

综述

NUDT15 基因型对儿童急性淋巴细胞白血病 6-MP 个体化治疗的影响

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[摘要] 6-巯基嘌呤(6-MP)是急性淋巴细胞白血病(ALL)维持治疗阶段的重要药物,其副作用包括肝毒性和骨髓抑制,不同个体对6-MP的耐受差异较大,6-MP治疗需个体化。巯嘌呤甲基转移酶(TPMT)活性缺乏与6-MP不耐受具有相关性。但亚洲患者TPMT等位基因的突变频率较低。近来发现存在NUDT15基因突变的ALL患者6-MP耐受剂量低于常规剂量。该文就NUDT15基因型对ALL患儿6-MP个体化治疗的影响进行综述。

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[关键词] 急性淋巴细胞白血病; NUDT15; 6-巯基嘌呤

Significance of NUDT15 gene in individualized treatment with 6-mercaptopurine in children with acute lymphoblastic leukemia

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Abstract: As an important drug during maintenance treatment of acute lymphoblastic leukemia (ALL), 6-mercaptopurine (6-MP) has several side effects, including hepatotoxicity and bone marrow suppression. Since its tolerability varies from person to person, 6-MP treatment should be individualized. The deficiency of thiopurine methyltransferase (TPMT) enzyme activity is associated with 6-MP intolerance. There is a lower frequency of mutation in TPMT alleles among Asian patients. Recent studies have shown that in ALL patients with NUDT15 gene mutation, the maximum tolerated dose of 6-MP is lower than the conventional dose. The article reviews the significance of NUDT15 gene in individualized treatment with 6-MP in children with ALL.

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Key words: Acute lymphoblastic leukemia; NUDT15; 6-Mercaptopurine

随着化疗方案的改进,儿童急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)的5年无事件生存率(event-free survival, EFS)已高达90%,而接受规范的维持治疗是基础^[1-3]。6-巯基嘌呤(6-mercaptopurine, 6-MP)是ALL维持治疗的重要药物,它通过抑制白血病细胞DNA和RNA合成从而影响嘌呤核苷酸合成而发挥抗癌作用。但6-MP治疗窗窄,最小有效剂量至中毒剂量的范围小,药代学个体差异大。因此,6-MP个体化治疗成为研究热点。研究^[4]发现硫代嘌呤甲基转移

酶(thiopurine S-methyltransferase, TPMT)参与6-MP代谢物的甲基化,其活性缺乏与6-MP不耐受具有相关性。但我国TPMT的等位基因突变频率低于欧美国家,并且一些具有正常TPMT活性的患者仍然可能发生6-MP相关的毒副作用,因此单纯以TPMT多态性不能完全解释硫嘌呤相关毒性的个体差异^[5-6]。近来发现具有NUDT15基因突变的ALL患者也不能耐受6-MP常规剂量^[7-10]。本文就NUDT15基因型对儿童ALL患者6-MP个体化治疗的影响进行综述。

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码蛋白的混合物，显示中等活性；纯合型表现为低等活性，包括双突变纯合型、双突变杂合型^[20-21]。

表 1 NUDT15 等位基因突变

NUDT15 等位基因	基因突变	突变位点	氨基酸改变
*1	野生型 (W)	无	野生型 (W)
*2	c.[36_37insGGAGTC; c.415C>T]	外显子 1 和 3	p.Val18_Val19insGlyVal/p.Arg139Cys
*3	c.415C>T	外显子 3	p.Arg139Cys
*4	c.416 G>A	外显子 3	p.Arg139His
*5	c.52G>A	外显子 1	p.Val18Ile
*6	c.36_37insGGAGTC	外显子 1	p.Val18_Val19insGlyVal

表 2 NUDT15 基因型及其活性

分类	基因型	活性
1 野生型 (C/C)	*1/*1	高等活性
2	*1/*2	中等活性
3	*1/*3	
4 杂合型 (C/T)	*1/*4	
5	*1/*5	
6	*1/*6	
7	*2/*2	低等活性
8	*3/*3	
9	*4/*4	
10	*5/*5	
11	*6/*6	
12	*2/*3	
13	*2/*4	
14 纯合型 (T/T)	*2/*5	
15	*2/*6	
16	*3/*4	
17	*3/*5	
18	*3/*6	
19	*4/*5	
20	*4/*6	
21	*5/*6	

3 不同 NUDT15 基因型在人群中的分布

研究^[22]表明 NUDT15 (rs116855232) 基因变异率在东亚人群最高 (9.8%)，其次是西班牙 (3.9%)，欧洲人群仅为 0.2%，而在非洲没有发现。Zhang 等^[23]对 1138 名 ALL、炎性肠病患者的荟萃分析显示，在亚洲 NUDT15 基因突变 C.415C>T 的等位基因 (C 和 T) 出现频率分别为 86.72% 和 13.28%。Moriyama 等^[19]在 270 例来自危地马拉、

新加坡、日本的 ALL 儿童中发现 4 种 NUDT15 基因突变：p.Arg139Cys、p.Arg139His、p.Val18Ile 和 p.Val18_Val19insGlyVal。日本、韩国、乌圭拉、黎巴嫩等多个地区均发现 NUDT15 基因突变，其对应变异率 (包括 CC 和 CT) 约为 20%、40%、17%、1%^[24-27]。

目前我国对 NUDT15 基因突变的研究相对较少。Liang^[28]在 304 例急淋患儿和 100 例克罗恩病患儿中发现 22.0% 存在 NUDT15 基因突变。中山大学^[29]对 253 名克罗恩病的研究发现，中国人群 NUDT15 基因突变率约为 22.5% (CT 20.9% vs TT 1.6%)。这些研究提示亚洲国家 NUDT15 基因突变频率较高^[22]。

4 NUDT15 基因型对 6-MP 个体化治疗的影响

研究^[30-32]发现，接受 6-MP 常规剂量治疗的 ALL 患者中存在 NUDT15 基因纯合突变的骨髓抑制最严重，杂合突变患者有中度至重度骨髓抑制，而 NUDT15 基因野生型的患者骨髓抑制最轻。

研究^[28-29]表明：中国台湾和日本的 NUDT15 突变基因杂合型 (CT) 患者的 6-MP 耐受剂量为野生型的 70% 左右，而韩国 NUDT15 基因杂合型 (CT) 患者 6-MP 剂量范围为 20%~80%，中国台湾、日本及韩国 NUDT15 突变基因纯合型 (TT) 患者的 6-MP 耐受剂量为野生型的 25%。此外，有研究^[33]指出年龄、6-TGN 水平也与 6-MP 耐受性密切相关。因此，关于具有 NUDT15 基因突变 ALL 患者的 6-MP 剂量原则还需要进一步大样本多中心研究。

研究还发现一些具有 NUDT15 基因突变患儿

同时伴有 TPMT 基因突变。Lee 等^[34] 研究显示, 3 例具有 NUDT15 基因纯合突变的克罗恩病患者同时具有 TPMT 基因突变杂合型, 不耐受 6-MP 治疗。但与之相反的是, 日本学者^[35] 对 92 名 ALL 患者的研究显示, NUDT15 基因型相同的患儿 TPMT 基因突变与维持治疗期间 6-MP 耐受剂量及毒性无关。因此 TPMT 基因突变与 NUDT15 基因突变对于 6-MP 不耐受是否具有协同作用尚未明确。

5 展望

综上所述, NUDT15 基因突变与 ALL 患者 6-MP 耐受性具有相关性, 尤其是亚洲人群。关于 ALL 患儿 6-MP 个体化治疗尚需要关注以下几个方面: 第一、地区、种族对 NUDT15 基因多态性的影响。第二、TPMT 基因突变与 NUDT15 基因突变对于 6-MP 耐受性的影响是否具有协同作用。第三、其他基因如编码三磷酸腺苷结合转运家族蛋白 4 (ABCC4)、脱嘌呤/脱嘧啶核酸内切酶 1 (APEX1) 等基因多态性是否与 6-MP 耐受性相关。

【参 考 文 献】

- [1] Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children[J]. N Engl J Med, 2015, 373: 1541-1552.
- [2] Pui CH, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: Progress through collaboration[J]. J Clin Oncol, 2015, 33(27): 2938-2948.
- [3] 于洁. 儿童急性淋巴细胞白血病维持治疗的发展和研究[J]. 儿科药志, 2009, 15(2): 3-6.
- [4] Lennard L, Cartwright CS, Wade R, et al. Thiopurine methyltransferase and treatment outcome in the UK acute lymphoblastic leukaemia trial ALL2003[J]. British J Haematol, 2015, 170(4): 550-558.
- [5] Maxwell RR, Cole PD. Pharmacogenetic predictors of treatment-related toxicity among children with acute lymphoblastic leukemia[J]. Current Haematol Malig Rep, 2017, 12(3): 176-186.
- [6] Yi ES, Choi YB, Choi R, et al. NUDT15 variants cause hematopoietic toxicity with low 6-TGN levels in children with acute lymphoblastic leukemia[J]. Cancer Res Treat, 2018, 50(3): 872-882.
- [7] Singh M, Bhatia P, Khera S. Emerging role of NUDT15 polymorphisms in 6-mercaptopurine metabolism and dose related toxicity in acute lymphoblastic leukaemia[J]. Leuk Res, 2017, 62: 17-22.
- [8] Zhu Y, Yin D, Su Y, et al. Combination of common and novel rare variants improves predictive sensitivity of thiopurine induced leukopenia in children with acute lymphoblastic leukemia[J]. Haematologica, 2018, 103(7): e293-e295.
- [9] Shah SA, Paradkar M, Desai D. Nucleoside diphosphate-linked moiety X-type motif 15 C415T variant as a predictor for thiopurine-induced toxicity in Indian patients[J]. J Gastroenterol Hepatol, 2017, 32(3): 620-624.
- [10] Yang JJ, Landier W, Yang W, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia[J]. J Clin Oncol, 2015, 33(11): 1235-1242.
- [11] 李志玲, 王鹤尧, 孙华君. 疏嘌呤类药物用于儿童急性淋巴细胞性白血病患者个体化治疗的研究进展[J]. 上海医药, 2015, 36(19): 12-15.
- [12] Karran P, Attard N. Thiopurines in current medical practice: molecular mechanisms and contributions to therapy-related cancer[J]. Nat Rev Cancer, 2008, 8(1): 24-36.
- [13] Takagi Y, Setoyama D, Ito R, et al. Human MTH3 (NUDT18) protein hydrolyzes oxidized forms of guanosine and deoxyguanosine diphosphates: comparison with MTH1 and MTH2[J]. J Biol Chem, 2012, 287(25): 21541-21549.
- [14] Kim HT, Choi R, Won HH, et al. NUDT15 genotype distributions in the Korean population[J]. Pharmacogenet Genomics, 2017, 27(5): 197-200.
- [15] Asada A, Nishida A, Shioya M, et al. NUDT15 R139C-related thiopurine leukocytopenia is mediated by 6-thioguanine nucleotide-independent mechanism in Japanese patients with inflammatory bowel disease[J]. J Gastroenterol, 2016, 51(1): 22-29.
- [16] Hashiguchi K, Hayashi M, Sekiguchi M, et al. The roles of human MTH1, MTH2 and MTH3 proteins in maintaining genome stability under oxidative stress[J]. Mutat Res, 2018, 808: 10-19.
- [17] Singh M, Bhatia P, Khera S. Emerging role of NUDT15 polymorphisms in 6-mercaptopurine metabolism and dose related toxicity in acute lymphoblastic leukaemia[J]. Leuk Res, 2017, 62: 17-22.
- [18] Moriyama T, Yang YL, Nishii R, et al. Novel variants in and thiopurine intolerance in children with acute lymphoblastic leukemia from diverse ancestry[J]. Blood, 2017, 130(10): 1209-1212.
- [19] Moriyama T, Nishii R, Perez-Andreu V, et al. NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity[J]. Nat Genet, 2016, 48(4): 367-373.
- [20] Fong WY, Ho CC, Poon WT. Comparison of direct sequencing, real-time PCR-high resolution melt (PCR-HRM) and PCR-restriction fragment length polymorphism (PCR-RFLP) analysis for genotyping of common thiopurine intolerant variant alleles NUDT15 c415C>T and TPMT c719A>G (TPMT*3C)[J]. Diagnostics (Basel, Switzerland), 2017, 7(2): pii: E27.
- [21] Ho CC, Fong WY, Lee YH. Novel tetra-primer ARMS-PCR assays for thiopurine intolerance susceptibility mutations NUDT15 c415C>T and TPMT c719A>G (TPMT*3C) in East Asians[J]. Genes, 2017, 8(10): pii: E285.
- [22] Yang JJ, Landier W, Yang W, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia[J]. J Clin Oncol, 2015, 33(11): 1235-1242.

- [23] Zhang AL, Yang J, Wang H, et al. Association of NUDT15 c.415C>T allele and thiopurine-induced leukocytopenia in Asians: a systematic review and meta-analysis[J]. *Ir J Med Sc*, 2018, 187(1): 145-153.
- [24] Sato T, Takagawa T, Kakuta Y, et al. NUDT15, FTO and RUNX1 genetic variants and thiopurine intolerance among Japanese patients with inflammatory bowel diseases[J]. *Intest Res*, 2017, 15(3): 328-337.
- [25] Kim H, Seo H, Park Y, et al. APEX1 polymorphism and mercaptopurine-related early onset neutropenia in pediatric acute lymphoblastic leukemia[J]. *Cancer Res Treat*, 2018, 50(3): 823-834.
- [26] Soler AM, Olano N, Méndez Y, et al. TPMT and NUDT15 genes are both related to mercaptopurine intolerance in acute lymphoblastic leukaemia patients from Uruguay[J]. *Br J Haematol*, 2018, 181(2): 252-255.
- [27] Zgheib NK, Akika R, Mahfouz R, et al. NUDT15 and TPMT genetic polymorphisms are related to 6-mercaptopurine intolerance in children treated for acute lymphoblastic leukemia at the Children's Cancer Center of Lebanon[J]. *Pediatr Blood Cancer*, 2017, 64(1): 146-150.
- [28] Liang DC, Yang CP, Liu HC, et al. NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwan Chinese children with acute lymphoblastic leukemia[J]. *Pharmacogenomics J*, 2016, 16(6): 536-539.
- [29] Zhu X, Wang XD, Chao K, et al. NUDT15 polymorphisms are better than thiopurine S-methyltransferase as predictor of risk for thiopurine-induced leukopenia in Chinese patients with Crohn's disease[J]. *Aliment Pharmacol Ther*, 2016, 44(9): 967-975.
- [30] Brandalise SR, Pinheiro VR, Aguiar SS, et al. Benefits of the intermittent use of 6-mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in children: randomized trial from the Brazilian Childhood Cooperative Group--protocol ALL-99[J]. *J Clin Oncol*, 2010, 28(11): 1911-1918.
- [31] Asada A, Nishida A, Shioya M, et al. NUDT15 R139C-related thiopurine leukocytopenia is mediated by 6-thioguanine nucleotide-independent mechanism in Japanese patients with inflammatory bowel disease[J]. *J Gastroenterol*, 2016, 51(1): 22-29.
- [32] Rudin S, Marable M, Huang RS, et al. The promise of pharmacogenomics in reducing toxicity during acute lymphoblastic leukemia maintenance treatment[J]. *Genomics Proteomics Bioinformatics*, 2017, 15(2): 82-93.
- [33] Moriyama T, Nishii R, Lin TN, et al. The effects of inherited NUDT15 polymorphisms on thiopurine active metabolites in Japanese children with acute lymphoblastic leukemia[J]. *Pharmacogenet Genomics*, 2017, 27(6): 236-239.
- [34] Lee YJ, Hwang EH, Park JH, et al. NUDT15 variant is the most common variant associated with thiopurine-induced early leukopenia and alopecia in Korean pediatric patients with Crohn's disease[J]. *Eur J Gastroenterol Hepatol*, 2016, 28(4): 475-478.
- [35] Tanaka Y, Kato M, Hasegawa D, et al. Susceptibility to 6-MP toxicity conferred by a NUDT15 variant in Japanese children with acute lymphoblastic leukaemia[J]. *Br J Haematol*, 2015, 171(1): 109-115.

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