单核苷酸多态性对消化道恶性肿瘤化疗药物反应和毒性的影响

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摘要 长期以来绝大多数化疗药物的疗效在不同个体间的差异受到临床医生的高度关注，其药物反应和毒性不仅与患者的年龄、性别以及药物间相互作用等因素有关，而且和参与药物代谢的蛋白或酶的表达水平有关。单核苷酸多态性是基因组中最常见的一种遗传变异，为了揭示个体之间因基因学的差异导致的化疗药物反应以及毒副作用的差异性，近年来对单核苷酸多态性与化疗药物反应及毒性之间相关性的研究和报道逐渐增多。但对各种单核苷酸多态性能否作为化疗药物反应及毒副作用的预测指标未得出统一定论。本文以消化道恶性肿瘤常用化疗药物为例，分别对5-氟尿嘧啶(5-FU)类、铂类、紫杉类和伊立替康相关的单核苷酸多态性(SNP)进行综述。

关键词 单核苷酸多态性(SNP) 胃癌 大肠癌 化疗

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Correlation between the Single-nucleotide Polymorphism and the Curative Effect/Side Effect of Chemotherapy for Malignant Gastrointestinal Tumor

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Abstract For a long time, clinicians have been paying increasing attention to the differences in the efficacy of anticancer drugs among various patients. The curative effects and possible side effects of chemotherapy are not only related to factors such as age, gender, and drug interactions but also to the expression of the proteins or enzymes involved in the metabolism of chemotherapeutic drugs. Single-nucleotide polymorphism is the most common form of genetic variation. Studies on the correlation between single-nucleotide polymorphism and the effects or side effects of chemotherapy have been increasingly conducted to investigate the differences in the therapeutic effects and side effects of drugs, which are caused by the genetic variations among individuals. However, single-nucleotide polymorphism has not been ascertained as a predictor of the effects and side effects of chemotherapy. The current study reviewed the single-nucleotide polymorphism correlated with fluorouracil, platinum, paclitaxel, and irinotecan, taking chemotherapeutic drugs for malignant gastrointestinal tumor as the example.

Keywords Single-nucleotide polymorphism; Gastric cancer; Colorectal cancer; Chemotherapy

单核苷酸多态性(single nucleotide polymorphism，SNP)是指不同个体的基因在某一特定核苷酸位置上存在的单个不同碱基的现象，且频率至少大于1%。其中转换最为常见，且在GC序列上出现最为频繁，可能是因为CpG二核苷酸上的胞嘧啶残基是基因组中最易发生突变的位点。SNP不均匀地分布于整个基因组中，在非编码序列中的分布要多于编码序列，前者约为后者的4倍。目前，5-FU类、铂类、紫杉类和拓扑异构酶Ⅰ抑制剂已广泛应用于胃癌和大肠癌的一线和二线辅助化疗和新辅助化疗中。在过往的临床化疗治疗中发现，同分期、同病理类型、同化疗方案的患者，其疗效与生存率却截然不同。为了达到更佳的治疗效果，减少对化疗药物不敏感的患者所承受的毒副反应，根据可靠的指标预测化疗药物的反应率和毒副反应的发生率已变得尤为重要。近年来对于SNP的研究和报道也逐渐增多。现分别对5-FU类、铂类、紫杉类和伊立替康相关的SNP进行综述。

1 5-FU作用相关SNP

1.1 胸苷酸合成酶(TS)

TS是DNA合成途径中重要的限速酶，可以催化细胞的增殖反应。5-FU进入体内后其代谢产物和TS结合，使TS失去催化活性，DNA合成受限，导致细胞生长受到抑制甚至死亡。Vignoli等[1]研究发现，TS低表达可获得较长的无瘤生存率(DFS)。具体原因可能是因为TS高表达需要大量的5-FU抑制其活性，

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从而常规剂量的5-FU会出现反应率降低。Peters等[2]研究发现，TS高表达的进展期胃癌患者，对5-FU化疗敏感性差。最新的研究发现TS高表达本身就具有致癌潜能以及诱导肿瘤进展的作用[3]。

TS表达受到多种因素调节[4]，包括1个位于5′-非翻译区的28 bp重复序列（VNTR）的多态性和2个分别位于5′和3′-非翻译区的SNP。此外，有学者认为TS表达还会受性别的影响，可能与ER对TS的负向调节有关[5]。

VNTR多态性决定TS的表达水平。野生型包含3个重复序列（3R），突变型则有2个重复序列（2R），亚洲人突变率不足10%[6-7]。3R在TS mRNA的表达和翻译较2R有更强的促进作用[8]。Pàez等[9]发现3R/3R基因型的结直肠癌患者对5-FU的化疗更为敏感。而一项丹麦的研究发现，2R/2R较纯合野生型及杂合型对于5-FU治疗更敏感，而Ⅲ或Ⅳ级的毒副反应发生率2R/2R较后二者高5~10倍[10]。在3R等位基因的第2个重复序列中位于第12位的核苷酸可发生G→C的替换，即SNP（G>C）。该SNP可以废除3R促进TS翻译。因此3G的基因型会导致TS高表达，而基因型为2R/2R、3C/3C和2R/3C的TS则相对低表达[11]。亚洲60%以上患者均为TS高表达。Hur等[12]在对一组进展期直肠癌患者研究中发现，在接受氟尿嘧啶新辅助化疗后，TS相对低表达的患者出现较明显的肿瘤降期以及淋巴结降期。

位于3′-非翻译区的SNP通过影响TS mRNA的稳定性导致TS表达下降[8,13]。大肠癌患者中，50%的Duke′s C期患者基因型为3′-UTR 6-/6+bp，76.5%的Duke′s D期也带有该基因型[14]。有研究表明，与野生型相比，带有突变型基因的患者其疾病进展时间会缩短[15]。在胃癌及大肠癌患者中，具有6-/6-bp和6-/6+bp表型的患者对以5-FU为基础的化疗较6+/6+bp更为敏感[16-17]。

近年来，有关TS联合基因型对化疗反应和预后影响的研究报道较多。Fernandez等[14]认为基因型为G&6+/6+的大肠癌患者对氟尿嘧啶耐药且预后差，具有该基因型的胃癌患者预后最差。

1.2　二氢嘧啶脱氢酶（DPD）

DPD是5-FU分解代谢过程中的限速酶，影响5-FU的疗效及毒性。DPD表达水平升高可加速5-FU在肿瘤组织中的分解，减少肿瘤部位的药物浓度。Terashima等[18]通过放免法测定140例胃癌患者DPD活性，发现DPD的活性越低，肿瘤对5-FU越敏感。DPD发生突变将导致5-FU严重的毒性反应[19-20]。其中发生突变频率最高的等位基因是IVS14+1 G>A，将显著提高5-FU相关的致命性骨髓抑制的发生率。法国一项对IVS14+1 G>A、2846 A>T、1679T>G研究发现，患者只要携带任何一个SNP，5-FU产生的Ⅲ、Ⅳ度毒副反应的发生率将显著提高[21]。

1.3　亚甲基四氢叶酸还原酶（MTHFR）

MTHFR是减少合成TS所需的还原的叶酸辅助因子。该基因的变异会增加对结肠癌的易感性。其中有2个最常见的SNP分别与改变酶活性和5-FU的高细胞毒性有关，分别为677C>T转换（$ala^{222}val$）和1298A>C颠换（$glu^{428}ala$）。一项法国的研究揭示了这2个SNP对于FOLFOX治疗的影响。结果显示不携带和分别携带有1个、2个、3个等位基因的结直肠癌的患者，对FOLFOX的反应率分别为37%、53%、63%和80%[22]。不仅说明MTHFR的SNP可能对FOLFOX化疗疗效有预测作用，而且反应的程度与拥有等位基因的数量呈正相关。Fernández等[23]的另一项研究显示，大肠癌患者在接受5-FU治疗后，具有MTHFR 677C>T的患者可获得较长的无瘤生存期和总生存期。而1298 C/C会因抑制MTHFR活性而增加5-FU的毒性反应[24]。

2　与铂类作用相关的SNP

铂类的细胞毒作用主要是形成铂-DNA复合物，从而抑制DNA的复制和转录。DNA损伤修复能力增强是导致铂类化疗疗效下降的主要原因。目前研究最多的SNP主要存在于核苷酸切除修复途径和碱基切除修复途径。

2.1　DNA修复酶

2.1.1　XRCC1　XRCC1是碱基切除修复（BER）家族中的成员之一，其功能性SNP $arg^{399}gln$被认为是铂类化疗反应的预测指标[25]。Suh等[26]发现，携带^{399}gln等位基因的患者行奥沙利铂为主的化疗后其有效率更高。Ruzzo等[27]在对胃癌的相同研究中发现突变型的中位生存时间约为野生型的1.5倍。

2.1.2　XPD　XPD是核酸切除修复（NER）家族中的一员，作用于由铂类导致的DNA损伤的修复过程。XPD的表达水平与对铂类化疗敏感性有关[28]。XDP基因转座子的751A>C（$lys^{751}gln$）突变频率最高。具有lys/lys、lys/gln和gln/gln表型的大肠癌患者对5-FU与奥沙利铂联合化疗的反应率分别为76%、45%和40.9%[29]。且纯合野生型的患者较其他患者可获得更长的生存期。此外，切除修复交叉互补基因组1（ERCC1）可从5′端切除受损的DNA，其mRNA表达水平与铂类药物的敏感性相关[30]。一项对166例大肠癌接受FOLFOX4化疗的研究发现，ERCC 354C>T纯合突变型的PFS显著低于其他患者[31]。

2.1.3　6-甲基鸟嘌呤-DNA甲基转移酶　6-甲基鸟嘌呤-DNA甲基转移酶直接参与DNA直接颠倒反转

的修复过程。同时对化疗药物产生耐药作用。Park等[32]对接受奥沙利铂治疗的进展期结直肠癌患者MGMT 2535G>T(rsl625649)进行了研究,发现TT基因型患者PFS低于其他基因型患者,认为2534G>T SNP在一定程度上对奥沙利铂化疗反应有预测作用。

2.2 谷胱甘肽-s-转移酶(GST)

GSTP1是GST家族的主要成员,含有两个SNP,一个为313(A>G),存在ile^{105}val;另一个为341C>T,存在ala^{114}val。^{105}ile多态性与肿瘤细胞对铂类化疗敏感性有关[33]。临床研究显示,GSPT1可作为对奥沙利铂化疗敏感性的预测指标[34]。进展期胃癌患者中,纯合型^{105}ile/^{105}ile中位生存期为7个月,而杂合突变型和纯合突变型中位生存期为9.5个月[30],且前者由奥沙利铂引起的Ⅲ、Ⅳ级累积性神经毒性反应发生率明显高于后二者[35]。Goekkurt等[36]研究显示,^{105}val/^{105}val基因型的胃癌患者铂类化疗有效率为76%,明显高于ile/ile和ile/val患者的有效率(21%),且^{105}val/^{105}val基因型的患者中位生存时间(15个月)也明显高于ile/ile和ile/val(6个月)患者。此外,Seo等[37]研究发现GSTM1缺失的胃癌患者,接受FOLFOX化疗后可获得更长的DFS。

3 与伊立替康、紫杉醇作用相关SNP

3.1 P-糖蛋白

P-糖蛋白与疏水性药物的转运有关,如紫杉醇、多柔比星等。其编码基因ABCB1的SNP主要包括:外显子26的同义SNP3435C>T以及2677G>T。Hamidovic等[38]认为具有C3435T纯和野生基因型的细胞,其表面P糖蛋白的表达远高于纯和突变基因型的细胞,并表现出对化疗药物的低反应率。而Chang等[39]发现具有3435CC基因型的患者对化疗的反应率高于具有3435CT和3435TT基因型的患者,并且前者较后两者获得更长的PFS。C3435T和G2677T的野生型与伊立替康所致的骨髓移植和腹泻有关。

3.2 鸟苷二磷酸-葡萄糖苷酸转移酶(UGT)

UGT1A1是伊立替康活性代谢物(SN-38)在肝内代谢过程中重要的酶之一。而SN-38的水平与伊立替康的毒性有关。UGT1A1的活性差异通常是由其启动子的多态性造成,其启动子中的TATA框区域包含有5~8个TA重复序列,尤以6个TA重复序列最常见,变异型因含有7个TA重复序列而形成UGT1A1*28。随着TA重复次数增多,UGT1A1表达水平下降,导致SN-38含量增多,发生伊立替康毒副作用的风险增加。UGT1A1*28等位基因在高加索人种的出现频率约为35%,而在东亚则相反,UGT1A1*6、*27和*60的发生率更高[40]。Cote等[41]和Liu等[42]研究发现具有UGT1A1*28基因型的患者接受伊立替康治疗后其白细胞减少症和腹泻的发生率更高。

近年来,大量有关功能性的SNP的发现和提出为个体化治疗提供了理论基础,但临床研究结果却存在很大争议。笔者认为主要原因大致可归咎为以下两点:1)同一SNP的各种基因型在不同种族人群中分布频率确实存在较大差异,以至于其野生型和突变型所代表的基因型不同。同时针对同一种族人群的大宗病例研究尚少,研究结果缺乏说服力;2)对于某一类化疗药物敏感性的影响不是由单个基因的单个SNP的表达情况,而是由多个基因多个SNP的表达共同决定。因此,在今后的研究中要注意以下几点:1)试验设计确保合理性和严谨性,研究对象的入组条件应统一严谨,种族种群应尽量单一,尽可能多地将相关的SNP包含在内;2)试验过程确保检测的准确性;3)分析过程确保全面,要考虑联合基因型之间对化疗疗效的影响。虽然目前单核苷酸多态性对于消化道恶性肿瘤化疗的影响尚无确切定论,但毋庸置疑的是,以药物基因组学为基础的个体化疗已经是今后胃肠癌化疗治疗的方向。相信,随着更大样本量的临床研究结果的出现,单核苷酸多态性对化疗药物作用的影响会更加清楚。

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·病例报告与分析·

腺样囊性乳腺癌1例

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关键词 乳腺 腺样囊性癌 钼靶 彩超
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腺样囊性乳腺癌是一种罕见的乳腺癌，文献报道其发病率不足0.1%[1]，预后较好。本文报道1例如下。

患者女性，54岁，因发现左侧乳腺肿物半年伴疼痛于2010年1月入院。查体：左乳外上象限近乳晕区可扪及一约2 cm×2 cm×1.5 cm肿物，质硬，边界不清，与周围组织粘连，活动度差，压痛明显。双侧腋窝未扪及明显肿大淋巴结。彩超示：左乳低回声结节，13 mm×11 mm×7 mm，边界较清晰，形态欠规则，内部未见钙化。双侧腋下未触及明显肿大淋巴结。在局麻下行左侧乳腺肿物切除术。术后病理冰冻回报为腺样囊性癌或小管癌，行左侧乳腺改良根治术。病理示：左乳腺腺样囊性癌，腋窝淋巴结16枚未见癌转移。给予AC方案化疗4次，未行放疗。化疗后随访1年，未见复发转移。

小结 乳腺腺样囊性癌（ACC）发病率低，据文献报道发病率不足0.1%[1]，与原发在腮腺、肺、食管、皮肤、宫颈、喉和巴氏腺的腺样囊性癌的形态学一致，并且预后相对较好。ACC通常在体表可以触及，并且伴有疼痛[2]。但未发现肿瘤细胞侵犯神经[3]。文献报道ER和PR均为阴性[4]，也有文献报道超过一半患者ER或者PR表达阳性[5]。ACC在乳腺钼靶上通常描述为边缘光滑的或者小叶状的良性团块[6]，或者是不规则的团块[2,6]。乳腺钼靶也会出现假阴性的结果，主要是由于致密的乳腺组织和瘤体组织发生重叠。ACC在超声中被描述为低回声或者混杂的团块，外形不规则，与本文报道一致[2]。乳腺ACC多以外科切除治疗，局部肿块切除后续放疗以及乳房单切均可以获得较好的效果。乳腺ACC发病率低，且预后较好，由于极少发生腋窝淋巴结转移，Arpino等[5]报道的182例乳腺ACC病例中仅4例发生腋窝淋巴结转移（2.2%）。

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