

靶向抗癌药伊马替尼耐药性的研究进展

Advances in drug resistance of target-directed anti-cancer drug imatinib

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摘要:

伊马替尼作为第一代酪氨酸激酶抑制剂,已成功用于慢性粒细胞白血病慢性期的一线治疗,但耐药现象的出现,极大影响了伊马替尼的长期治疗效果。伊马替尼耐药机制复杂多样,大致归为两大类:依赖于BCR-ABL激酶活性的耐药机制和不依赖于BCR-ABL激酶活性的耐药机制。针对不同的耐药机制,人们提出了很多解决伊马替尼耐药性的方法,包括对新型酪氨酸激酶抑制剂的研究,联合下游信号通路抑制剂,以及对慢性粒细胞白血病干细胞的靶向用药等。

关键词: 伊马替尼;抗药性,肿瘤;白血病,髓样,慢性

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- [1]赵毅,韩海燕,张学进,等.伊马替尼治疗常规化学治疗失败的进展期慢性粒细胞白血病21例[J].中国新药与临床杂志,2007,26(9):715-717.
- [2]HOCHHAUS SA,SCHENK T,ERBEN P,et al.Cause andmanagement of therapy resistance[J].Best Pract Res ClinHaematol,2009,22(3):367-379.
- [3]BRANFORD S,RUDZKI Z,WALSH S,et al.Detection ofBCR-ABL mutations in patients with CML treated with imatinibis virtually always accompanied by clinical resistance, andmutations in the ATP phosphate-binding loop(P-loop)areassociated with a poor prognosis[J].Blood,2003,102(1):276-283.
- [4]姜志平,陈方平.伊马替尼治疗慢性粒细胞性白血病耐药机制研究进展[J].国际输血及血液学杂志,2007,30(2):176-181.
- [5]AN X, TIWARI AK, SUN YB, et al. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: a review [J]. Leuk Res, 2010, 34(10): 1255-1268.
- [6]GORRE ME, MOHAMMED M, ELLWOOD K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification [J]. Science, 2001, 293(5331): 876-880.
- [7]SCHINDLER T, BORNMANN W, PELLICENA P, et al. Structural mechanism for STI-571 inhibition

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参考文献

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- of abelson tyrosinekinase[J].Science,2000,289(5486):1938-1942.
- [8]WALZ C,SATTLER M.Novel targeted therapies to overcomeimatinib mesylate resistance in chronic myeloid leukemia(CML)[J].Crit Rev Oncol Hematol,2006,57(2):145-164.
- [9]WANG Y,CAI DL,BRENDEL C,et al.Adaptive secretion ofgranulocyte-macrophage colony-stimulating factor(GM-CSF)mediates imatinib and nilotinib resistance in BCR/ABL+pro-genitors via JAK-2/STAT-5 pathway activation[J].Blood,2007,109(5):2147-2155.
- [10]WARSCH W,KOLLMANN K,ECKELHART E,et al.HighSTAT5 levels mediate imatinib resistance and indicate diseaseprogression in chronic myeloid leukemia[J].Blood,2011,117(12):3409-3420.
- [11]NELSON EA,SHARMA SV,SETTLEMAN J,et al.A chemicalbiology approach to developing STAT inhibitors:molecularstrategies for accelerating clinical translation[J].Oncotarget,2011,2(6):518-524.
- [12]QUENTMEIER H,EBERTH S,ROMANI J,et al.BCR-ABL1-independent PI3Kinase activation causing imatinib-resistance[J].J Hematol Oncol,2011,4:6.
- [13]PACKER LM,RANA S,HAYWARD R,et al.Nilotinib andMEK inhibitors induce synthetic lethality through paradoxicalactivation of RAF in drug-resistant chronic myeloid leukemia[J].Cancer Cell,2011,20 (6):715-727.
- [14]O' HARE T,EIDE CA,DEININGER MW.Persistent LYNsignaling in imatinib-resistant,BCR-ABL-independentchronicmyelogenous leukemia[J].J Natl Cancer Inst,2008,100(13):908-909.
- [15]WU J,MENG F,KONG LY,et al.Association betweenimatinib-resistant BCR-ABL mutation-negative leukemia andpersistent activation of LYN kinase[J].J Natl Cancer Inst,2008,100(13):926-939.
- [16]OCHI T,FUJIWARA H,SUEMORI K,et al.Aurora-A kinase:a novel target of cellular immunotherapy for leukemia[J].Blood,2009,113(1):66-74.
- [17]YUAN H,WANG Z,ZHANG H,et al.Overcoming CML-acquired resistance by specific inhibition of Aurora A kinase inthe KCL-22 cell model[J].Carcinogenesis,2012,33(2):285-293.
- [18]GALSKI H,BERLINSKY S,SIMANOVSKY M,et al.Pgp-mediated resistance toward both imatinib and NK-cells killing ofaggressive minor CML blast subset can be reversed by Pgpmodulators [C].London:Nature Publishing Grp,2011:363-364.
- [19]NAKA K,HOSHII T,HIRAO A.Novel therapeutic approach toeradicate tyrosine kinase inhibitor resistant chronic myeloidleukemia stem cells[J].Cancer Sci,2010,101(7):1577-1581.
- [20]CHU S,MCDONALD T,LIN A,et al.Persistence of leukemiamstem cells in chronic myelogenous leukemia patients in prolongedremission with imatinib treatment[J].Blood,2011,118(20):5565-5572.
- [21]CORBIN AS,AGARWAL A,LORIAUX M,et al.Humanchronic myeloid leukemia stem cells are insensitive to imatinibdespite inhibition of BCR-ABL activity[J].J Clin Invest,2011,121(1):396-409.
- [22]马军.慢性粒细胞白血病伊马替尼耐药性的机制与对策[J].中华肿瘤防治杂志,2006,13(8):561-564.
- [23]VAIDAYA S,GHOSH K,VUNDINTI RB.Recent developmentsin drug resistance mechanism in chronic myeloid leukemia:areview[J].Eur J Haematol,2011,87(5):381-393.
- [24]周励,沈志祥.慢性髓性白血病治疗新药尼洛替尼[J].中国新药杂志,2010,19(17):1496-1499.
- [25]刘舒畅,张健存,陈赛娟.BCR-ABL蛋白激酶抑制剂的研究进展[J].中国医药工业杂志,2010,41 (4):293-297.
- [26]CORTS JE,KANTARJIAN HM,KIM DW,et al.Safety andfcacy of bosutinib(SKI-606)in chronic phase Philadelphiachromosome-positive chronic myeloid leukemia patients withresistance or intolerance to imatinib[J].Blood,2011,118(17):4567-4576.
- [27]O'HARE T,DEININGER MWN,EIDE CA,et al.Targeting theBCR-ABL signaling pathway in therapy-resistant philadelphiachromosome-positive leukemia[J].Clin Cancer Res,2011,17(2):212-221.
- [28]NOOR SM,BELL R,WARD AC.Shooting the messenger:targeting signal transduction pathways in leukemia and relateddisorders[J].Crit Rev Oncol Hemat,2011,78(1):33-44.

- [29]CHIEN CM,YANG SH,LIN KL,et al.Novel indoloquinolinederivative,IQDMA,suppresses STAT5 phosphorylation andinduces apoptosis in HL-60 cells[J].Chem Biol Interact,2008,176(1):40-47.
- [30]MLLER J,SPERL B,REINDL W,et al.Discovery ofchromone-based inhibitors of the transcription factor STAT5[J].Chembiochem,2008,9(5):723-727.
- [31]WEISBERG E,BANERJI L,WRIGHT RD,et al.Potentiationof antileukemic therapies by the dual PI3K/PDK-1 inhibitor,BAG956:effects on BCR-ABL-and mutant FLT3-expressingcells [J].Blood,2008,111(7):3723-3734.
- [32]MANCINI M,PETTA S,MARTINELLI G,et al.RAD 001(everolimus)prevents mTOR and Akt late re-activation inresponse to imatinib in chronic myeloid leukemia[J].J Cell Bio,2010,109(2):320-328.
- [33]CORTS J,ALBITAR M,THOMAS D,et al.Efficacy of thefarnesyl transferase inhibitor R115777 in chronic myeloid leukemiaand other hematologic malignancies[J].Blood,2003,101(5):1692-1697.
- [34]CORTS J,QUINT' S,CARDAMA A,GARCIA-MANERO G,et al.Phase 1 study of tipifarnib in combination with imatinib forpatients with chronic myelogenous leukemia in chronic phaseafter imatinib failure[J].Cancer,2007,110(9):2000-2006.
- [35]NGUYEN TK,RAHMANI M,HARADA H,et al.MEK1/2inhibitors sensitize Bcr/Abl+human leukemia cells to the dualAbl/Src inhibitor BMS-354/825[J].Blood,2007,109(9):4006-4015.
- [36]PACKER LM,RANA S,HAYWARD R,et al.Nilotinib andMEK inhibitors induce synthetic lethality through paradoxicalactivation of RAF in drug-resistant chronic myeloid leukemia[J].Cancer Cell,2011,20 (6):715-727.
- [37]LUNGHI P,MAZZERA L,CORRADI A,et al.Arsenic trioxide(ATO)interacts synergistically with MEK inhibitors to induceapoptosis in STI571-resistant Bcr-Abl mutants[C].Washington:Amer Soc Hematol,2009:857-857.
- [38]VALENT P.Standard treatment of Ph+CML in 2010:how,whenand where not to use what BCR/ABL1 kinase inhibitor?[J].Eur J Clin Invest,2010,40(10):918-931.
- [39]温晓舟,周芳,吴晓兰,等.P-糖蛋白抑制剂及其构效关系研究进展[J].中国临床药理学与治疗学,2010,15(7):814-820.
- [40]黄雷鸣,赵锦花,王国成,等.聚合物辅料对P-糖蛋白抑制机制的研究进展[J].药学学报,2010,45 (10):1224-1231.
- [41]STELLA C,KENNETH T,LIN G.Circumvention of multi-drugresistance of cancer cells by Chinese herbal medicines[J].ChinMed,2010,5(26):1-9.
- [42]ZHAO C,BLUM J,CHEN A,et al.Loss of β -catenin impairsthe renewal of normal and CML stem cells in vivo[J].Cancer Cell,2007,12(6):528-541.
- [43]NAKA K,HOSHII T,HIRAO A.Novel therapeutic approach toeradicate tyrosine kinase inhibitor resistant chronic myeloidleukemia stem cells[J].Cancer Sci,2010,101(7):1577-1581.
- [44]ITO K,BERNARDI R,MOROTTI A,et al.PML targeting eradicates quiescent leukaemia-initiating cells[J].Nature,2008,453(7198):1072-1078.