的策略来改善前列腺癌患者预后, 逆转肿瘤微环境免疫抑制状态, 增强疗效。尽管微管蛋白抑制剂在前列腺癌治疗中取得了显著的临床疗效, 但出现的耐药问题限制了其长期应用, 为此研究者们探索了新的解决办法, 包括开发新型微管蛋白抑制剂与三磷酸腺苷结合盒亚家族B成员1抑制剂、联合使用脂肪酸合成酶抑制剂与微管蛋白抑制剂、基于蛋白质降解靶向嵌合体技术开发降解剂等。未来研究需致力于新靶点开发、药物剂型改良和个体化联合方案制定, 以突破当前治疗瓶颈。

关键词 前列腺癌; 转移性去势抵抗性前列腺癌; 微管蛋白抑制剂; 多西他赛; 联合治疗; 耐药

Progress in the application of microtubulin inhibitors in prostate cancer

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ABSTRACT When prostate cancer (PCa) progresses to the metastatic castration-resistant stage, significant challenges arise in clinical treatment. Microtubulin inhibitors have become first-line drugs for the treatment of metastatic castration-resistant PCa due to their unique mechanism of action. Among them, taxanes (e.g. docetaxel and cabazitaxel) remain standard care with proven survival benefits, while other microtubule inhibitors (e.g. vincristine, colchicine) show limited clinical utility due to toxicity. Currently, the clinical approach primarily employs docetaxel-based triple therapy and combined with immune checkpoint inhibitors to improve the prognosis of PCa patients, reverse the immunosuppressive state of the tumor microenvironment, and enhance therapeutic efficacy. Despite the remarkable clinical efficacy of microtubule inhibitors in the treatment of PCa, the emergence of drug resistance has limited their long-term application. To address this issue, researchers have explored new solutions, including the development of novel microtubule inhibitors in combination with ATP-binding cassette subfamily B member 1 inhibitors, the concurrent use of fatty acid synthase inhibitors with microtubule inhibitors, and the development of degraders based on proteolysis-targeting chimeras technology. Future research should focus on target discovery, drug formulation optimization, and personalized approaches to overcome current therapeutic limitations.

KEYWORDS prostate cancer; metastatic castration-resistant prostate cancer; microtubule inhibitors; docetaxel; combination therapy; drug resistance

前列腺癌(prostate cancer, PCa)是男性常见的恶性肿瘤, 其发病率在美国癌症中居首位^[1], 在我国的发病率也逐渐上升^[2]。PCa具有转移性, 常发展为转移性激素敏感性前列腺癌(metastatic hormone-sensitive prostate cancer, mHSPC)。雄激素剥夺治疗(androgen deprivation therapy, ADT)是其核心疗法, 可通过降低雄激素水平抑制肿瘤生长, 但多数患者会进展为转移性去势抵抗

性前列腺癌(metastatic castration-resistant prostate cancer, mCRPC), 导致治疗困难^[3]。近年来, 微管蛋白抑制剂因其独特作用机制成为mCRPC的一线治疗药物^[4]。

微管蛋白是细胞骨架核心, 主要含 α 、 β 两种类型, 可通过动态组装形成微管结构, 对细胞分裂至关重要; 一旦微管蛋白平衡被干扰, 即可抑制肿瘤细胞有丝分裂, 诱导肿瘤细胞凋亡^[5]。此外, 微管蛋白还参与了雄激素受体(androgen receptor, AR)的核转运过程, AR与雄激素结合后, 可通过微管网络进入细胞核, 推动细胞增殖、迁移及上皮间质转化, 对PCa进展至关重要^[6]。微管蛋白抑制剂可分为两类, 一类是可促进微管蛋白聚合、稳定微管、阻滞细胞周期并诱导细胞凋亡的紫杉烷类药

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物;另一类是可抑制微管聚合、破坏微管蛋白平衡的长春新碱类和秋水仙碱类药物。两类皆不受基因突变和肿瘤免疫环境影响,适用范围广泛,且联合治疗潜力巨大,能与激素类药物、免疫检查点抑制剂等协同增效^[7]。基于此,本文拟对微管蛋白抑制剂在PCa中的应用进展归纳综述,包括临床疗效、联合应用新策略、耐药机制及应对策略等,以期对PCa临床治疗方案的优化提供新思路。

1 微管蛋白抑制剂的临床疗效

1.1 紫杉烷类微管蛋白抑制剂

1.1.1 紫杉醇

作为紫杉烷类药物中首个被应用于癌症化疗的药物,紫杉醇在抗肿瘤研究中展现出重要意义。紫杉醇可通过增加活性氧积累,促进缺氧诱导因子1 α 表达,激活c-Jun N末端激酶/胱天蛋白酶3信号通路,从而促进PCa PC3M细胞凋亡^[8]。紫杉醇虽具有抗肿瘤活性,但不良反应(如周围神经病变、中性粒细胞减少和黏膜炎等)明显,临床应用时需监测其不良反应并调整剂量,因此在用于PCa中受到限制^[9]。虽然相关研究发现紫杉醇与卡铂联合应用耐受性较好^[10],但随着多西他赛等更优药物的出现,紫杉醇被逐渐替代。

1.1.2 多西他赛

多西他赛是一种半合成紫杉醇衍生物,相比于紫杉醇,其对微管蛋白的亲和力更强,血浆半衰期更长,稳定微管的效率更高。在mCRPC治疗中,多西他赛单药治疗的中位总生存(overall survival, OS)期为13.89个月,中位无进展生存(progression-free survival, PFS)期为5.29个月,可显著延长患者生存时间并延缓疾病进展^[11]。即使在多种治疗方案失败后,多西他赛仍对mCRPC患者有效^[12]。一项回顾性研究分析了150例经AR靶向药物治疗失败后的mCRPC患者,发现多西他赛联合卡铂治疗的客观缓解率是多西他赛单药治疗的2.6倍;联合组患者30个月的OS率为70.7%,显著高于多西他赛单药组的38.9%和卡巴他赛单药组的30.3%^[13]。因此,多西他赛可作为AR靶向药物治疗失败后的有效治疗选择。

延长患者从mHSPC进展到mCRPC的时间是改善晚期PCa患者预后的关键。在mHSPC治疗中,3项随机对照试验(CHAARTED、GETUG-15和STAMPEDE研究)证实,多西他赛联合ADT可显著延长患者的OS期[风险比(hazard ratio, HR)=0.79, 95%置信区间(confidence interval, CI)(0.70, 0.88), $P<0.000\ 1$]; PFS期[HR=0.70, 95%CI(0.63, 0.77), $P<0.000\ 1$]和无失败生存(failure-free survival, FFS)期[HR=0.64, 95%CI(0.58, 0.71), $P<0.000\ 1$], 5年绝对改善率为9%~11%^[14]。然

而,多西他赛的疗效受转移瘤体积和临床分期影响,高瘤负荷、临床T4期患者获益最大,治疗第5年时患者的生存获益最为显著[PFS率为27%, 95%CI(17%, 37%); OS率为35%, 95%CI(24%, 47%)],而低瘤负荷合并后续转移患者获益不明显[PFS率为-1%, 95%CI(-15%, 12%); OS率为0%, 95%CI(-10%, 12%)]^[14]。因此,虽然多西他赛可显著延长高瘤负荷mHSPC患者的OS期,但低瘤负荷合并后续转移患者可能还需要其他的治疗方法。

1.1.3 卡巴他赛

卡巴他赛是第2代紫杉烷类抗肿瘤药物,具有强大的细胞毒性和诱导细胞凋亡能力^[15],被美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)推荐为mCRPC在多西他赛和新型激素疗法干预后的首选治疗方案,尤其适用于多西他赛治疗后病情进展的患者^[16]。相比传统紫杉烷类药物,卡巴他赛减少了脱发和外周神经病变等不良反应,但中性粒细胞减少的发生率较高。该不良反应可通过调整剂量有效管理,如将25 mg/m²、每3周1次的给药方案调整为16 mg/m²、每2周1次,可显著降低mCRPC患者3级或以上中性粒细胞减少的发生率(62.5% vs. 5.1%)^[17],这为在不影响卡巴他赛疗效的前提下提供了更安全的治疗选择。另外,卡巴他赛在患者疼痛缓解、生活质量改善等方面相较于AR靶向剂更好,其疼痛缓解率为46%,显著高于阿比特龙/恩杂鲁胺对照组的19%($P<0.000\ 1$);其PCa治疗功能评估问卷总评分中恶化时间的中位数也优于对照组[14.8个月 vs. 8.9个月, HR=0.72, 95%CI(0.44, 1.20), $P=0.21$];其PFS期也显著长于对照组[8.0个月 vs. 3.7个月, HR=0.54, 95%CI(0.40, 0.73), $P<0.001$]^[18]。由此可知,卡巴他赛在mCRPC治疗中疗效显著,可通过优化剂量有效控制不良反应,是mCRPC二线治疗的重要选择。

1.2 长春新碱类微管蛋白抑制剂

1.2.1 长春新碱

长春新碱作为一种经典的抗肿瘤药物,其抗肿瘤效应主要通过抑制微管蛋白聚合来实现。然而,由于其选择性较低且神经毒性较高,故其在PCa治疗中的应用受到限制。近年来,体外及动物模型研究揭示了其联合治疗策略(例如长春新碱与西地那非的联合应用)以及创新性药物递送系统(例如透明质酸包裹的疏醇化壳聚糖纳米制剂)的潜力^[19-20]。研究显示,长春新碱与西地那非联合可显著抑制PCa肿瘤生长,使肿瘤体积减小约80%^[19];上述纳米制剂可将长春新碱的释放时间延长,并降低全身毒性^[20]。此外,溶瘤麻疹病毒与长春新碱联合制成的纳米制剂可显著降低PC3细胞的活力,具有良好

的应用前景^[21]。未来需通过更多临床试验来验证联合治疗及递送系统的安全性和有效性,以期克服长春新碱的毒性限制。

1.2.2 长春瑞滨

长春瑞滨是长春新碱的衍生物,其神经毒性低于长春新碱,骨髓抑制为其剂量限制性毒性。一项Ⅱ期临床试验中,41例化疗耐药的PCa患者接受长春瑞滨(30 mg/d,每周3次)联合地塞米松(1 mg/d)治疗,结果显示,长春瑞滨组患者的中位PFS期为4个月[95%CI(2.8, 6.9)],OS期为17.5个月[95%CI(10.8, 24.5)],且毒性轻微^[22]。一项Ⅰ期临床试验结果显示,替西罗莫司联合长春瑞滨治疗晚期实体瘤的最大耐受剂量为替西罗莫司25 mg(每周1次)和长春瑞滨20 mg/m²(每2周1次);该研究共入组了19例患者,其中2例为PCa患者,结果发现,1例PCa患者的症状部分缓解,1例PCa患者病情稳定,表明上述两药的耐受性良好^[23]。然而,由于样本量太小,后续仍需进一步扩大样本量来探索长春瑞滨与其他药物的协同作用,开发更有效的治疗策略。

1.3 秋水仙碱

秋水仙碱是一种经典的抗有丝分裂药物,其可通过抑制微管蛋白聚合,阻止细胞有丝分裂,诱导细胞凋亡,从而发挥抗肿瘤作用;还可通过抑制NOD样受体蛋白3炎症小体激活,减少肿瘤微环境中的炎症反应,从而抑制肿瘤生长^[24-25]。秋水仙碱可克服多药耐药,尤其是紫杉烷类药物耐药^[26]。研究显示,秋水仙碱对PC3细胞的半数抑制浓度为22.99 ng/mL,可使细胞周期停滞在G₂/M期,降低线粒体膜电位,并提高早期和晚期凋亡细胞比例^[27]。尽管如此,秋水仙碱的临床应用仍受限于其骨髓抑制和胃肠道反应等全身毒性,故尚未获批用于PCa治疗。未来需通过更多临床试验来验证其安全性和有效性,以充分发挥其在PCa治疗中的作用。

2 微管蛋白抑制剂联合疗法在PCa治疗中的新策略

2.1 基于多西他赛的三联疗法

三联疗法中,多西他赛与ADT及AR通路抑制剂联合应用可显著提高抗肿瘤疗效。ARASENS研究结果显示,ADT联合达罗他胺和多西他赛治疗,可显著延长mHSPC患者的OS期[HR=0.68,95%CI(0.57, 0.80)],这一生存获益在各个亚组(包括初治患者、复发患者、高/低肿瘤负荷患者以及高/低危患者)中均保持一致^[28]。日本Ⅲ期ARASENS亚组分析结果进一步证实,三联疗法可显著延缓mHSPC患者进展至mCRPC,且安全性和耐受性良好^[29]。因此,三联疗法已被多项国际指南推荐为mHSPC的标准治疗方案。

2.2 联用免疫检查点抑制剂

近年来,免疫疗法在肿瘤治疗中发展潜力较大,但其在PCa中效果有限,这可能与PCa免疫浸润少、T细胞活性低及程序性死亡受体1(programmed death-1, PD-1)/程序性死亡受体配体1(programmed death-ligand 1, PD-L1)高表达有关^[30]。多西他赛和卡巴他赛能调节免疫微环境,逆转PCa免疫抑制,例如多西他赛可激活环鸟苷酸-腺苷酸合成酶/干扰素基因刺激因子信号通路,促进干扰素传导,增强淋巴细胞浸润^[31]。一项针对30名mCRPC患者的研究显示,多西他赛联合替雷利珠单抗(PD-1抑制剂)治疗相比于替雷利珠单抗单药治疗,可显著延长患者中位PFS期[3.12个月 vs. 1.70个月, $P=0.0044$]^[31]。由此可知,微管蛋白抑制剂与免疫检查点抑制剂联用具有很大潜力,有望改善PCa免疫治疗效果,但需更多临床试验验证。

3 微管蛋白抑制剂在PCa中的耐药机制及解决方案

尽管微管蛋白抑制剂在PCa治疗中取得了显著的临床疗效,但出现的耐药问题限制了其长期应用。其耐药机制复杂,涉及微管蛋白结构改变、药物外排增强等,为此研究者们开发了新型微管蛋白抑制剂(如VERU-111、ABI-231)。笔者总结了微管蛋白抑制剂在PCa中的耐药机制及解决方案,以期为耐药PCa患者提供更有有效的治疗选择。

3.1 微管蛋白抑制剂在PCa中的耐药机制

3.1.1 ABCB1介导的药物外排增加

PCa对微管蛋白抑制剂(尤其是紫杉烷类药物)的耐药性复杂,涉及细胞内在改变和肿瘤微环境,主要耐药机制为三磷酸腺苷(adenosine triphosphate, ATP)结合盒亚家族B成员1(ATP-binding cassette subfamily B member 1, ABCB1)通过水解ATP将抗癌药物泵出肿瘤细胞,降低药物浓度,削弱药效^[32]。研究表明,ABCB1过表达可导致PCa细胞对多西他赛和卡巴他赛耐药,未经化疗的PCa患者ABCB1表达较低,而其经多西他赛治疗后ABCB1表达显著升高^[33]。

3.1.2 微管蛋白亚型表达异常

微管蛋白亚型表达异常,特别是微管蛋白 $\beta 3$ (tubulin $\beta 3$, TUBB3)过表达会加速微管的解聚速率,抑制磷酸酶和张力蛋白同源物的表达,激活磷脂酰肌醇3-激酶/蛋白激酶B信号通路,增强肿瘤细胞耐药性;另外, TUBB3还可介导多西他赛和卡巴他赛的交叉耐药^[34]。因此, TUBB3或将成为紫杉烷类药物的耐药生物标志物,有助于治疗前预测反应,优化治疗方案,避免耐药。

3.1.3 信号通路异常激活

多西他赛耐药PCa细胞中的白细胞介素11(interleukin-11, IL-11)自分泌增加,从而激活Janus激酶1(Janus kinase 1, JAK1)/信号转导及转录活化因子4(signal transducer and activator of transcription 4, STAT4)信号通路,进一步STAT4磷酸化入核并与环磷酸腺苷反应元件结合蛋白结合,调控抗凋亡基因表达,增强肿瘤细胞存活能力和DNA修复能力,从而抵抗多西他赛的细胞毒性作用^[35]。此外,在多西他赛耐药PCa细胞中,Notch3表达上调并与TUBB3结合,从而激活促分裂原活化的蛋白质激酶(mitogen-activated protein kinase, MAPK)信号通路,进而增强耐药性;同时,MAPK信号通路还可调控脂质代谢,改变细胞膜组成和流动性,减少药物摄取和分布^[36]。

3.1.4 脂质代谢重编程

脂质代谢重编程可显著影响PCa对多西他赛的耐药性。与多数肿瘤细胞依赖糖酵解产生能量的Warburg效应不同,PCa细胞主要靠脂肪酸氧化来获取能量^[37]。研究显示,无脂肪饲料喂养可延长PCa异种移植小鼠的OS期,延缓mHSPC向mCRPC转化^[38]。PCa细胞脂代谢紊乱可导致脂肪酸合成酶(fatty acid synthase, FASN)过度表达,驱动脂肪酸合成,从而导致脂质堆积,阻碍靶向微管蛋白的功能,增强耐药性^[39]。

3.2 微管蛋白抑制剂耐药的解决方案

3.2.1 开发新型微管蛋白抑制剂与ABCB1抑制剂

VERU-111是一种新型秋水仙碱类微管蛋白抑制剂,能抑制微管蛋白 β 转录,诱导微管解聚,抗肿瘤效果显著。该药物半数抑制浓度低,非ABCB1底物,对耐药PCa细胞系抗增殖效果显著。在I b/II期试验中,VERU-111表现出良好的耐受性和疗效,中位PFS期达12个月,目前已进入III期研究^[40]。ABI-231同为新型秋水仙碱类微管蛋白抑制剂,能抑制微管蛋白聚合,诱导肿瘤细胞凋亡,克服紫杉醇耐药PC-3细胞的耐药性,脱靶风险低^[41]。此外,已获美国FDA批准的新型ABCB1抑制剂(如elacridar、zosuquidar、laniquidar和tariquidar等)正在开发中,这些药物在实验模型中显示出逆转紫杉烷类药物耐药的潜力,但在II期临床试验中因低特异性和毒性问题,应用有限^[42]。最新研究表明,非ABCB1底物药物吉西他滨对紫杉烷类药物耐药的PCa细胞展现出强烈的细胞毒性,有望为耐药PCa患者提供新的治疗选择^[43]。

3.2.2 联合使用FASN抑制剂与微管蛋白抑制剂

FASN抑制剂与微管蛋白抑制剂的联合使用,为解决PCa对紫杉烷类药物耐药提供了新途径。研究表明,FASN抑制剂(如TVB-3166、Fasnall)与多西他赛在对紫

杉烷类药物耐药的PCa细胞(如PC3-TxR、DU145-TxR细胞)中显示出明显的协同效应,可显著降低肿瘤细胞活力^[44]。这表明FASN抑制剂能有效提升微管靶向药物的抗肿瘤效果,为克服紫杉醇耐药提供了新的治疗思路。

3.2.3 基于PROTAC技术开发降解剂

蛋白质降解靶向嵌合体(proteolysis-targeting chimeras, PROTAC)技术利用细胞的泛素-蛋白酶体系统,促使蛋白质降解来对抗肿瘤耐药,与常规抑制剂相比,不易受突变影响,有望解决传统药物耐药问题^[45]。化合物4f作为一种基于PROTAC技术开发的新型降解剂,可通过降解细胞色素P450 1B1(cytochrome P450 family 1 subfamily B member 1, CYP1B1),显著降低PCa DU145细胞对多西他赛的耐药性,且对CYP1B1的选择性指数为140.1,表现出良好的降解效率和选择性;此外,其生物利用度较高,有望减少非特异性毒性^[46]。这种基于PROTAC技术的靶向降解策略在PCa耐药治疗中具有广阔的应用前景,值得进一步深入研究。

4 总结与展望

靶向微管蛋白的抗癌策略在PCa治疗中潜力显著。紫杉烷类药物(如多西他赛、卡巴他赛)能抑制肿瘤生长并缓解免疫抑制,但长期使用易引发耐药、中性粒细胞减少、神经病变等副作用。为此,研究者们探索了多种新策略:一是开发靶向其他微管蛋白结合位点的药物,包括能够减少体内毒性的纳米制剂(如长春新碱纳米制剂)和能克服TUBB3及ABCB1耐药的新型抑制剂(如秋水仙碱位点抑制剂),但安全性仍需验证;二是采用双靶点策略,联合微管蛋白抑制剂与其他小分子药物,以应对药物外排增加等多重耐药机制,但可能引发新的耐药问题。近年来,PROTAC技术因其独特的蛋白降解机制受到关注,可靶向传统不可成药靶点,有望克服耐药性,然而,基于该技术制备的药物分子量较大,易导致递送困难,后续仍需进一步优化递送系统。

参考文献

- [1] DESAI K, BARALO B, KULKARNI A, et al. Cancer statistics; the United States vs. worldwide[J]. J Clin Oncol, 2024, 42(Suppl.16): e23276.
- [2] XIA C F, DONG X S, LI H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants[J]. Chin Med J (Engl), 2022, 135(5): 584-590.
- [3] FERRETTI S, MERCINELLI C, MARANDINO L, et al. Metastatic castration-resistant prostate cancer: insights on current therapy and promising experimental drugs[J]. Res Rep Urol, 2023, 15: 243-259.
- [4] LOWRANCE W T, MURAD M H, OH W K, et al. Castration-resistant prostate cancer: AUA guideline

- amendment 2018[J]. *J Urol*, 2018, 200(6): 1264-1272.
- [5] CHEN Q H. Crosstalk between microtubule stabilizing agents and prostate cancer[J]. *Cancers (Basel)*, 2023, 15(13):3308.
- [6] WANG L, KONG B, WANG J Q, et al. A novel targeted microtubules transformable nanopeptide system yields strong anti-prostate cancer effects by suppressing nuclear translocation of androgen receptors[J]. *Adv Mater*, 2024, 36(48):e2407826.
- [7] YAKKALA P A, KAMAL A. Dual-targeting inhibitors involving tubulin for the treatment of cancer[J]. *Bioorg Chem*, 2025, 156:108116.
- [8] ZHANG Y, TANG Y D, TANG X Q, et al. Paclitaxel induces the apoptosis of prostate cancer cells via ROS-mediated HIF-1 α expression[J]. *Molecules*, 2022, 27(21):7183.
- [9] CHEN C S, SMITH E M L, STRINGER K A, et al. Co-occurrence and metabolic biomarkers of sensory and motor subtypes of peripheral neuropathy from paclitaxel[J]. *Breast Cancer Res Treat*, 2022, 194(3):551-560.
- [10] KENTEPOZIDIS N, SOULTATI A, GIASSAS S, et al. Paclitaxel in combination with carboplatin as salvage treatment in patients with castration-resistant prostate cancer: a Hellenic oncology research group multicenter phase II study[J]. *Cancer Chemother Pharmacol*, 2012, 70(1):161-168.
- [11] BYEON S, KIM H, KIM J, et al. Docetaxel rechallenge in metastatic castration-resistant prostate cancer: a retrospective, single-center study[J]. *Investig Clin Urol*, 2020, 61(6):588-593.
- [12] 郑军, 郭文浩, 李世健, 等. 多西他赛治疗转移性去势抵抗性前列腺癌患者的剂量选择及预后影响因素分析[J]. *国际泌尿系统杂志*, 2022, 42(4):599-603.
- [13] KWON E D, SHAH P H, et al. Therapeutic sequencing improves outcomes for patients with progressive mCRPC[J]. *Prostate*, 2020, 80:1216-1224.
- [14] VALE C L, FISHER D J, GODOLPHIN P J, et al. Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials[J]. *Lancet Oncol*, 2023, 24(7):783-797.
- [15] CEVIK O, ACIDERELI H, TURUT F A, et al. Cabazitaxel exhibits more favorable molecular changes compared to other taxanes in androgen-independent prostate cancer cells[J]. *J Biochem Mol Toxicol*, 2020, 34(9):e22542.
- [16] SCHAEFFER E M, SRINIVAS S, ADRA N, et al. Prostate cancer, version 4.2023, NCCN clinical practice guidelines in oncology[J]. *J Natl Compr Canc Netw*, 2023, 21(10):1067-1096.
- [17] OUDARD S, RATTI R, VOOG E, et al. Biweekly vs. triweekly cabazitaxel in older patients with metastatic castration-resistant prostate cancer: the CABASTY phase 3 randomized clinical trial[J]. *JAMA Oncol*, 2023, 9(12):1629-1638.
- [18] FIZAZI K, KRAMER G, EYMARD J C, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study[J]. *Lancet Oncol*, 2020, 21(11):1513-1525.
- [19] HSU J L, LEU W J, HSU L C, et al. Phosphodiesterase type 5 inhibitors synergize vincristine in killing castration-resistant prostate cancer through amplifying mitotic arrest signaling[J]. *Front Oncol*, 2020, 10:1274.
- [20] NASEER F, AHMAD T, KOUSAR K, et al. Formulation of surface-functionalized hyaluronic acid-coated thiolated chitosan nano-formulation for the delivery of vincristine in prostate cancer: a multifunctional targeted drug delivery approach[J]. *J Drug Deliv Sci Technol*, 2022, 74:103545.
- [21] ANJUM S, NASEER F, AHMAD T, et al. Co-delivery of oncolytic virus and chemotherapeutic modality: vincristine against prostate cancer treatment: a potent viro-chemotherapeutic approach[J]. *J Med Virol*, 2024, 96(7):e29748.
- [22] DI DESIDERO T, DEROSA L, GALLI L, et al. Clinical, pharmacodynamic and pharmacokinetic results of a prospective phase II study on oral metronomic vinorelbine and dexamethasone in castration-resistant prostate cancer patients[J]. *Invest New Drugs*, 2016, 34(6):760-770.
- [23] PIATEK C I, RAJA G L, JI L Y, et al. Phase I clinical trial of temsirolimus and vinorelbine in advanced solid tumors[J]. *Cancer Chemother Pharmacol*, 2014, 74(6):1227-1234.
- [24] KUREK J, MYSZKOWSKI K, OKULICZ-KOZARYN I, et al. Cytotoxic, analgesic and anti-inflammatory activity of colchicine and its C-10 sulfur containing derivatives[J]. *Sci Rep*, 2021, 11(1):9034.
- [25] HU J X, XU J M, ZHAO J L, et al. Colchicine ameliorates short-term abdominal aortic aneurysms by inhibiting the expression of NLRP3 inflammasome components in mice[J]. *Eur J Pharmacol*, 2024, 964:176297.
- [26] YANG J J, SONG D K, LI B Q, et al. Replacing the tropolonic methoxyl group of colchicine with methylamino increases tubulin binding affinity with improved therapeutic index and overcomes paclitaxel cross-resistance[J]. *Drug*

Resist Updat, 2023, 68; 100951.

- [27] ERGUL M, BAKAR-ATES F. Investigation of molecular mechanisms underlying the antiproliferative effects of colchicine against PC3 prostate cancer cells[J]. Toxicol In Vitro, 2021, 73; 105138.
- [28] HUSSAIN M, TOMBAL B, SAAD F, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial [J]. J Clin Oncol, 2023, 41(20); 3595-3607.
- [29] UEMURA M, KIKUKAWA H, HASHIMOTO Y, et al. Darolutamide in Japanese patients with metastatic hormone-sensitive prostate cancer: phase 3 ARASENS subgroup analysis[J]. Cancer Med, 2024, 13(21); e70029.
- [30] WANG C, ZHANG Y, GAO W Q. The evolving role of immune cells in prostate cancer[J]. Cancer Lett, 2022, 525; 9-21.
- [31] MA Z H, ZHANG W W, DONG B J, et al. Docetaxel remodels prostate cancer immune microenvironment and enhances checkpoint inhibitor-based immunotherapy[J]. Theranostics, 2022, 12(11); 4965-4979.
- [32] CEVATEMRE B, BULUT I, DEDEOGLU B, et al. Exploiting epigenetic targets to overcome taxane resistance in prostate cancer[J]. Cell Death Dis, 2024, 15(2); 132.
- [33] LIMA T S, SOUZA L O, IGLESIAS-GATO D, et al. Itraconazole reverts ABCB1-mediated docetaxel resistance in prostate cancer[J]. Front Pharmacol, 2022, 13; 869461.
- [34] SEKINO Y, HAN X R, KAWAGUCHI T, et al. TUBB3 reverses resistance to docetaxel and cabazitaxel in prostate cancer[J]. Int J Mol Sci, 2019, 20(16); 3936.
- [35] CHENG B S, LI L F, LUO T L, et al. Single-cell deconvolution algorithms analysis unveils autocrine IL11-mediated resistance to docetaxel in prostate cancer via activation of the JAK1/STAT4 pathway[J]. J Exp Clin Cancer Res, 2024, 43(1); 67.
- [36] SUN X C, ZHANG Y, XIN S Y, et al. NOTCH3 promotes docetaxel resistance of prostate cancer cells through regulating TUBB3 and MAPK signaling pathway[J]. Cancer Sci, 2024, 115(2); 412-426.
- [37] ZHANG Z L, WANG W X, KONG P P, et al. New insights into lipid metabolism and prostate cancer: review [J]. Int J Oncol, 2023, 62(6); 74.
- [38] KIM N H, JEGAL J, KIM Y N, et al. The effects of *Aronia melanocarpa* extract on testosterone-induced benign prostatic hyperplasia in rats, and quantitative analysis of major constituents depending on extract conditions[J]. Nutrients, 2020, 12(6); 1575.
- [39] AHMAD F, CHERUKURI M K, CHOYKE P L. Metabolic reprogramming in prostate cancer[J]. Br J Cancer, 2021, 125(9); 1185-1196.
- [40] MARKOWSKI M C, TUTRONE R, PIECZONKA C, et al. A phase I b/II study of sabizabulin, a novel oral cytoskeleton disruptor, in men with metastatic castration-resistant prostate cancer with progression on an androgen receptor-targeting agent[J]. Clin Cancer Res, 2022, 28(13); 2789-2795.
- [41] CHEN H, DENG S S, WANG Y X, et al. Structure-activity relationship study of novel 6-aryl-2-benzoylpyridines as tubulin polymerization inhibitors with potent antiproliferative properties[J]. J Med Chem, 2020, 63(2); 827-846.
- [42] LAI J N, TSENG Y J, CHEN M H, et al. Clinical perspective of FDA approved drugs with P-glycoprotein inhibition activities for potential cancer therapeutics[J]. Front Oncol, 2020, 10; 561936.
- [43] SEO H K, LEE S J, KWON W A, et al. Docetaxel-resistant prostate cancer cells become sensitive to gemcitabine due to the upregulation of ABCB1[J]. Prostate, 2020, 80(6); 453-462.
- [44] SOUCHEK J J, LALIWALA A, HOUSER L, et al. Fatty acid synthase inhibitors enhance microtubule-stabilizing and microtubule-destabilizing drugs in taxane-resistant prostate cancer cells[J]. ACS Pharmacol Transl Sci, 2023, 6(12); 1859-1869.
- [45] YEDLA P, BABALGHITH A O, ANDRA V V, et al. PROTACs in the management of prostate cancer[J]. Molecules, 2023, 28(9); 3698.
- [46] CHEN P, WANG S B, CAO C Y, et al. α -naphthoflavone-derived cytochrome P450 (CYP) 1B1 degraders specific for sensitizing CYP1B1-mediated drug resistance to prostate cancer DU145: structure activity relationship[J]. Bioorg Chem, 2021, 116; 105295.

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