doi:10.3969/j.issn.1006－4931.2021.05.001

吉西他滨的药效学与药动学及其节拍化疗研究进展*

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摘要:目的 综述吉西他滨的药效动力学(简称药效学)与药物代谢动力学(简称药动学)及其在节拍化疗中的研究进展,为临床制定安全有效的给药方案提供借鉴。**方法** 以“gemcitabine”“pharmacodynamics”“pharmacokinetics”“metronomic chemotherapy”为关键词,查询 PubMed 及 Web of Science 等数据库中收录的相关文献,并从药效学作用、药动学过程、节拍化疗中的研究进展 3 个方面进行综述。**结果与结论** 吉西他滨属胞嘧啶核苷类抗肿瘤药物,用于多种实体肿瘤尤其是胰腺癌与肺癌的治疗。吉西他滨是最早应用于节拍化疗的抗肿瘤药物之一,单用或与顺铂、紫杉醇等多种细胞毒类药物联用化疗效果良好,临床疗效显著。

关键词:吉西他滨;药物效应动力学;药物代谢动力学;节拍化疗;疗效

中图分类号:R969.1;R979.1 **文献标志码:**A **文章编号:**1006－4931(2021)05－0001－05

Pharmacodynamics and Pharmacokinetics of Gemcitabine and Its Research Progress in Metronomic Chemotherapy

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Abstract: Objective To review the pharmacodynamics and pharmacokinetics of gemcitabine and its research progress in metronomic chemotherapy, and to provide a reference for the formulation of its safe and effective clinical dosing regimen. **Methods** The "gemcitabine" "pharmacodynamics" "pharmacokinetics" and "metronomic chemotherapy" were taken as keywords to search the relevant documents included in the PubMed and Web of Science databases for reviewing the pharmacodynamic effect, pharmacokinetic process and the research progress of metronomic chemotherapy. **Results and Conclusion** Gemcitabine is a kind of cytosine nucleoside antitumor drug, which is used in the treatment of a variety of solid tumors, especially pancreatic cancer and lung cancer. Gemcitabine is one of the earliest antineoplastic agents used in metronomic chemotherapy, and gemcitabine alone or in combination with various cytotoxic drugs such as cisplatin and paclitaxel has shown good chemotherapy effects and clinical efficacy.

Key words: gemcitabine; pharmacodynamics; pharmacokinetics; metronomic chemotherapy; efficacy

吉西他滨(2′,2′二氟脱氧胞苷,dFdC)为胞嘧啶核苷类抗肿瘤药物,是目前最常用的抗肿瘤化学治疗(简称化疗)药物之一,是胰腺癌治疗的基础性药物,广泛用于乳腺癌、卵巢癌、膀胱癌及非小细胞肺癌等多种实体肿瘤的治疗[1－12],也用于治疗急性白血病等多种血液系统肿瘤[13－15]。其毒副作用相对较轻,还用于儿童恶性肿瘤的化疗方案。化疗通常是以细胞毒性药物为基础,采用最大耐受剂量(MTD)间歇给药,通过抑制或杀死肿瘤细胞而达到阻止肿瘤细胞增殖、浸润和转移的目的,给药间歇期较长,存活的少量肿瘤细胞极有可能重新恢复生长,最终导致抗肿瘤疗效不佳[16]。传统化疗方法通常伴有极其严重的不良反应,较大程度地影响患者的生存质量。HAPEREN 等[17]于 2000 年首次提出与 MTD 治疗方法不同的低剂量节拍化疗方法,即患者通过连续给予远低于 MTD 的化疗药物,最大限度地缩短给药间歇期,达到持久抑制肿瘤生长的目的,减轻化疗药物的毒副作用,进一步提高肿瘤患者的生存质量。吉西他滨是最早应用于节拍化疗的抗肿瘤药物之一,临床疗效显著。为此,以“gemcitabine”“pharmacodynamics”“pharmacokinetics”“metronomic chemotherapy”为关键词,查询 PubMed 及 Web of Science 等数据库中收录的相关文献,综述吉西他滨的药效动力学(简称药效学)作用与药物代谢动力学(简称药动学)过程,以及其在节拍化疗中的研究进展,以期为临床制定安全、有效的给药方案提供借鉴。

1 药效学作用

吉西他滨在细胞内可经脱氧胞苷激酶磷酸化,生成活性二磷酸吉西他滨(dFdCDP)和活性三磷酸吉西他滨(dFdCTP),分别抑制核糖核苷酸还原酶和脱氧核糖核酸(DNA)合成[18]。核糖核苷酸还原酶是核苷酸通路中

*基金项目:国家自然科学基金[81972814]。

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的关键酶之一，对肿瘤细胞的生长至关重要。胞苷脱氨酶的快速失活能导致吉西他滨最终代谢为2′，2′－二氟脱氧尿苷（dFdU）。脱氧胞苷激酶是吉西他滨发挥抗肿瘤活性的限制因素，多个体外模型研究结果均表明，脱氧胞苷激酶的活性与肿瘤耐药的发生关系密切[19－20]，如肿瘤细胞中的脱氧胞苷激酶的活性与肿瘤细胞对吉西他滨的敏感性之间呈明显正相关。因此，可将脱氧胞苷激酶的表达水平作为预测肿瘤细胞对吉西他滨药物敏感性的指标[21]。

活性dFdCDP通过抑制核糖核苷酸还原酶来诱导三磷酸脱氧核苷的消耗，阻断DNA的合成[22]。活性dFdCTP既能掺入DNA中抑制3′5′－核酸外切酶活性，阻止DNA修复，导致S期细胞发生周期特异性停滞和凋亡；也能掺入核糖核酸（RNA）中抑制RNA合成，从而发挥抗肿瘤作用[23－24]。具体作用机制见图1。

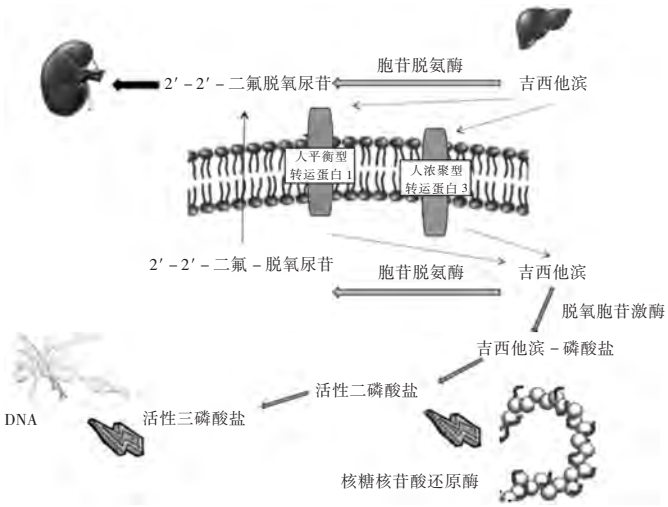

图1 吉西他滨的抗肿瘤作用机制

Fig. 1 Antitumor mechanism of gemcitabine

在高浓度下，dFdU会产生细胞毒性[25－26]，且其具有放射致敏作用。因此，在单独或与放疗等治疗方法联用时，应关注吉西他滨此类作用的影响[27]。

2 药动学过程

2.1 代谢过程

吉西他滨具有亲水性，不易通过扩散进入细胞，多通过膜核苷转运蛋白进行转运[28]。吉西他滨通过胞嘧啶核苷脱氨酶的催化反应最终代谢为dFdU，大部分能在肝脏中被快速代谢，在血液中的代谢较为缓慢。此外，约10%未被代谢的吉西他滨可经肾脏滤过排出[29]。

2.2 单用时的药动学特征

吉西他滨的体内过程个体差异明显。以标准临床输注方案给药，吉西他滨的血浆浓度通常在15～30 min后达到稳态水平。在40～3 650 mg/m^{2}剂量下呈线性药动学过程，当剂量高于3 650 mg/m^{2}时，血浆浓度的线性关系将消失，更高剂量下则呈现非线性药动学过程[29－31]。吉西他滨给药剂量为800，1 000，1 250，2 350，5 700 mg/m^{2}时，达到稳态时的血浆浓度分别为24，32，50～70，68～79，320～512 μmol/L。

吉西他滨在血浆中的清除速度[半衰期（$t_{1/2}$）为5～20 min]很快，在给药后最初的24 h内，超过75%的吉西他滨被代谢为dFdU，并从尿液中排出。吉西他滨的清除率与线性范围内的剂量（最高3 650 mg/m^2）无关，与肌酐清除率成正比，且男性的清除率通常较高，是女性的1.5倍[19]。吉西他滨代谢产物dFdU的$t_{1/2}$为2～24 h，给药1周后体内的药物浓度仍大于1 μmol/L[32]。由于不能与血浆蛋白质结合，血浆中的dFdU浓度可高达460 μmol/L[19]。

2.3 联用时的药动学特征

吉西他滨常与其他细胞毒性药物或靶向药物联用，有研究观察了联合用药对吉西他滨药动学特征的影响。在吉西他滨与顺铂或紫杉醇的联用中，未发现顺铂与紫杉醇对吉西他滨和其代谢产物dFdU的药动学过程有任何影响[33－34]；未观察到血管内皮生长因子受体（VEGFR）抑制剂SU5416对吉西他滨的药动学产生影响[35]；硼替佐米对细胞内吉西他滨具有活化的选择性作用[36]。吉西他滨也有可能对其他药物产生影响，如可增强顺铂加合物的形成等[33]。

2.4 代谢产物活性dFdCTP的药动学特征

dFdCTP通过抑制肿瘤细胞DNA的合成而发挥抗肿瘤作用。应用吉西他滨治疗时，肿瘤细胞内的dFdCTP会不断增加，并可达到饱和状态。当吉西他滨的血浆浓度为20 μmol/L时，细胞内dFdCTP的形成速度最快[37－38]，并以10 mg/（m^2·min）的速率进行输注能实现肿瘤细胞内dFdCTP的最佳蓄积[30，38]。因此，许多临床试验拟通过延长吉西他滨的输注时间及增加药物剂量来获得最佳疗效[39－40]。可见，吉西他滨的抗肿瘤疗效有时间依赖性。吉西他滨在体内的驻留时间较长，可获得最佳的抗肿瘤疗效，且毒副作用较少，因此口服给药可能更有益[41]。口服吉西他滨制剂的生物利用度低，首次通过清除率高，胃肠道毒性（包括恶心呕吐和腹泻）较强，临床仍多采用注射给药方式。

3 节拍化疗中的研究进展

3.1 作用机制

在诸多恶性肿瘤的治疗中，吉西他滨的节拍化疗给药方案能显著降低肿瘤组织中各种促血管生成分子蛋白的表达水平，且能诱导肿瘤相关成纤维细胞的凋亡[42]。因此，与最大耐受剂量给药方案相比，吉西他滨节拍化疗对恶性肿瘤的治疗具有良好的耐受性与疗效。

目前，人们对吉西他滨节拍化疗作用机制的认识尚不全面。吉西他滨节拍化疗是通过抑制肿瘤血管新生而发挥抗肿瘤作用[42]，这可能是因其能引起体内抗肿瘤 T 细胞免疫[43]。

抗肿瘤血管新生作用：血管内皮生长因子（VEGF）在肿瘤发生、生长和转移过程中发挥重要作用，是促进血管新生最关键的生长因子。在裸鼠胰腺癌模型上，吉西他滨节拍化疗（每周 2 次）能影响肿瘤血管新生，且能下调促血管生成因子的表达，显著抑制肿瘤细胞的生长速度[42]。

免疫调节作用：吉西他滨的活性代谢产物杀伤免疫细胞的过程可影响体内免疫应答的各个阶段，因而吉西他滨也被视为一种免疫抑制剂。吉西他滨对免疫系统的作用过程较复杂，而有关节拍化疗对免疫系统作用的研究鲜有报道。近年来，人们逐渐意识到免疫系统在节拍化疗中的重要作用。在小鼠肿瘤模型中，采用吉西他滨每隔 4 d 给予 50 mg/kg 的给药方案，与对照组比较，肿瘤的生长速度明显减慢，且体内 T 细胞的功能没有受到损害。表明吉西他滨的节拍化疗能缓解 T 细胞介导的免疫抑制，并在体内引起抗肿瘤 T 细胞免疫，从而发挥抗肿瘤作用[43]。

减少骨髓源性抑制细胞的数量：随着人们对肿瘤微环境研究的不断深入，骨髓源性抑制细胞（MDSCs）在肿瘤发展过程中的作用越来越受到关注。MDSCs 是由未成熟的髓系细胞组成的异质性细胞群体，MDSCs 的标志物为 $Gr1^+CD11b$，在调控肿瘤患者的免疫功能中扮演着关键角色。一项基础研究显示，经吉西他滨节拍化疗方案给药后，通过流式细胞术检测荷瘤小鼠外周血中 MDSCs 的标志物 $Gr1^+CD11b$，结果与对照组比较，外周血中的 $Gr1^+CD11b$ 明显降低。可见，吉西他滨节拍化疗可通过减少 MDSCs 的数量，促进抗肿瘤相关的免疫应答，从而抑制肿瘤细胞的生长[43]。

3.2 临床应用

节拍化疗：肾癌是一种与血管生成密切相关的肿瘤。GNONI 等[44]评估了西班牙医疗中心 40 例患者采用吉西他滨节拍化疗方案（500 mg/m^2，每天 2 次，持续 14 d）治疗肾癌的临床效果，结果总有效率有所提升，其整体生存率和无进展生存期也有明显改善，患者耐受性良好，毒副反应低。膀胱癌的发生与多种危险因素有关，包括吸烟、职业暴露和糖尿病等。吉西他滨节拍化疗能使难治性或复发性膀胱癌患者得到可观的总体反应率，治疗胰腺癌疗效显著，能抑制肿瘤血管新生，且患者耐受性良好，毒性反应低[45]。

节拍化疗联合给药：贝伐单抗是吉西他滨节拍化疗联合给药中最常见的一种抗血管新生药物。一项评估吉西他滨节拍给药联合贝伐单抗治疗非小细胞肺癌的疗效研究显示，接受治疗的患者整体生存率和无进展生存期均显著改善，且未发生严重的骨髓抑制、胃肠道、神经系统等毒副作用[46]。此外，BERRUTI 等[47]分别对吉西他滨与 5－氟尿嘧啶、卡培他滨节拍化疗联用治疗肾癌的疗效进行了研究，结果表明，接受治疗的患者耐受性良好，毒副反应低，且无进展生存期也得到一定改善。

3.3 药动学－药效学（PK－PD）模型应用

由于缺乏必要的研究和理论指导，临床开展节拍化疗不得不依赖经验用药，为了建立精准的治疗方案，PK－PD 结合的数学模型应运而生[48－49]。20 世纪 80 年代，UNADKAT 等[50]将药动学和药效学结合起来，成功解释了筒箭毒碱药效滞后于血药浓度的现象，是 PK－PD 模型理论发展的里程碑。CICCOLINI 等[51]建立了吉西他滨节拍化疗的 PK－PD 数学模型，在诸多治疗方案中通过计算机模拟选择最佳治疗方案，并在荷瘤小鼠体内实验中进行了验证，确定了吉西他滨节拍化疗的最佳给药剂量为 0.5～1.0 mg/kg。

4 展望

吉西他滨是众多临床抗肿瘤治疗方案中的基础药物，为了提高其抗肿瘤活性，降低毒性，研究者拟探究其在体内外水平上各反应分子的活化步骤，以及药效学、药动学和胞苷脱氨酶活性[52－54]，而这些研究不仅可能成为接受吉西他滨化疗患者预后的有效指标，也可能开发出新型化学衍生物、前药或纳米药物[53,55]。

另外，虽然有关吉西他滨节拍化疗的研究仍有一定局限性，但在临床应用中也充分体现了其强大的潜力。通过探索其节拍化疗的作用机制，能更好地指导临床用药，可为临床制订安全、有效的化疗方案提供借鉴。

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(收稿日期:2020 – 06 – 16;修回日期:2020 – 08 – 28)