

帕唑帕尼在癌症中的研究进展

李崴¹, 刘伟¹, 尤嘉琮², 周贵明¹

1天津医科大学总医院超声科, 2天津医科大学总医院, 天津市肺癌研究所, 天津市肺癌转移与肿瘤微环境重点实验室, 天津 300052

[摘要] 血管生成是肿瘤生长和转移不可或缺的过程, 帕唑帕尼(Pazopanib)是一种血管内皮生长因子受体(VEGFR)抑制剂, 通过抑制对肿瘤供血的新血管生成而抑制肿瘤。有研究发现, Pazopanib可通过调节Raf-MAPK/ERK(MEK)-ERK通路抑制肿瘤, 也可直接作用于小鼠肉瘤病毒癌基因同源B-raf基因。Pazopanib可抑制肝癌DU-145和HRC-45细胞的增殖。Pazopanib已被证实适用于肾细胞癌、软组织肉瘤、上皮性卵巢癌和非小细胞肺癌和一些恶性血液病等的治疗。在本文中对Pazopanib的临床前研究进行综述和回顾, 为进一步临床研究提供参考。

[关键词] 血管生成抑制剂; 肿瘤; 帕唑帕尼

[中图分类号] R979.1 [文献标识码] A [文章编号] 1672-2809(2015)14-0023-05

Research progress in cancer in pazopanib

LI Wei, LIU Wei, YOU Jia-cong, ZHOU Gui-ming

1 Ultrasonography Department of Tianjin Medical University General Hospital; 2 Tianjin Medical University General Hospital, Tianjin Lung Cancer Institute, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin, 300052, China

[Abstract] Angiogenesis is a process of growth and metastasis of tumor, indispensable, pazopanib is a vascular endothelial growth factor receptor inhibitor, through the inhibition of blood supply to the tumor angiogenesis and tumor suppression. It is found that Pazopanib can inhibit tumor by regulating Raf-MAPK/ERK (MEK) -ERK pathway, and also can be directly acting on the B-raf gene of mouse sarcoma virus oncogene. Pazopanib can inhibit the proliferation of DU-145 and HRC-45 cells in liver cancer. Pazopanib has been proved to be suitable for the treatment of renal cell carcinoma, soft tissue sarcoma, epithelial ovarian cancer, and non small cell lung cancer and some malignant hematological diseases. In this article, the clinical research of Pazopanib is summarized and reviewed, which provides reference for further clinical research.

[Key words] Angiogenesis inhibitor; Tumor; Pazopanib

目前, 癌症已成为人类健康最大的威胁之一, 虽然手术、化疗、放疗等癌症的治疗手段有了较大进步, 但其疗效已经遇到瓶颈^[1]。血管形成是正常的生理现象, 与毛细血管的形成和伤口愈合密切相关^[2], 在肿瘤的发生和发展中也起到重要的作用。Folkman等人研究发现^[3], 新的毛细血管的形成是由某种扩散因子介导的, 可称为肿瘤

血管生成因子(TAF), TAF可诱导其所在部位的肿瘤血管的形成, 去除TAF可能会产生抗血管性生成效应。TAF指血管内皮生长因子(VEGF)家族、血小板生长因子(PDGF)家族和一些抗血管生成相关因子、炎症性媒介、酶、激素、寡糖、造血因子和细胞黏附分子^[4]。血管生成和抗血管生成细胞因子二者平衡失调可能造成肿瘤血管的形成, 血管的生成过程包括几个不同的步骤, 每一步都取决于特殊的影响因子, 并且不同步骤之间可能具有直接或者间接的联系^[5]。

在所有影响血管生成的因素中, VEGF和PDGF是两个最不可或缺的影响因子。VEGF家族包括: VEGF(或者叫VEGF-A)、胎盘生长因子(PlGF)、

基金项目: 本文受国家自然科学基金(No.81000950)资助。

通讯作者: 周贵明, 男, 副主任技师, 超声科主任, 医学硕士, 硕士研究生导师。主要从事从事超声诊断工作。E-mail: zhouguming_ugok@126.com

收稿日期: 2015-3-18 接受日期: 2015-5-20

VEGF-B、VEGF-C和VEGF-D^[6]。VEGF配体可与三个具有不同特异性和亲和性的酪氨酸激酶受体结合：VEGF受体-1(VEGFR-1)/(Flt-1)；VEGFR-2/人类激酶插入域受体(KDR)/flk-1；VEGFR-3/Flt4^[7]。VEGFR-1和VEGFR-2均是胚胎血管系统生成所必须的，二者所出现的纯合突变均会危及生命^[4]。研究证实经过VEGFR-2通路传递的VEGF信号对促进血管生成的至关重要^[6,7]。研究发现VEGFR-2可以逆转VEGFR-1的作用，VEGFR-3和其配体VEGF-C、VEGF-D共同指导淋巴管的生成^[6]。

PDGF家族包括5个二聚体配体：AA、BB、CC、DD和AB^[8,9]。这些亚型通过酪氨酸激酶的 α 和 β 受体形成同源或者异源二聚体，这些二聚体可以通过募集多种与血管生成有关的细胞因子而发挥细胞学效应^[10]。干细胞因子受体(CSFR)/c-Kit是一类造血干细胞内的酪氨酸激酶，研究发现CSFR/c-Kit参与多种恶性肿瘤，在肥大细胞白血病中通过突变诱导受体持续活化，在小细胞肺癌和恶性黑色素瘤中通过自分泌环路是肿瘤细胞产生c-Kit^[11]。

Pazopanib是一种口服的具有生物相容性多靶点酪氨酸激酶受体抑制剂^[12]，其结构中类似ATP部分可以形成与酪氨酸激酶受体结合的氢键，然后与ATP竞争性结合胞内酪氨酸激酶受体，抑制ATP诱导活化^[13]。帕唑帕尼可特异性抑制VEGFR-1/-2/-3、PDGFR- α / β 、M-CSF受体/fms和CSFR/c-kit^[14]。

1 Pazopanib在实体肿瘤中的研究

研究发现Pazopanib可以直接靶向v-raf小鼠肉瘤病毒致癌基因同族体B(B-Raf)^[15]。体内移植瘤实验表明Pazopanib可抑制人类乳腺癌细胞系231-BR-HER2向脑的转移，但不是通过抗血管生成途径。由于231-BR-HER2细胞存在B-Raf突变，意味着抗增殖通路Raf-MAPK/ERK(MEK)-ERK途径被阻断。这种直接抑制效应也证明B-Raf是抗血管生成的一个新的靶点。通过量化血管的密度和面积发现，Pazopanib抑制肿瘤细胞的B-Raf与它的抗血管生成活性有关^[16]。除了B-Raf，如WM3918细胞中表达的PDGFR β 、VEGFR1和VEGFR3等相关靶点均

对Pazopanib敏感^[16]。在脑转移过程中活化的星形胶质瘤细胞亚群表达p-PDGFR β ，帕唑帕尼可抑制p-PDGFR β 的表达。星形胶质瘤细胞表达p-PDGFR β 可能是发生转移的重要标志，则帕唑帕尼在治疗乳腺癌患者的脑转移具有潜在的价值^[17]。

在对比舒尼替尼和帕唑帕尼对肾癌细胞的抑制能力的研究中发现，舒尼替尼和帕唑帕尼对细胞的抑制机制不同。用不同浓度的舒尼替尼和帕唑帕尼处理八株肾癌RCC细胞，结果显示帕唑帕尼对RCC细胞的抑制能力较低，实验表明帕唑帕尼不能诱导RCC细胞凋亡^[18]。也有研究发现帕唑帕尼具有抑制肝细胞癌增殖、侵袭和转移的能力^[19]。

在卵巢癌中的研究显示，当使用低剂量口服环磷酰胺、口服伊立替康或者紫杉醇分别与帕唑帕尼联合使用时显示出无效或者轻微的抗肿瘤活性。但是当低剂量的拓扑替康与帕唑帕尼联合使用显示了良好的抗肿瘤活性^[20]。帕唑帕尼具有强大的抗肿瘤活性，有研究表明在最初使用同时口服拓扑替康/帕唑帕尼治疗的小鼠仍然能存活180天。使用帕唑帕尼25mg/kg组、125mg/kg组和口服拓扑替康组的小鼠，存活率分别是41天、41天、90天^[20]。

已经证实帕唑帕尼与拓扑替康在包括神经母细胞瘤、骨肉瘤，横纹肌肉瘤等多种细胞系内存在协同效应^[21,22]。体外实验表明，单独使用帕唑帕尼对骨肉瘤细胞系无作用。而在人神经母细胞瘤细胞SK-N-BE(2)中，额外使用帕唑帕尼可以造成拓扑替康从65.0ng/ml到35.1ng/ml范围内的IC50降低^[21]。进行体内实验发现，通过观察循环血管生成因子，如循环内皮血管生成因子(CEC)、循环内皮祖细胞(CEP)和微型血管密度等，联合使用帕唑帕尼和拓扑替康可以显著发挥抗肿瘤特性和抑制肿瘤血管生成，继而增加了患者生存率。针对后续治疗的进一步的研究发现，定期口服拓扑替康和帕唑帕尼可以造成SK-N-BE(2)细胞移植瘤模型产生获得性耐药肿瘤，该细胞系曾经被证实对联合使用拓扑替康和帕唑帕尼表现出敏感性。该研究认为Glut-1和己糖激酶-2与获得性耐药有关，并推断高糖酵解代谢是联合治疗获得性耐药的关键机制^[23]。

2 Pazopanib在恶性血液病中的研究

帕唑帕尼不但对恶性实体瘤有效,同时对恶性血液病也具有治疗作用。一系列的体内和体外实验发现,在慢性淋巴细胞白血病(CLL)细胞中帕唑帕尼可以下调抗凋亡蛋白XIAP和MCL1,诱导剂量依赖性和剂量选择性的凋亡,二者均是通过降低VEGF受体磷酸化效应发挥作用的^[24]。在帕唑帕尼类似实验中,当氟达拉滨与帕唑帕尼联合使用则显示出显著的增强效应。按照100mg/kg标准治疗移植瘤小鼠3周,可使肿瘤抑制率达到77%。

帕唑帕尼治疗多种恶性肿瘤的报告已不在少数,帕唑帕尼是否可以促进细胞凋亡仍然存在争论。一项关于帕唑帕尼的移植瘤模型研究发现,与对照组相比两个治疗组的肿瘤生长显著降低(30mg/kg组),有些组甚至出现了完全抑制现象(100mg/kg组)^[25]。统计分析发现,30mg/kg组和100mg/kg组的总生存率分别是41天和51天,而对照组的则为20天,说明延长的生存时间与帕唑帕尼的浓度显著相关。然而,进一步的TUNNEL实验对治疗组的肿瘤部分研究发现与对照组对比出现显著的细胞凋亡情况。同时,该研究还显示,帕唑帕尼与常规和新型疗法均具有疗效^[25]。当单独使用抗血管生成抑制剂产生的显著抗血管生成活性和令人失望的临床结果之间产生了巨大差距时,引起人们对帕唑帕尼的使用方法产生了新的思考,如联合化疗使用。通过³H[dT]对细胞增殖的检测,免疫调节药物如雷利度胺、actimid和硼替佐米,以及低剂量的DNA破坏药物均为CI < 1,说明这些药物与帕唑帕尼具有协同作用^[26]。

3 在临床1期和2期实验中的生物标志物分析

收集临床 I / II 期NSCLC患者登记后进行多途径的、I / II 期、非盲法、单因素的实验,根据肿瘤体积改变、血清细胞因子或血管生成因子(CAFs)的变化对帕唑帕尼的疗效进行评价。血浆CAF的变化可以作为肿瘤状态的标记分子。有研究发现CAF与帕唑帕尼的治疗有关,在治疗过程中可溶的VEGFR-2降低了1.35倍,胎盘生长因子增加了18.04倍,IL-12与肿瘤的治疗密切相关。在对肿瘤治疗过

程中的CAF变化的研究发现,sVEGFR2可能是肿瘤缩小的一个潜在标记分子。肿瘤缩小程度越大,sVEGFR2将会降得越低。另一方面,CAF水平的基线可以作为肿瘤治疗的预测因素。11个CAF的基线水平可以用来预测肿瘤的治疗效果,包括:IL-12、HGF、IL-16、IP-10、SDF-1 α 、IL-2R α 、IL-3、IFN- α 2、TRAIL、M-CSF和PIGF。有研究表明,多种标记联合使用,如IL-12和HGF联合使用预测效果优于单独标记预测,并且可以区别有效部位与无效部位且准确率达81%^[27]。

期肾细胞癌CAF研究证实,sVEGFR2可预测患者对帕唑帕尼的疗效^[28]。在治疗的第十二周sVEGFR2低于基线水平表明sVEGFR2与肿瘤变化密切相关($P=0.00002$),而VEGF和Svegfr1未观察到与肿瘤变化的相关性。Tran等研究发现,IL-6是帕唑帕尼诱导的无进展生存期(PFS)延长的显著预测标志,尤其是前期经细胞因子处理后的患者,预测效果更好^[29]。VHL蛋白是调节血管生成的关键因素,在肾细胞癌患者中常出现VHL的功能性损坏,VHL基因改变(突变或者甲基化)发生率高达90%^[28]。然而,研究发现VHL状态与肿瘤变化或PFS无相关性,与sVEGFR1和VEGF类似^[28,30]。以上研究结果否定了以前关于VHL/HIF通路元件可以用来预测帕唑帕尼治疗肾细胞癌患者的临床疗效,同时提示我们,需要进一步的研究更加有效的预测标志物。

综上所述,目前体外临床前期实验表明,帕唑帕尼可以抑制包括人类乳腺、前列腺、肾、肝、肺和卵巢癌等肿瘤的生长。临床药理分析已经阐述了帕唑帕尼的基本特征。第一阶段的针对癌症晚期患者实验表明,帕唑帕尼治疗的稳态出现在每日一次800mg剂量组。另一项研究显示,帕唑帕尼在高于40mmol/L的浓度可发挥较好的治疗效果。一些基础研究阐明了帕唑帕尼抗肿瘤血管生成的分子机制。除了已经发现的B-Raf靶点外,与帕唑帕尼作用相关的Raf-MEK-ERK信号通路也被证实起到了关键作用。越来越多的针对帕唑帕尼疗效的生物标志物的探究已经展开。几个 I / II 期的临床实验数据也为我们提供了几个可供选择的CAF,并且提示如IL-6,IL-12,HGF和sVEGFR2与临床疗效相关,并且也

可以作为疗效的生物标志物或者预测符合该治疗方法的适宜患者。

与化疗相比,抗血管生成治疗方法在癌症治疗过程中是一个新的方向。虽然该方法可以抑制原发性肿瘤的生长,但这种方法是否会造成原发灶缺氧和促进原发性和转移性肿瘤的生长仍然存在争论^[31]。在体外、体内研究和获得性耐药小分子酪氨酸激酶受体抑制剂之间的差距还需要更多的创新研究和治疗方案。生物标志物方向的探索可以帮助筛选符合治疗方法的敏感性患者。帕唑帕尼的结合治疗和小剂量疗法以及一些其他的药物治疗方法是一个新的研究方向。已经发现了一些与帕唑帕尼具有协同效应的药物,而且体内研究也证实了帕唑帕尼和拓扑替康在小剂量治疗方面具有很好的疗效。癌症的临床前研究和临床研究迫切需要扩大适应症范围和增加临床疗效,为此还需要进行深入的

参考文献

- [1] Bagnyukova TV, Serebriiskii IG, Zhou Y, et al. Chemotherapy and signaling: how can targeted therapies supercharge cytotoxic agents? [J]. Cancer Biol Ther, 2010, 10: 839-853.
- [2] Bhargava P, Robinson MO. Development of second generation VEGFR tyrosine kinase inhibitors: current status [J]. Curr Oncol Rep, 2011, 13: 103-111.
- [3] Folkman J. Anti-angiogenesis: new concept for therapy of solid tumors [J]. Ann Surg, 1972, 175: 409-416.
- [4] Liekens S, DeClercq E, Neyts J. Angiogenesis: regulators and clinical applications [J]. Biochem Pharmacol, 2001, 61: 253-270.
- [5] Schöffski P. Pazopanib in the treatment of soft tissue sarcoma [J]. Expert Rev Anticancer Ther, 2012, 12: 711-723.
- [6] Lohela M, Bry M, Tammela T, et al. VEGFs and receptors involved in angiogenesis versus lymphangiogenesis [J]. Curr Opin Cell Biol, 2009, 21: 154-165.
- [7] Roberts DM, Kearney JB, Johnson JH, et al. The vascular endothelial growth factor (VEGF) receptor Flt-1 (VEGFR-1) modulates Flk-1 (VEGFR-2) signaling during blood vessel formation. Am J Pathol 2004; 164: 1531-5. signaling during blood vessel formation [J]. Am J Pathol, 2004, 164: 1531-1535.
- [8] Alvarez RH, Kantarjian HM, Cortes JE. Biology of platelet-derived growth factor and its involvement in disease [J]. Mayo Clin Proc, 2006, 81: 1241-1257.
- [9] Bergsten E, Uutela M, Li X, et al. PDGF-D is a specific, protease-activated ligand for the PDGF beta-receptor [J]. Nat Cell Biol, 2001, 3: 512-516.
- [10] Rini B, Al-Marawi MY. Pazopanib for the treatment of renal cancer [J]. Expert Opin Pharmacother, 2011, 12: 1171-1189.
- [11] Masson K, Rönstrand L. Oncogenic signaling from the hematopoietic growth factor receptors c-Kit and Flt3 [J]. Cell Signal, 2009, 21: 1717-1726.
- [12] GlaxoSmithKline RTP. NC 27709 VOTRIENT (pazopanib tablets) Prescribing Information, including Boxed Warning. 2012.
- [13] Keisner SV, Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma [J]. Drugs, 2011, 71: 443-454.
- [14] Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity [J]. Mol Cancer Ther, 2007, 6: 2012-2021.
- [15] Gril B, Palmieri D, Qian Y, et al. Pazopanib reveals a role for tumor cell B-Raf in the prevention of HER2+ breast cancer brain metastasis [J]. Clin Cancer Res, 2011, 17: 142-153.
- [16] Gril B, Palmieri D, Qian Y, et al. The B-Raf status of tumor cells may be a significant determinant of both antitumor and anti-angiogenic effects of pazopanib in xenograft tumor models [J]. PLoS ONE, 2011, 6: e25625.
- [17] Gril B, Palmieri D, Qian Y, et al. Pazopanib inhibits the activation of PDGFR beta-expressing astrocytes in the brain metastatic microenvironment of breast cancer cells [J]. Am J Pathol, 2013, 182: 2368-2379.
- [18] Canter D, Kutikov A, Golovine K, et al. Are all multi-targeted tyrosine kinase inhibitors created equal? An in vitro study of sunitinib and pazopanib in renal cell carcinoma cell lines [J]. Can J Urol, 2011, 18: 5819-5825.
- [19] Zhu XD, Zhang JB, Fan PL, et al. Antiangiogenic effects of pazopanib in xenograft hepatocellular carcinoma models: evaluation by quantitative contrast-enhanced ultrasonography [J]. BMC Cancer, 2011, 11: 28.
- [20] Hashimoto K, Man S, Xu P, et al. Potent preclinical impact of metronomic low-dose oral topotecan combined with the antiangiogenic drug pazopanib for the treatment of ovarian cancer [J]. Mol Cancer Ther, 2010, 9: 996-1006.
- [21] Kumar S, Mokhtari RB, Sheikh R, et al. Metronomic oral topotecan with pazopanib is an active antiangiogenic regimen in mouse models of aggressive pediatric solid tumor [J]. Clin Cancer Res, 2011, 17: 5656-5667.
- [22] Hackl C, Man S, Francia G, et al. Metronomic oral topotecan prolongs survival and reduces liver metastasis in improved preclinical orthotopic and adjuvant therapy colon cancer models Gut [J]. 2012, 62: 259-271.
- [23] Kumar S, Mokhtari RB, Oliveira ID, et al. Tumor dynamics in response to antiangiogenic therapy with oral metronomic topotecan and pazopanib in neuroblastoma xenografts. Transl Oncol 2013; 6: 493-503.
- [24] Paesler J, Gehrke I, Gandhirajan RK, et al. The vascular endothelial growth factor receptor tyrosine kinase inhibitors vatalanib and pazopanib potently induce apoptosis in chronic lymphocytic leukemia cells in vitro and in vivo [J]. Clin Cancer Res, 2010, 16: 3390-3398.
- [25] Podar K, Tonon G, Sattler M, et al. The small-molecule VEGF receptor inhibitor pazopanib (GW786034B) targets both tumor and endothelial cells in multiple myeloma [J]. Proc Natl Acad Sci U. S. A, 2006, 103: 19478-19483.
- [26] Ferrara N, Hillan KJ, Gerber HP, et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer [J]. Nat Rev Drug Discov, 2004, 3: 391-400.
- [27] Nikolinakos PG, Altorki N, Yankelevitz D, et al. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor

shrinkage in early-stage non-small cell lung cancer patients treated with pazopanib[J]. Cancer Res, 2010, 70: 2171-2179.

- [28] Hutson TE, Davis ID, Machiels JH, et al. Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib(GW786034), a multi-kinase angiogenesis inhibitor. 2008 ASCO Annual Meeting Proceedings[J]. J Clin Oncol, 2008, 26(15S Suppl): 5046.
- [29] Tran HT, Liu Y, Zurita AJ, et al. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis

of phase 2 and phase 3 trials[J]. Lancet Oncol, 2012, 13: 827-837.

- [30] Choueiri TK, Fay AP, Gagnon R, et al. The role of aberrant VHL/HIF pathway elements in predicting clinical outcome to pazopanib therapy in patients with metastatic clear-cell renal cell carcinoma[J]. Clin Cancer Res, 2013, 19: 5218-5226.
- [31] Pàez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis[J]. Cancer Cell, 2009, 15: 220-231.

(上接第13页)特点,加之MDS患者仍亟需新的治疗药物,这使得氯法拉滨成为治疗MDS的潜在的选择。近些年的一系列研究证实,氯法拉滨不仅为儿童ALL患者的重要治疗选择,其在AMI和MDS的I和II临床试验中,也获得了很好的ORRs。最常见的氯法拉滨相关的不良事件为骨髓抑制、恶性、呕吐、腹泻、心动过速、发热、疲劳、一过性肝功能异常、皮疹、手足综合征和黏膜炎。但是尽管氯法拉滨在治疗MDS中取得的进步,单仍需进一步开发更有效、更安全的治疗MDS患者的方法,且需开展进一步的研究来确定氯法拉滨在治疗MDS中的作用、剂量及疗程等。

参考文献

- [1] Bonate PL, Arthaud L, Cantrell WR Jr, et al. Discovery and development of clofarabine: a nucleoside analogue for treating cancer[J]. Nat Rev Drug Discov, 2006, 5(10): 855-863.
- [2] King KM, Damaraju VL, Vickers MF, et al. A comparison of the transportability, and its role in cytotoxicity, of clofarabine, cladribine, and fludarabine by recombinant human nucleoside transporters produced in three model expression systems[J]. Mol Pharmacol, 2006, 69(1): 346-353.
- [3] Jeha S, Gandhi V, Chan K, et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia[J]. Blood, 2004, 103: 784-789.
- [4] Jabbour E, Garcia-Manero G, Xiao L, et al. Outcome of patients (pts) with low and intermediate-1 risk myelodysplastic syndrome (MDS) after hypomethylating agent (HMA) failure[J]. Blood, 2013, 122: abstract 388.
- [5] Kantarjian H, Gandhi V, Cortes J, et al. Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia[J]. Blood, 2003, 102(7): 2379-2386.
- [6] Cooper T, Ayres M, Nowak B, et al. Biochemical modulation of cytarabine triphosphate by clofarabine[J]. Cancer Chemother Pharmacol, 2005, 55(4): 361-368. Epub 2004 Oct 16.
- [7] Estey E, Plunkett W, Dixon D, et al. Variables predicting response to high dose cytosine arabinoside therapy in patients with refractory

acute leukemia[J]. Leukemia, 1987, 1(8): 580-583.

- [8] Xie KC, Plunkett W. Deoxynucleotide pool depletion and sustained inhibition of ribonucleotide reductase and DNA synthesis after treatment of human lymphoblastoid cells with 2-chloro-9-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)adenine[J]. Cancer Res, 1996, 56(13): 3030-3037.
- [9] Faderl S, Gandhi V, O'Brien S, et al. Results of a phase 1-2 study of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukemias[J]. Blood, 2005, 105(3): 940-947.
- [10] Faderl S, Gandhi V, Verstovsek S, et al. Clofarabine plus cytarabine combination is active in newly diagnosed patients age ≥ 50 with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [J]. Blood, 2004, 104: abstract 875.
- [11] Faderl S, Ravandi F, Huang X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome[J]. Blood, 2008, 112(5): 1638-1645.
- [12] Burnett AK, Russell NH, Hunter AE, et al. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival[J]. Blood, 2013, 122(8): 1384-1394.
- [13] Pr  bet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure[J]. J Clin Oncol. 2011, 29(24): 3322-3327.
- [14] Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy[J]. Cancer, 2010, 116(16): 3830-3834.
- [15] Lim SH, McMahan J, Zhang J, et al. A phase II study of low dose intravenous clofarabine for elderly patients with myelodysplastic syndrome who have failed 5-azacytidine[J]. Leuk Lymphoma, 2010, 51(12): 2258-2261.
- [16] Nazha A, Garcia-Manero G, Kantarjian HM, et al. Clofarabine plus low-dose cytarabine for the treatment of patients with higher-risk myelodysplastic syndrome (MDS) who have been relapsing after, or are refractory to, hypomethylating agent therapy[J]. Blood, 2013, 122: abstract 1525.
- [17] Locke F, Agarwal R, Kunnavakkam R, et al. A novel clofarabine bridge strategy facilitates allogeneic transplantation in patients with relapsed/refractory leukemia and high-risk myelodysplastic syndromes[J]. Bone Marrow Transplant, 2013, 48(11): 1437-1443.