

卡培他滨治疗结直肠癌的毒效标志物的研究进展

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摘要: 结直肠癌是临床较常见的恶性肿瘤之一, 给社会带来沉重的负担。卡培他滨是口服氟尿嘧啶类前体药物, 用于多种恶性肿瘤的化疗。化疗中, 原发性和继发性耐药仍然较为普遍, 且个体差异大, 因剂量限制性毒性而导致的延迟给药和降低剂量, 影响了生存预后。当前, 随着精准医疗的发展, 许多卡培他滨毒效和疗效的标志物被发现。近年来有关卡培他滨治疗结直肠癌的毒效标志物主要有临床病理指标、代谢酶表达、基因多态、表观遗传学和代谢组学的预测指标。分析表明单一指标的预测准确度不高, 而联合各类预测指标建立的模型有可能显著提高毒效预测的准确度。

关键词: 卡培他滨; 氟尿嘧啶; 结直肠癌; 药物基因组学; 基因多态性; 毒性反应

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Research progress on toxicity and prognostic markers of capecitabine in treatment of colorectal cancer

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Abstract: Colorectal cancer is one of the most common malignant tumors in clinical, which brings heavy burden to society. Capecitabine is an oral pro-drug of 5-fluorouracil, which is used in the treatment of various malignancy. Primary and secondary drug resistance is still common in the chemotherapy, and the inter-individual difference is great. Delayed remedy and reduced dose caused by dose-limiting toxicity affected prognosis. The recent studies of toxicity and prognostic markers of capecitabine in treatment of colorectal cancer are mainly from clinicopathological index, metabolic enzyme expression, gene polymorphism, epigenetics, and metabolomics. The analysis shows that the accuracy of single marker is not high, and the model established by combining various predictive markers may significantly improve the accuracy of toxicity and prognostic prediction.

Key words: capecitabine; 5-fluorouracil; colorectal cancer; pharmacogenomics; gene polymorphism; toxicity

结直肠癌是临床上较常见的恶性肿瘤之一, 发病率在女性中居第2位, 男性中居第3位, 给社会带来沉重的负担^[1]。卡培他滨是口服的治疗结直肠癌的氟尿嘧啶类药物, 与氟尿嘧啶相比, 卡培他滨的疗效相当, 且副反应可控, 致死率较氟尿嘧啶低, 使用更安全、方便^[2-3]。然而, 与其他化疗药物一样, 卡培他滨也面临着临床难题。一方面, 结直肠癌对

卡培他滨的原发性和继发性耐药仍然较为普遍, 且个体差异大; 另一方面, 因剂量限制性毒性导致的延迟给药或降低剂量, 影响了生存预后^[4]。虽然年龄、身体状态等临床病理特征和给药剂量、频率等治疗因素可以解释个体化差异的一部分原因, 但不能阐述其根源。因此, 研究卡培他滨治疗结直肠癌的毒效标志物及作用机制, 识别出最有可能受益

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的特定个体,是实现精准治疗的需要。

卡培他滨是氟尿嘧啶的前体药物,经肝脏或肿瘤内的羧酸酯酶(CES)、胞嘧啶核苷脱氨酶(CDA)和胸苷磷酸化酶(TYMP)三步作用生成氟尿嘧啶^[3]。在肿瘤细胞内,氟尿嘧啶经乳清酸磷酸核糖基转移酶(OPRT)直接转化为一磷酸氟尿苷(FUMP),或经尿苷磷酸化酶和尿苷激酶两步反应生成FUMP,FUMP再经两步磷酸化分别生成二磷酸氟尿苷(FUDP)和三磷酸氟尿嘧啶(FUTP)。FUDP去磷酸化生成一磷酸脱氧氟尿苷(FdUMP),FdUMP通过抑制肿瘤细胞内的胸苷酸合酶(TYMS)进而干扰DNA的复制、合成和修复。FUDP经还原和磷酸化反应生成三磷酸氟脱氧尿苷(FdUTP),FUTP、FdUTP可分别掺入RNA和DNA中,破坏核酸结构,促进细胞死亡^[5]。氟尿嘧啶在肝脏内经二氢嘧啶脱氢酶(DPD)等分解为氟代 β -丙氨酸(FBAL),最终经尿液排泄^[6]。

目前,氟尿嘧啶治疗结直肠癌的毒效标志物的相关研究较多,但是这些标志物在卡培他滨治疗中的验证相对较少。卡培他滨毒效标志物的研究主要围绕着代谢过程展开,包括影响药物代谢的临床病理学差异和代谢酶的水平,以及影响代谢酶表达的基因多态、表观遗传学等标志物。本文主要探讨卡培他滨治疗结直肠癌的毒性反应和疗效标志物的研究现状。

1 临床病理学指标

部分早期的研究表明临床病理学指标与卡培他滨毒性相关。Ilich等^[7]的研究显示结直肠癌辅助化疗的患者中,女性更易产生毒性,风险比(OR)为2.04。Cassidy等^[8]和Poole等^[9]显示肌酐清除率与卡培他滨毒性风险成反比。Meulendijks等^[10]的一项大样本回顾性研究证实:肾功能、体表面积、年龄、治疗前血浆尿嘧啶浓度是3级以上毒性反应的独立预测因子,OR分别为0.85/(10 mL min⁻¹ 1.73⁻¹ m⁻²)、0.33 /m²、1.14/10年、2.41/(10 ng mL⁻¹),年龄与致死性的毒性相关,OR为5.75,曲线下面积(AUC)为0.690。尚未有研究证实这些临床病理指标与卡培他滨疗效相关。

临床病理学指标影响卡培他滨毒性的机制,推测与卡培他滨的代谢能力相关。Ilich等^[7]推测卡培他滨是水溶性药物,因此去脂肪体质量低的女性较男性代谢慢,易产生毒性。Gieschke等^[11]和Cassidy等^[12]的研究证实:年龄、性别、体表面积、肌酐清

除率与卡培他滨代谢产物5'-DFUR和FBAL的浓度存在关联,推测老年人、女性、体表面积小、肌酐清除率低的患者肾脏代谢卡培他滨的能力弱,所以易产生毒性。由于这些临床病理学指标并不是产生卡培他滨毒性的直接因素,因此尽管有一定的预测价值,但敏感度和特异度不高,预测价值有限。

2 代谢酶表达水平

影响药物毒效的直接因素是代谢酶的活性,因此,早期卡培他滨毒效标志物的研究常常围绕代谢关键酶,如DPD、TYMP、CDA等表达进行。人体内70%~90%氟尿嘧啶会通过DPD分解代谢^[13],因此DPD基因的表达是卡培他滨毒效标志物的研究重点。Miriam等^[14]报道肿瘤组织中DPD蛋白的浓度与PFS和OS相关,DPD低浓度的患者具有更好的预后[无进展生存期(PFS):8.9 vs 7.2个月,总生存期(OS):21.5 vs 16.9个月]。Vallbøhm等^[15]也发现肿瘤组织中DPD mRNA高水平的患者更易卡培他滨耐药,而低mRNA水平患者的PFS更长。

其他关键酶也存在类似的研究,Uchida等^[16]发现结直肠癌转移灶中TYMS、DPD、ERCC1、TYMP的mRNA水平较原发灶高,原发灶的TYMS mRNA高水平与早期进展有关(43% vs 17%),而转移灶TS mRNA低表达患者总生存期更长(417 vs 294 d);原发灶ERCC1 mRNA高水平与耐药有关[治疗失败时间(TTF):85 vs 162 d]。Miriam等^[14]的研究同时发现间质细胞OPRT蛋白高含量的患者生存获益(OS:21.5 vs 17.2个月)。Lindebjerg等^[17]研究发现肿瘤组织中TYMS蛋白的含量与卡培他滨响应相关。Meropol等^[18]研究发现TYMP的表达与卡培他滨响应相关。

虽然这些关键酶的表达可以作为卡培他滨的疗效标志物,但是预测价值仍然不理想,而且缺乏毒性标志物的相关研究。

3 基因多态标志物

相比代谢酶基因的表达,基因的多态性更能反映个体化的差异。因此,随着基因测序技术的发展,基因多态标志物的研究成为了热点。据报道,存在50余种与DPD有关的突变位点,导致约5%人群体内DPD缺乏活性^[19-20]。Deenen等^[21]发现:DPD c.1905+1G>A(*2A, IVS14+1G>A, rs3918290)、c.2846A>T(rs67376798)、c.1236G>A、c.2194G>A(rs1801160)和c.496A>G(rs2297595)突变位点与腹泻相关,c.496A>G位点与2~3级手足综合征

(HFS) 相关, c.1905+1G>A 位点的患者全部出现 3~4 级毒性反应。该研究同时指出: 单个位点的突变与总生存率无关, 而单倍型与总存活率相关。Pellicer 等^[22]发现 DPD 内含子 rs12119882 位点, 以及与 DPD 毗邻的 ENOSF1 基因 rs699517 位点突变也与毒性相关。Rosmarin 等^[23]报道 DPD 内含子 rs12132152 和 rs12022243 位点, ENOSF1 基因 rs2612091 内含子位点也与卡培他滨毒性相关。Loganayagam 等^[24]和 Rosmarin 等^[25]的研究证实了 DPD c.1905+1G>A 和 c.2846A>T 位点的预测毒性的能力, Loganayagam 等^[24]同时还发现了 c.1601G>A (rs1801158) 和 c.1679T>G (rs55886062) 位点与 3~4 级毒性相关。Falvella 等^[26]也证实发现 DPD c.496A>G 位点突变与毒性相关。随后, Deenen 等^[27]一项更大样本的研究证实了 DPD c.1905+1G>A 和 c.1236G>A 与卡培他滨毒性相关突变, 其中, c.1905+1G>A 与威胁生命的严重毒性密切相关, 可指导剂量的调整, 提高卡培他滨个体治疗的安全性。

其他代谢关键酶的基因多态性标志物也相继被发现, Loganayagam 等^[24]报道了 TYMS c.1494del6b (rs34489327) 纯合体型与严重毒性相关, 甲基四氢叶酸还原酶(MTHFR)基因 c.1298C>A(rs1801131) 纯合体型可预测手足综合征, CDA c.-92A>G (rs602950) 和 c.-451C>T (rs532545) 联合突变可预测 2~4 级腹泻。Pellicer 等^[22]报道了 TYMS rs2853741, CDA c.435C>T (rs1048977)、c.79A>C (rs2072671) 和 rs12726436, SLC22A7 c.1269C>T (rs2270860) 和 rs4149178, 以及 UMPS rs2279199 和 rs4678145 位点与卡培他滨毒性相关。Jennings 等^[28]报道了 TYMP c.1412C>T (rs11479) 与卡培他滨严重毒性相关。García-González 等^[29]和 Gonzalez-Haba 等^[30]报道了 CDA c.79A>C (rs2072671) 和 ABCB1 c.3435T>C (rs1045642)、c.1236C>T(rs1128503) 位点与卡培他滨毒性相关, Caronia 等^[31]也证实了 CDA 基因 c.-451C>T 位点与 HFS 的相关性, 并且其连锁突变位点 rs3215400 与 HFS 的关联更强, 该位点突变可以增强约 5.7 倍 CDA mRNA 的表达。

相比代谢酶表达水平的检测, 基因多态的检测更为简单、侵袭性更小。但是, 基因多态的标志物仍然面临着敏感性和特异性低的问题。而多个位点的联合检测可能显著提高预测的准确度, 但这也意味着需要更大的样本量。

4 表观遗传学标志物

基因的表达不仅取决于核酸的序列, 还受表观遗传学的调节。因此卡培他滨的毒效还可能受表观遗传的影响。Min 等^[32]研究显示 CpG 岛甲基化表型 (CIMP) 高的患者接受氟尿嘧啶类药物辅助化疗可获得更长的无复发生存期 (RFS)。Noguchi 等^[33]和 Ezzeldin 等^[34]研究发现不少 DPD 蛋白缺乏的患者未检测出 DPD 的突变, 但在非编码区的启动子的高甲基化下调了 DPD 的表达, 影响着肿瘤细胞对氟尿嘧啶的响应及毒性。然而, Amstutz 等^[35]和 Savva-Bordalo 等^[36]研究却表明, DPD 启动子高甲基化不是氟尿嘧啶化疗严重毒性的预后因素。当前, 缺乏 CpG 岛甲基化标志物在卡培他滨毒性反应和疗效预测中的研究。

表观遗传学的另一研究对象是 miRNA 的表达水平。Hansen 等^[37]报道 miR-126 的表达与结直肠癌辅助化疗疗效相关, 低 miR-126 水平可能降低血管完整性, 增加毛细血管渗透压, 导致卡培他滨 EOX 化疗敏感性下降。Takahashi 等^[38]报道: miR-148a 高甲基化可引起 miR-148a 低表达, 致使 III~IV 期结直肠癌患者氟尿嘧啶治疗预后不佳。细胞实验也发现了一些潜在的标志物, 如 Borralho 等^[39]的研究指出高 miR-143 水平可增加结直肠癌细胞系 HCT116 对氟尿嘧啶的敏感性, 而 Hirota 等^[40]在肺癌的细胞系实验中发现 miR-143 可抑制 DPD 蛋白的表达; Boni 等^[41]在细胞实验中发现 miR-192 和 miR-215 能下调 TYMS 的表达, 增强氟尿嘧啶抵抗; 细胞实验发现 miR-129 是氟尿嘧啶靶酶 TYMS 的抑制剂, miR-129 高表达可致氟尿嘧啶耐药^[42]; Song 等^[43]发现 miR-140 可增加结直肠癌细胞对氟尿嘧啶敏感。这些实验证实 miRNA 可通过调节氟尿嘧啶代谢关键酶基因的表达而发挥作用。

表观遗传标志物作为基因多态标志物的补充, 成为了卡培他滨毒效标志物的未来研究方向之一。然而, 现有的表观遗传学标志物的研究主要是基于氟尿嘧啶对肿瘤细胞系的研究, 缺乏卡培他滨在结直肠癌患者中的临床观察性研究。

5 代谢组学标志物

药物的代谢差异不仅与个体的遗传信息相关, 还受到环境、饮食等诸多因素的影响。因此, 代谢组学作为对遗传和环境变化较敏感的生化过程的最终产物, 也被用于药物安全性和毒性评价的研究。研究显示治疗前血清低密度脂类含量高的结直肠癌

患者,接受卡培他滨治疗时更易发生严重副反应^[44]。该研究推测可能机制是因为血脂高的患者炎症反应高,易发生毒性,或因为脂类可增加与卡培他滨的结合,提高药物的浓度。Yap 等^[45]发现血清和红细胞内的叶酸水平是HFS的独立危险因子,Chan 等^[46]也发现血清高叶酸浓度与2级以上的卡培他滨毒性相关,但是具体的作用机制尚不清楚。迄今为止,卡培他滨治疗结直肠癌毒效的代谢组学的研究相对较少。

6 结语

目前,围绕代谢途径关键酶的一系列卡培他滨治疗结直肠癌的毒效标志物相继被发现。卡培他滨标志物的研究,有许多方面值得进一步关注和深入。首先,化疗药物的毒性和疗效存在相关性,如Hofheinz 等^[47]指出发生HFS患者的生存明显获益(PFS: 29.0 vs 11.4个月,OS: 75.8 vs 41.0个月),然而,既往的标志物研究往往将毒性和疗效分开,未关注之间的关联。其次,不同的毒性反应的发生机制存在着差异,如Hofheinz 等^[47]报道HFS患者发生胃肠毒性、疲劳的概率高,但HFS与血液毒性无关联,而既往部分报道并没有将不同的毒性区分开进行研究。再次,既往报道未探讨毒效标志物与不同组织(肿瘤、癌旁、血液、尿液或其他发生毒性反应的靶组织等)之间的关系。此外,由于患者人群、样本量、给药方案和剂量等诸多因素的差异,各研究之间往往存在差异,缺乏多中心、大样本的研究。另外,现有的大部分研究基于欧美人群,是否适合国内人群尚需进一步验证。最后,虽然单一的指标具有一定的预测作用,但是准确度不高,而且卡培他滨的毒性和疗效不仅与药物或毒性成分在体内的浓度有关,还与患者的免疫、炎症等系统状态有关。因此,随着各类组学技术的发展,联合临床病理信息、代谢酶表达、基因多态、表观遗传学和代谢组学的标志物构建的联合预测模型,可能显著提高预测的准确度。

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