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· 综述 ·

伊马替尼在儿童慢性粒细胞白血病的药动学研究进展

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Pharmacokinetic Research Progress of Imatinib in Pediatric Chronic Myeloid Leukemia

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伊马替尼(imatinib,IMA)是一种酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI),对肿瘤相关靶点具有明显的抑制作用,能够有效治疗儿童慢性粒细胞白血病(chronic myeloid leukemia,CML)。目前,IMA 在儿童 CML 的药效学与药动学数据较少。笔者以"imatinib""pediatric patients""chronic myeloid leukemia""pharmacodynamics""pharmacokinetics"为关键词,查询 PubMed 及 Web of Science 等数据库,就 IMA 在儿童 CML 的药动学研究进展作一综述,为制定合理的用药方案提供参考。

1 TKI 治疗 CML 的研究概况

IMA 在成功治疗成人 CML 之后,也逐步应用于儿童(<18 岁)CML[1-2]。TKI 是目前肿瘤靶向治疗的主要手段,主要通过与酪氨酸激酶 ABL-1 的三磷酸腺苷(ATP)竞争,抑制 CML 的致癌融合基因产物 BCR-ABL-1 而发挥作用[3]。IMA 之所以能够有效治疗 CML,不仅是因为其对肿瘤相关靶点的抑制作用,还与其药动学特征有关[4]。IMA 口服给药后可迅速吸收,生物利用度达 98%且不受食物的影响[5]。肝药酶 CYP450 能够使 IMA 去甲基化生成 *N*-去甲基伊马替尼(CGP 74588),也会抑制酪氨酸激酶的活性[6-7]。IMA 的药动学特征个体间差异较大,而在个体内差异较小,因而需要进行治疗药物监测。此外,IMA 血药浓度与治疗效果关系密切:IMA 血药浓度>1 μg/mL 时,在成人显现出良好的治疗效果[8],

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但尚未在儿童 CML 中得到验证。因此,对于使用 IMA 治疗后疗效不理想或治疗失败的 CML 应进行血药浓度监测,以排除血药浓度过低,而使用 IMA 后的不良反应则可能与血药浓度过高有关[8-9]。

尽管 IMA 用于 CML 临床疗效显著,但由于耐药性的产生及患者不耐受,仍有约 1/3 接受 IMA 治疗的儿科患者因疗效不佳而终止治疗,耐药性按照发病时间可分为原发性耐药和继发性耐药[10-12]。有研究[13]显示,约 5%的 CML 患儿因 BCR-ABL1 激酶域突变引起耐药,导致 IMA 敏感性降低。如果减量治疗依旧发生毒性反应,就可诊断患者对 IMA 不耐受[14-15]。IMA 仍是目前获批用于儿童 CML 的唯一 TKI。为提高耐受性并降低耐药性,现已经开发出新一代的 TKI,如达沙替尼、尼罗替尼、博舒替尼和波纳替尼,并已获准用于成人 CML。这些 TKI 均以 BCR-ABL1 的 ATP 结合口袋为靶点,而仅在亲和力方面存在差异[16]。有研究[7]表明,多种 CYP450 单加氧酶参与 TKI 的代谢过程,并且遗传、药物相互作用和食物摄入等因素可能影响其活性。所有 TKI 都具有较高的血浆蛋白结合率,且细胞内的 TKI 浓度受药物转运蛋白的调节,即外排泵和摄取泵。

2 IMA 在儿童的药动学特征

IMA 目前可供选择的剂型仅有薄膜包衣片,尚无可根据儿童体质量或体表面积给药的液体剂型。IMA 应在每天早餐后的同一时间服用。然而,对于儿科患者,晚上入睡前服用 IMA 能够减少不良反应(如恶心、呕吐)的发生[17]。IMA 具有局部刺激作用,建议以坐姿使用温水(250 mL;<3 岁至少 120 mL)辅助服药。对于年龄较小的患儿,鉴于其无法吞服完整的药片,可以考虑将药物片剂研末,然后分散在适量温水或苹果汁中,或将药物粉末与苹果泥或酸奶混合后服用。这是因为苹果汁或苹果泥的 pH 约为 3.5,而 IMA 在酸性条件下溶解度增加,可以促进吸收。相关研究[18-19]表明,患儿服用 IMA 之后,7 d 血药浓度才能达到稳定状态,慢性期/晚期 CML 患儿推荐的剂量分别为 260 mg/m^2 和 340 mg/m^2,与成人 CML 推荐剂量相当;IMA 及其活性代谢产物 CGP 74588 在儿童的药动学特征与成人一致,单室模型能够充分反映 IMA 的血药浓度,而 CGP 74588 则在双室药动学模型中则有更好的体现;当 IMA 的剂量达到 570 mg/m^2(小于最大耐受剂量)时,患儿的耐受性良好。因此,推荐 CML 患儿的起始剂量为 260 mg/m^2 或 340 mg/m^2,加速发展期为 400 mg/m^2,急性期为 500 mg/m^2[17],并建议将每日剂量分成 2 等份进行服用[20]。

儿童 CML 中位年龄在 11~13 岁,发病率与年龄呈正相关[2]。当前婴幼儿 CML 的治疗经验较少,仅有 2 例分别来自中国和巴西的 1 岁婴幼儿及 1 例来自美国的 15 个月婴幼儿[21-23]。有研究[23]显示,每日给予 100 mg(1 岁婴幼儿)或 200 mg(15 个月婴幼儿)IMA,耐受性良好;尚无婴幼儿 CML 的药动学参数与稳态血药浓度数据。

在 IMA 产生的靶外副作用中,75%成年 CML 的体质量指数(BMI)增加,从而引发了关于 IMA 药时曲线下面积(AUC)是否与体质量相关的讨论[24-26]。一项 CML-PAED 前瞻性试验[27]结果表明,41%(23/56)患儿的 BMI 增加,体质量是目前发现的唯一能显著影响 CML 患儿 IMA 清除率的协变量,个体间差异从 52%降至 32%。然而,该研究并未评价急性期 CML α_1-酸性糖蛋白(AGP)水平的变化。

2.1 吸收

无论成人还是儿童 CML,IMA 口服给药生物利用度为 98%,且不受食物或抗酸剂的影响[5,7,18,28]。此外,反复给药也不会显著影响药动学特征,但患儿个体差异会严重影响临床疗效[29]。有研究[30]表明,IMA 的再吸收不受膳食成分(脂肪、蛋白质等)影响。目前已发现葡萄柚汁可通过降低 CYP3A4 的活性增加药物(环孢素、硝苯地平、西地那非、三唑仑等)的血液浓度,而 IMA 也被 CYP3A4 代谢[31]。个体间 CYP3A4 的表达和活性存在很大的差异。一项关于 10 例 CML 患儿同时服用 250 mL 葡萄柚汁的试验结果表明,IMA 的药动学特征并未受到服用葡萄柚汁的影响[32]。另有研究[33]指出,成人 CML 患者饮用含人参(抑制 CYP3A4)的能量饮料能够引起迟发性 IMA 肝毒性。不仅大多数成人将中草药饮品作为补充药物服用,恶性疾病患儿也如此[34],这显然具有用药安全隐患。例如,圣约翰草虽是一种较温和的抗抑郁药,但其可通过诱导 CYP3A4 来降低 IMA 的血液浓度,使 IMA 疗效大大降低[35]。由于药物相互作用可能很强烈,且用药经验有限,强烈建议接受 IMA 治疗的患儿避免使用其他药物。

2.2 分布

IMA 约 95%与血浆蛋白结合,尤其是白蛋白和酸性糖蛋白(AGP)。高 AGP 水平导致 IMA 和 CGP 74588 的血浆未结合部分较低,因此它们的肝脏清除率较低[19]。与对照组相比,组织培养基中 1.5 mg/mL 的高 AGP 水平(正常为 0.5~1.2 mg/mL)在体外使 CML 胚细胞中 IMA 的细胞内浓度降低至<10%[36]。IMA 的表观分布容积适中,为 2~4 L/kg[23]。药物难以渗透到中枢神经系统[37];跨膜多药耐药转运蛋白 ABCB1 和 ABCG2 被认为可以减少中枢神经系统对 IMA 的摄取,因为在动物研究中,它们的抑制作用使中枢神经系统穿透力增加了 2~10 倍[38-40]。有研究表明可能与药物遗传学相关,中国 CML 患儿在给定剂量下的 IMA 血浆浓度高于白种人[41]。显然,在 IMA 分布中,治疗 CML 患儿成功的决定性因素是细胞对 IMA 的摄取[42]。细胞药物摄取主要是由 hOCT1 介导的,有机阴离子转运多肽 1A2(OATP1A2)在一定程度上介导[43-44]。

2.3 代谢

IMA 主要通过 CYP450 转化成活性代谢产物 CGP 74588,与 IMA 发挥相同的药理作用[19]。CYP3A4、CYP3A5 与 CYP2C8 主要参与 IMA 母体药物的代谢,其

他酶如 CYP1A2、CYP2D6、CYP2C9 和 CYP2C19 可能只起到次要的作用[45]。无论是成人还是儿童患者，CGP 74588 稳态血药浓度在 IMA 的 5%～35%范围内[18,46-47]。有研究[48]显示，在成人患者稳态血药浓度中，CGP 74588/IMA 值为 0.69，个体间变异性为 71%，个体内变异性为 43%。另有研究[49-50]表明，在患者接受 12 个月的慢性治疗后，IMA 的清除率与最初相比增加了 33%。其原因可能与参与 IMA 代谢的酶和转运蛋白的上调有关。此外，儿科患者数据显示，CGP 74588 的血药浓度水平也是随着时间的推移而降低，且无法根据目前潜在机制得出明确的结论[51]。然而，儿科患者中比较常见的疗效不佳可以使用此种现象来解释。众所周知，CYP3A4 诱导剂或抑制剂的联合用药会对 IMA 的代谢产生影响。虽然 CYP3A4 诱导剂（如苯妥英钠、利福平等）可减少 IMA 的暴露，但抑制剂（如酮康唑）将增加血药浓度水平，并可能增加母体药物的毒性[29,52]。IMA 本身是强效的 CYP3A4 抑制剂，因此与其共同给药的药物（如环孢素、辛伐他汀等），它们的清除率可大大降低[53-54]。此外，儿科患者经常使用的药物如蛋白泵抑制剂和抗糖尿病药也会影响 IMA 的代谢[7,55]。

2.4　排泄

IMA 半衰期为 14～23 h[5,37,56]。在儿科患者中，CGP 74588 的消除时间在给药第一天的 11～27 h，达到稳态血药浓度的时间约为 16 h，与 IMA 相似[18]。儿科患者的这一消除参数与成人患者并不同，成人患者中 CGP 74588 的消除时间比母体药物长。鉴于 CGP 74588 对 BCR-ABL1 的抑制作用与 IMA 有着相同的效果，推测 CGP 74588 在儿科患者中发挥抗白血病活性的作用可能弱于成人患者[46]。有关儿童患者进行单剂量摄入 ^{14}C 放射标记 IMA 1 周后的研究显示，80%的剂量已被排泄，主要排泄方式是粪便（67%），少数通过尿液（13%）排出[57-58]。

3　展望

IMA 在儿科 CML 治疗中发挥着重要作用，为提高其抗肿瘤活性，降低毒性且获得良好的耐受性，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[59-62]，而这些研究不仅可能成为接受 IMA 化疗患者预后的有效指标，也可能开发出新型化学衍生物。另外，有关 IMA 在我国儿科 CML 治疗中的研究较少，故目前临床用药方案的调整均需借鉴国外的治疗方案，因此，通过探讨 IMA 的药效学特征、药动学过程，能够更好地指导儿科 CML 临床用药，为临床制定安全、有效的化疗方案提供借鉴。

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· 综述 ·

原发性高草酸尿症 1 型发病机制研究进展

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Progress of Pathogenesis of Primary Hyperoxaluria Type 1

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原发性高草酸尿症(primary hyperoxalurias,PH)是一种罕见的由于肝细胞内乙醛酸代谢缺陷导致内源性草酸生成过多的常染色体隐性遗传病,主要表现为反复尿路结石、肾钙质沉着症及进行性肾功能损害。PH 有 3 种临床类型:PH1、PH2、PH3。其中,PH1 最常见和最严重,由 *AGXT* 基因编码的丙氨酸乙醛酸氨基转移酶

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