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组蛋白去乙酰化酶抑制剂在急性髓系白血病中的应用*

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摘要 急性髓系白血病（AML）是造血干/祖细胞恶性克隆性疾病，以骨髓、血液和其他组织中髓系起源的异常原始细胞增殖为特征。“3+7”诱导方案（蒽环类药物联合阿糖胞苷）一直是治疗AML的基石，但仍有部分AML患者无法耐受强化疗或完全缓解后复发，目前AML的总体疗效仍不乐观。因此，寻找新药物以提高AML患者疗效具有重要的临床意义。越来越多的研究证明，表观遗传对AML的发生、发展起重要作用。组蛋白去乙酰化酶抑制剂（HDACi）是表观遗传修饰的分子靶向药物，可抑制组蛋白去乙酰化酶（HDAC）的活性，上调组蛋白赖氨酸的乙酰化水平，目前已应用于AML临床研究中，在联合治疗中显现出良好的耐受性与治疗效果。本综述介绍了HDAC和HDACi的分类依据以及在临床上的应用，阐述了伏立诺他、贝利司他、帕比司他、戊丙酸、恩替诺特、西达本胺等6种HDACi在AML中的临床前研究结果和临床应用研究进展，讨论了HDACi与其他抗癌药物联用在AML中的作用机制，并对HDACi今后的发展提出了建议，期望为临床治疗AML提供参考。

关键词 急性髓系白血病，组蛋白去乙酰化酶抑制剂，组蛋白去乙酰化酶，表观遗传学
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急性髓系白血病（acute myeloid leukemia，AML）是造血干/祖细胞恶性克隆性疾病，以骨髓、血液和其他组织中髓系起源的异常原始细胞的增殖为特征。目前针对AML的治疗方案主要有“3+7”标准诱导治疗（即蒽环类药物联用阿糖胞苷（cytarabine，ara-C））、异基因造血干细胞移植（Allo-HSCT）和靶向药物治疗。然而，AML细胞通常高水平表达P-糖蛋白，介导化疗药物外排，使AML细胞对化疗产生耐药性，导致许多患者对化疗不具备敏感性或完全缓解（complete response，CR）后复发，且部分患者因无法耐受强化疗或缺乏供者而无法采用Allo-HSCT疗法。因此，寻找新药物以提高AML患者的疗效具有重要的临床意义。表观遗传失调在许多疾病的发病机制中起着关键作用，尤其是癌症。研究显示，部分AML患者存在表观遗传调节基因突变，比如DNMT3A、IDH和TET2，同时这类突变有潜在的可逆性，这已然成为AML的治疗靶点之一。组蛋白去乙酰化酶抑制剂（histone deacetylase inhibitors，HDACi）可调节组蛋白乙酰化和去乙酰化之间的平衡，从表观遗传学上改变原癌基因和/或抑癌基因的表达，在多种肿瘤治疗方面发挥重要作用，成为肿瘤领域内研究的热点，在近几年研究中常与其他抗癌药物联用治疗AML，具有良好的协同作用。

1 组蛋白去乙酰化酶与癌症

真核生物染色质的基本结构是由组蛋白和DNA组成的核小体[1]。核小体由147 bp的DNA缠绕组蛋白八聚体近1.75圈形成[2]。通常情况下，组蛋白的乙酰化有利于降低DNA与组蛋白八聚体的亲和力，导致核小体结构松弛，从而使各种转录因子和协同转录因子特异性结合DNA结合位点，

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促进基因转录[3-5]。组蛋白去乙酰化酶（histone deacetylase，HDAC）能催化组蛋白去乙酰化，与带负电荷的DNA紧密结合，使染色质呈压缩状态，抑制基因转录。在癌细胞中，HDAC的过度表达不利于某些特定基因的表达，包括一些抑癌基因[6-7]。研究表明，胃癌、结直肠癌、乳腺癌、肺癌、子宫平滑肌肉瘤和血液系统恶性肿瘤等都表现出异常的HDAC表达，同时癌症预后不良与HDAC的过度表达有关[8-16]。进一步的研究表明，*HDAC*基因敲除可促进癌细胞凋亡和癌细胞分化蛋白的重新表达，同时诱导细胞周期停滞和抑制细胞分裂[17-20]。HDACi是一类可以抑制HDAC活性的抗肿瘤药物，可上调组蛋白赖氨酸的乙酰化水平，并诱导抑癌基因染色质构象开放，从而抑制肿瘤进展[21]。近年来，由美国食品药品监督管理局（U.S. Food and Drug Administration，FDA）批准的HDACi主要限制于血液系统恶性肿瘤的治疗，如T细胞淋巴瘤和多发性骨髓瘤，针对AML的HDACi的研究正在积极进展中。

2 HDAC及HDACi概述

根据与酵母对应物的序列相似性以及对催化条件的依赖性，HDAC家族的18个成员分为HDACI、II、III、IV四类。I类（HDAC1、2、3、8）与酵母Rpd3具有同源性，广泛位于细胞核，少部分可定位于细胞质或其他的细胞器；II类包括IIa（HDAC4、5、7、9）和IIb（HDAC6、10），与酵母Hda1同源，主要分布于细胞质；HDACIII类称为Sirtuins（Sirt），由Sirt1~Sirt7组成，与酵母Sirt2具有同源性，主要存在于细胞核、细胞质和线粒体[22]；IV类只有最新发现的HDAC11，主要位于细胞核，它是HDAC中最小的蛋白质，其生物学功能也是最不为人所知的，但最新研究表明，它可切割赖氨酸侧链上的长链酰基修饰[23]。HDACI、II、IV类都需要锌离子来催化其活性，而HDACIII类需要烟酰胺腺嘌呤二核苷酸才能催化其活性[24]。HDAC的编配与正常细胞和肿瘤细胞的细胞发育密切相关，HDAC的失调是血液系统恶性肿瘤从起始到转移的关键驱动因素。I类HDAC中的HDAC1被检测到在AML t (15;17)、t (8;21)和inv (16)亚型中启动子处沉积增加[25]，HDAC3在APL亚型中高表达，且HDAC3的表达水平与PML-RARα呈正相关[26]，HDAC8在AML inv (16)亚型中过表达[27]。II类HDAC中HDAC4在FLT3-ITD阳性AML患者中的表达水平显著高于FLT3野生型AML患者，在AML M5患者中的表达水平明显高于未浸润者[28]，HDAC10的敲低可显著减弱FLT3-ITD阳性AML细胞耐药性[29]。III类HDAC中的Sirt1在AML患者骨髓的$CD34^+CD38^-$细胞中表达水平升高，并且在FLT3-ITD阳性AML患者的$CD34^+$细胞中的表达水平显著高于FLT3野生型AML患者[30]，Sirt3通过调节线粒体氧化磷酸化使AML产生化疗耐药[31]，*Sirt5*基因缺失会影响AML相关癌基因对原代造血细胞的转化，同时也会减弱AML症状[32]。IV类HDAC目前在AML中的研究较少。HDAC过度表达可引起AML细胞增殖，抑制其活性可诱导AML细胞周期停滞[27]，HDAC低表达的患者预后也比较良好[33]。在AML病例中尚未检测到*HDAC*基因突变，但有研究发现，HDAC被异常招募到癌基因融合蛋白中，如AML1-ETO、CBFβ-MYH11、PML-RARA和MLL-MLLT3等融合蛋白在启动和促进AML发生中发挥重要作用[34-35]。例如，AML1-ETO可招募HDAC1、HDAC2和HDAC3，使AML1靶基因沉默，从而阻断细胞分化和转化[36]。此外，HDAC还在整体水平上表现出免疫调节特性，通过调节免疫系统的主要成分PD-L1、CTLA-4、调节性T细胞、细胞毒性T淋巴细胞和抗原提呈细胞[37-39]，调控AML的发生发展。例如，HDAC10的表达与抗原提呈细胞中MHC II类分子的呈递有关[40]，抑制HDAC后的浆细胞样树突状细胞可通过激活*IFN*基因转录产生I型IFN，从而诱导AML细胞分化[41]。综上，抑制HDAC可作为AML的治疗靶点。HDACi可分为5类化合物。a. 异羟肟酸类，例如曲古菌素A、伏立诺他、贝利司他、帕比司他等。曲古菌素A是第一个被发现能抑制HDAC的天然羟肟酸[42]，但由于其毒性较大，目前仅停留在临床前研究阶段。伏立诺他和贝利司他先后被FDA批准用于临床治疗皮肤T细胞淋巴瘤，帕比司他被FDA和欧洲药品管理局（European Medicines Agency，EMA）批准用于治疗多发性骨髓瘤[43]。b. 短链脂肪酸类，例如丙戊酸、丁酸和苯丁酸，其中丙戊酸被用于治疗癫痫、躁郁症和偏头痛[44]。c. 苯甲酰胺类，例如恩替诺特。d. 环肽类，例如罗米地辛、trapoxin A、trapoxin B等，其中罗米地辛被FDA和EMA批准用于临床治疗复发性和难治性（relapsed or

refractory，r/r）皮肤T细胞淋巴瘤。e. 其他类，例如Sirtuins抑制剂、depudecin等[45]。由此可见，HDACi已然应用到癌症的治疗当中并且有很好的发展前景。目前，HDACi已显示出诱导AML细胞分化、细胞周期停滞和凋亡的能力。其机制可能主要与HDACi通过抑制HDAC活力从而诱导抑癌基因染色质构象开放，促进癌基因损伤以及阻止癌基因融合蛋白招募HDAC有关（图1）。尽管HDACi的临床前结果很有希望，但并不如AML的常规疗法在临床上有效。与各种抗癌药物的联合策略正在进行临床试验，显示出显著的抗AML活性，这给治疗AML提供了一个很好的选择，特别是对于那些不适合强化疗和对化疗耐药的AML患者。

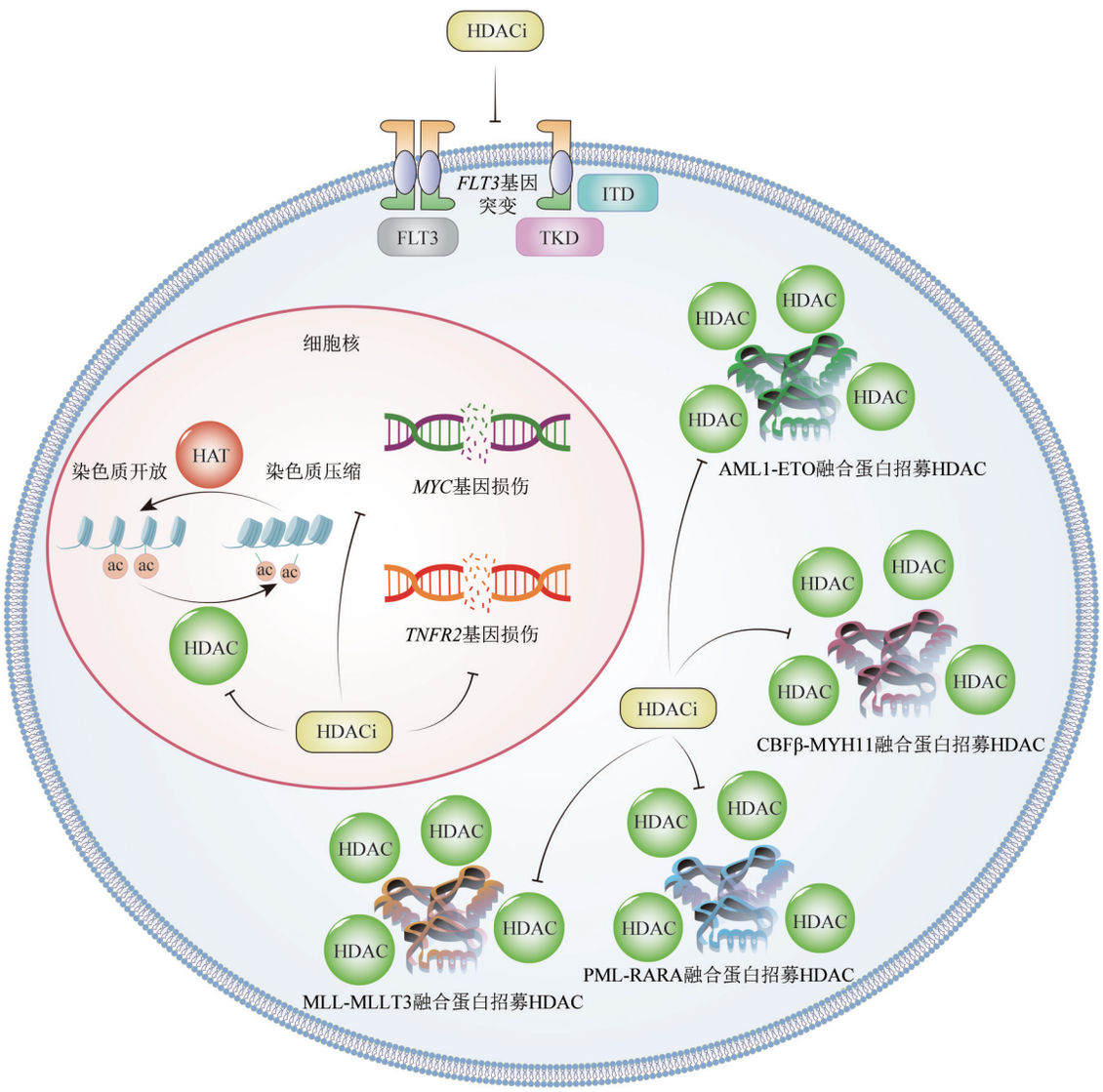

Fig. 1　Mechanism of action of HDACi in AML cells

图1　HDACi在AML细胞中的作用机制

HDACi通过抑制HDAC活力进而诱导肿瘤抑制基因染色质构象开放、促进癌基因损伤、阻止癌基因融合蛋白异常招募HDAC以及抑制*FLT3*基因突变，从而发挥抗急性髓系白血病作用。HDACi：组蛋白去乙酰化酶抑制剂；HDAC：组蛋白去乙酰化酶；HAT：组蛋白乙酰化酶；FLT3：FMS样酪氨酸激酶3；ITD：内部串联重复突变；TKD：酪氨酸激酶结构域点突变；ac：乙酰化。

3 HDACi在AML中的应用进展

3.1 伏立诺他（SAHA，Vorinostat，Zolinza）

伏立诺他分子式为$C_{14}H_{20}N_2O_3$（图2），分子质量为264.32，是一种口服白色结晶粉末状的抗肿瘤药物，可抑制I类HDAC中的HDAC1、HDAC2和HDAC3以及II类HDAC中HDAC6的酶活性。2006年10月6日，FDA批准Zolinza（伏立诺他胶囊）用于治疗原发性皮肤T细胞淋巴瘤[46]，就此成为FDA批准的第一代HDACi。临床前研究发现，SAHA可抑制AML细胞的活性，诱导其凋亡[47]和细胞周期停滞[48-49]，并且与地西他滨、ara-C或依托泊苷等常用化疗药物联用的治疗效果更明显[50-51]，这些可能与SAHA诱导AML细胞DNA双链断裂和氧化损伤有关[52]。值得注意的是，SAHA还可与pan-Aurora抑制剂[53]、Weel激酶抑制剂[54]、BET抑制剂[55]、FLT3抑制剂[56]等联用，通过促进抑癌基因的表达或抑制酶依赖的肿瘤增殖系统以及抑制*FLT3*基因突变，可更大程度损伤AML细胞，抑制或消退AML异种移植模型鼠的肿瘤生长。SAHA与其他药物的耦合物在治疗AML中发挥的作用也不容小觑。例如，SAHA与胡椒碱耦合物[57]、SAHA与芹黄素耦合物[58]均可抑制AML细胞生长。SAHA与芹黄素耦合物甚至比SAHA与ara-C联用对AML细胞的杀伤作用还高出至少20倍，且在有效逆转AML小鼠模型肿瘤形成的同时，还能确保关键器官的安全，显示出治疗AML的可行性和良好的安全性。

2009年，美国多个研究中心开展II期临床实验证明了SAHA作为单一疗法对治疗AML效果不尽人意，CR率几乎为0，不推荐单独应用SAHA治疗AML患者[59]。2013年，美国癌症研究协会设计了SAHA联合ara-C和依托泊苷治疗AML患者的I期临床试验，结果显示这种联合用药对受试者有较高的临床效益（CR率为38.8%），并推荐SAHA在ara-C和依托泊苷治疗前11~14 d服用，用量为200 mg，2次/d，连续服用7 d的治疗效果显著[60]。同年，美国多研究中心I、II期试验探索SAHA联合阿扎胞苷（Azacitidine，AZA）和吉妥珠单抗治疗老年r/r AML患者的有效性，结果表明，该方法的客观缓解率（objective response rate，ORR）高达41.9%，这为治疗老年AML患者提供了一个可靠的新选择[61]。但在2017年，英国伯明翰大学开展的一项II期临床试验显示，SAHA与AZA联合治疗效果与单独AZA治疗效果的CR和ORR相比并没有显著提高（CR率分别为22%和26%，ORR率分别为41%和42%）[62]。2015年，加拿大和美国多个研究中心开展的一项开放标签的I期临床试验发现，SAHA联合地西他滨对初次治疗的AML患者具有临床活性，并且同步给药的治疗效果更好（单独西他滨组CR率为13%，联合SAHA组为30%）[63]。2017年，美国华盛顿大学临床I期试验发现，SAHA联合地西他滨和ara-C治疗*KMT2A*基因部分串联重复的AML患者有显著疗效[64]。2022年，美国多个研究中心开展了一项I期临床试验，采用SAHA、地西他滨、粒细胞集落刺激因子（granulocyte colony stimulating factor，G-CSF）联合治疗r/r AML儿童患者，结果显示，这种疗法不仅耐受性好，而且生物学活性好，对患有r/r AML的儿童有效，特别是对有表观遗传学改变的患者（ORR率为54%）[65]。目前看来，SAHA与其他抗肿瘤药物的联用在临床前和临床试验中都取得了有希望的结果，但还需要进一步探索出更为有效、更具针对性的方案。

3.2 贝利司他（Belinostat，PXD101，Bel）

贝利司他，分子式为$C_{15}H_{14}N_2O_4S$（图2），分子质量为318.34，是一种在结构上类似于SAHA，由异羟肟酸衍生的HDACi。相较于SAHA，它具有更高的血脑屏障渗透率，可广泛抑制所有依赖锌的HDAC，对I类HDAC中的HDAC1、2和3和II类HDAC中的HDAC6、9和10以及IV类中的HDAC11均有很高的亲和力。Bel于2014年获FDA批准用于治疗r/r外周T细胞淋巴瘤[66]。在体外Bel与维甲酸联用可使AML细胞株NB4和HL-60周期停滞于G0/G1期，抑制其增殖，还可诱导和加速粒细胞分化[67]。Bel与硼替佐米联合给药可通过阻断NF-κB信号通路，显著提高AML和淋巴细胞系白血病细胞的凋亡率[68]。Bel联用组蛋白甲基酶抑制剂和全反式维甲酸通过促进癌症信号通路相关基因启动子或基因区域组蛋白的H4超乙酰化发挥抗AML的作用[69]。

2014年，美国多中心II期临床试验发现Bel单用对AML的治疗效果并不好（无一人达到CR）[70]。2021年，弗吉尼亚联邦大学梅西癌症中心I期临床试验发现，Bel联合硼替佐米对治疗AML患者的总体疗效有限（仅两名患者达到CR，其余患者因不良事件发生或疾病持续进展而停止了这项研究[71]）。2023年，弗吉尼亚联邦大学梅西

癌症中心Ⅰ期临床试验发现，Bel联用Weel激酶抑制剂对治疗AML患者几乎没有疗效[72]。未来对Bel治疗AML的研究应集中于与其他药物的联合应用，同时需要大量大规模的临床试验来探索Bel在AML中的临床应用价值。

3.3　帕比司他（Panobinostat，Farydak，Pan）

帕比司他，分子式$C_{21}H_{23}N_3O_2$（图2），分子质量为349.42，主要针对HDAC1、2、3、6，于2015年被FDA批准与硼替佐米和地塞米松联合治疗多发性骨髓瘤[73]。Pan可降低AML细胞中控制DNA修复和细胞周期检查点关键调节蛋白的表达水平，诱导组蛋白H3和H4超乙酰化，从而导致DNA损伤和细胞凋亡，在原始AML细胞样本中显现出强大的抗AML活性[74-75]。与SAHA相比，Pan的IC_{50}值的中位数显著降低，但其效力至少高出SAHA 10倍[76]。当Pan与AZA联用，可通过降低外周血和骨髓中细胞TNFR2的水平或下调癌基因（例如*MYC*）和表观遗传修饰物（例如KDM2B、SUV39H1）在癌症中的过度表达，诱导AML细胞凋亡、抑制AML细胞增殖，延缓大多数白血病小鼠的寿命[77-80]。必须要指出的是，此药会导致病人严重腹泻或心律失常，甚至有致命的心脏事件发生。

2015年，西班牙开展的一项Ib和II期临床试验表明，Pan与伊达比星、ara-C联用对治疗老年AML有良好的治疗效果（CR率为64%），且对微小残留病患者的疗效更为可观，同时提出Pan的最大耐受量为10 mg/d，以此接受治疗，具有良好的耐受性[81]。2017年，美国多个研究中心的Ib/II期临床试验发现，在AZA的基础上加PAN并没有提高治疗AML患者的效果（单用AZA CR率30.8%，联用Pan CR率为22.2%）[82]。2018年，德国多个研究中心开展的Ⅰ期临床试验发现，Pan单一用药几乎没有疗效，但Pan与ara-C、米托蒽醌联合应用对AML患者却有明显临床效益（单一用药组CR率为3.3%，联合用药组CR率达到31%）[83]。2019年美国多个研究中心开展了一项Ⅰ期临床试验，采用Pan联合ara-C、伊达比星联合治疗65岁以下AML患者，结果显示，ORR率为60.9%，其中43.5%达到CR，17.4%达到CR但计数不完全恢复，且推荐Pan的治疗使用剂量为20 mg/d[84]。2020年美国田纳西州孟菲斯市医学院开展了一项Ⅰ期临床试验，采用Pan与氟达拉滨、ara-C联合治疗24岁以下的患者，47%患者获得CR，其中75%患者获得了阴性的微小残留病状态[85]。由此可见，Pan单独使用对AML患者效果也不明显，但与化疗药物一起使用对AML患者表现出了可耐受的安全性和有效性，对微小残留病患者尤其有益。另外，对于65岁以上的患者推荐剂量为10 mg/d，65岁以下的患者可增加到20 mg/d。

3.4　丙戊酸（Valproic acid，VPA）

丙戊酸，分子式为$C_8H_{16}O_2$（图2），分子质量为144.21，是临床上用于治疗癫痫、双向情感障碍和偏头痛的短链脂肪酸，能特异性抑制HDAC2。体外研究发现，VPA可通过诱导*RASSF1A*基因的表达发挥抗AML细胞毒性作用[86]，但也可增加参与化疗耐药基因的表达（例如*MAKKPK2*、*HSP90AA1*、*HSP90AB1*和*ACTB*）[87]。在Kasumi-1 AML细胞系与*RUNX1-RUNX1T1*融合癌基因建立的小鼠异种移植模型中发现，VPA通过上调p21启动子区的组蛋白H3、H4超乙酰化，导致p21表达增加，诱导G0/G1停滞，达到抗肿瘤作用[88-89]。先前的研究鼓励将VPA与全反式维甲酸（all-trans-retinoic acid，ATRA）联合使用，这种组合能更好地诱导AML细胞的分化[90]，并且发现在ATRA耐药的APL变体中，使用VPA可以恢复其对ATRA的敏感性[91]。

2014年德国奥地利比较伊达比星、ara-C和ATRA联合治疗与在此方案上增加VPA治疗60岁以上AML患者的疗效，结果VPA组的CR率低于标准组（40%：52%），且早期死亡率较高（26%：14%）[92]。2015年美国坦普尔大学医学院II期临床试验发现，在地西他滨的基础上加入VPA并没有比单用地西他滨更能改善AML患者的预后（单独西他滨组CR率为31%，加入VPA组为37%）[93]。2020年德国多个研究中心开展了一项II期临床试验，试验分为地西他滨、地西他滨+VPA、地西他滨+ATRA、地西他滨+VPA+ATRA等4组，结果显示，单用地西他滨组客观有效率为8.5%，地西他滨+VPA为17.5%，地西他滨+ATRA为26.1%；地西他滨+VPA+ATRA为18.0%[94]。以上研究提示，VPA与ATRA联用对AML细胞具有明显的体外活性，但在临床上应用的效果并不可观。

3.5　恩替诺特（Entinostat，MS-275）

恩替诺特，分子式$C_{21}H_{20}N_4O_3$（图2），分子质量为376.41，是一种针对HDAC1、HDAC2人工合成的苯甲酰胺类HDACi[95]，能使组蛋白H3、H4过度乙酰化[96]。恩替诺特可下调bcl-2的表达，增

加p21的表达，诱导AML细胞生长停滞和凋亡；另一方面，恩替诺特可通过抑制AML细胞中热休克蛋白90的伴侣活性而诱导FLT3的降解，这表明恩替诺特可能对FLT3-ITD阳性AML患者的治疗有用[97]。恩替诺特的体内疗效也已在小鼠模型中得到证实[98]。2014年，美国多个研究中心开展了一项II期临床组间试验，AZA联合或不联合恩替诺特治疗骨髓增生异常综合征和AML伴骨髓发育不良患者，结果显示在AZA中加入恩替诺特并不能增加其临床疗效（AZA组CR率为12%，联合恩替诺特组为8%）[99]。目前对恩替诺特在AML中的作用机制认识较少，研究大多基于体外试验和动物实验，缺少人体试验，针对恩替诺特对AML的治疗仍有很多问题亟待解决。

3.6　西达本胺（Chidamide，爱普沙，HBI-8000）

西达本胺，化学式为$C_{22}H_{19}FN_4O_2$（图2），分子质量为390.41，是一种苯甲酰胺类HDACi，可以抑制HDAC1、HDAC3、HDAC10，临床上适用于既往至少接受过一次全身化疗的r/r性外周T细胞淋巴瘤患者，自2015年起在中国用于治疗外周T细胞淋巴瘤[100]。由于其抗肿瘤效力，西达本胺也被用于研究治疗骨髓瘤、非小细胞肺癌和乳腺癌等。近期有研究表明，西达本胺可通过调节HDAC3-AKT-P21-CDK2信号通路增加r/r AML细胞对蒽环类药物的敏感性[101]，单独使用西达本胺或者与ara-C联用在体外对AML细胞发挥抗肿瘤作用[102]，可能与通过将AML细胞阻滞于G0/G1期从而抑制AML细胞增殖有关。另外，西达本胺还可抑制小鼠皮下瘤的增殖[103]。

2018年中国郑州大学附属肿瘤医院采用西达本胺、地西他滨联合CHAG预激方案治疗r/r AML患者，结果显示，这种方案治疗r/r AML疗效显著（CR率为62.5%，其中40%达到微小残留病灶阴性）[104]。2020年中国深圳大学采用地西他滨和ara-C联合西达本胺治疗r/r AML患者，结果显示ORR率为46.2%[105]。2021年中国苏州大学开展了一项II期临床试验，采用西达本胺联合地西他滨、ara-C、伊达比星和G-CSF治疗r/r AML患者，结果显示，ORR为74.3%，血液学完全恢复率为42.9%，形态学无白血病率为14.3%[106]。这些结果表明，联合西达本胺用药可能是更有效治疗r/r AML患者的一个方向，但需要在更大比例的人群中进行进一步的评估。

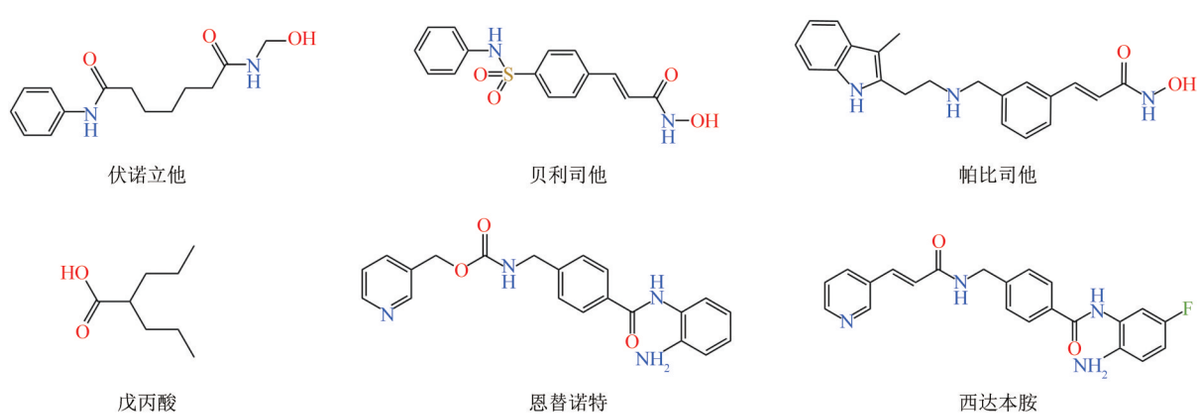

Fig. 2　Chemical formula of histone deacetylase inhibitor

图2　组蛋白去乙酰化酶抑制剂的化学结构式

4　讨论与总结

尽管对AML的了解有了很大的进步，新的和不断发展的治疗方法减少了药物毒性作用，提高了患者存活率，也为患者带来了希望，但仍需更高效的治疗手段。肿瘤的表观遗传治疗药物主要包括DNA甲基转移酶抑制剂、异柠檬酸脱氢酶抑制剂、HDACi和组蛋白甲基转移酶抑制剂等。其中异柠檬酸脱氢酶抑制剂ivosidenib和enasidenib被FDA和EMA批准用于r/r AML[107]，DNA甲基转移酶抑制剂AZA被FDA批准口服用于治疗强化诱导化疗后首次CR却无法完成强化治疗的患者以及选择不进行Allo-HSCT的AML患者[108]，HDACi Pracinostat和AZA组合疗法于2016年被FDA授予

突破性疗法认定，用于治疗75岁以上或不适合强化化疗的新诊断AML患者。虽然单独使用HDACi治疗AML结果并不乐观，HDACi与其他抗癌药物联合应用却有显著疗效。与单一治疗法相比，联合用药以一种典型的协同或叠加方式通过关键靶向途径提高疗效，增加AML对化疗的敏感性，减少肿瘤生长和转移潜力，抑制细胞有丝分裂活性，诱导细胞凋亡，调节骨髓微环境等[109]。如本综述第**3**节所提到：Pan与AZA联用，可通过降低外周血和骨髓中细胞TNFR2的水平或下调癌基因和表观遗传修饰物在癌症中的过度表达，诱导AML细胞凋亡、抑制AML细胞增殖；SAHA与FLT3抑制剂等联用时，可抑制*FLT3*基因突变；西达本胺可通过调节HDAC3-AKT-p21-CDK2信号通路增加r/r AML细胞对蒽环类药物的敏感性；VPA和羟基脲可通过增加AML细胞对自然杀伤（natural killer，NK）细胞的敏感性来增强NK细胞介导的抗白血病作用[110]。另外，AML对HDACi的敏感性可能与泛素连接酶RNF5密切相关[111]。

在提高治疗效果的同时，联合治疗也带来了一些不良反应（表1）。目前的HDACi主要是针对多种亚型的泛HDAC抑制剂，副作用明显，如疲劳、血小板减少、恶心、呕吐、腹泻等，近年来研究的下一代HDACi主要集中在类别或亚型选择性上，与非选择性抑制剂相比，可以提供更好的风险-收益概况。比如针对HDAC10的选择性抑制剂[112]、针对HDAC6的选择性抑制剂[113]和针对HDAC8的选择性抑制剂[114]，可以最大限度地提高药理作用，并最大限度地减少泛HDAC抑制剂的副作用。许多小分子选择性HDACi已进入临床研究，预计会在不久的将来获得批准作为治疗剂。因此，寻找HDACi与其他药物的最佳组合方案和最佳给药时机以平衡疗效与不良反应是此后治疗AML的一大挑战，继续开发毒副作用更小、作用位置更精准的选择性HDACi是未来此药物发展的关键点。

Table 1　Adverse reactions of histone deacetylase inhibitors in acute myeloid leukemia

表1　组蛋白去乙酰化酶抑制剂在急性髓系白血病中应用的不良反应

HDACi	类型	可抑制的HDAC	临床联用药物	不良反应	文献
伏立诺他	异羟肟酸	I类1、2、3，II类	单独使用	肺炎、中枢神经系统出血、头晕和乏力	［59］
			地西他滨+阿糖胞苷	发热性中性粒细胞减少、导管相关感染腹泻、恶心、乏力、嗜中性粒细胞减少、丙氨酸氨基转移酶升高	［64］
			地西他滨	疲劳、恶心、腹泻、厌食、呕吐、脱水	［63］
			阿扎胞苷+吉妥珠单抗	细胞减少、感染性并发症	［61］
			阿糖胞苷+依托泊苷	腹泻、恶心、发烧、呕吐和疲劳	［60］
贝利司他	异羟肟酸	I类1、2、3，II类6、9、10，IV	单独使用	非血液学毒性反应、脱水发热中性粒细胞减少、乏力、恶心、呕吐、AST/ALT升高、虚弱和腹部不适、中枢神经系统血肿	［70］
帕比司他	异羟肟酸	III类、IV类	阿扎胞苷	中性粒细胞减少症、血小板减少症、贫血	［82］
			阿糖胞苷+伊达比星	腹泻、恶心、呕吐、食欲减退、口腔炎、乏力	［84］
			氟达拉滨+阿糖胞苷	贫血、胃肠道疾病、呕吐、口腔粘膜炎、发热性中性粒细胞减少症、血小板计数下降、中性粒细胞计数下降、肺部感染	［85］
丙戊酸	短链脂肪酸	I类、IIa类	地西他滨	血小板减少、贫血、肺炎、发热性中性粒细胞减少症	［93］
			地西他滨+全反式维甲酸	血小板减少、贫血、肺炎、发热性中性粒细胞减少症	［94］
恩替诺特	苯甲酰胺	I类1、2	阿糖胞苷	中性粒细胞减少热、疲劳、血小板减少	［99］
西达本胺	苯甲酰胺	HDAC1、3、10	阿糖胞苷+地西他滨	肺炎、恶心、乏力、呕吐、低钾血症、低蛋白血症、发热性中性粒细胞减少症	［105］
			地西他滨+阿糖胞苷+伊达比星	感染性休克后肝肾功能严重恶化、血小板底下、中性粒细胞减少症	［106］

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Application of Histone Deacetylase Inhibitor in Acute Myeloid Leukemia*

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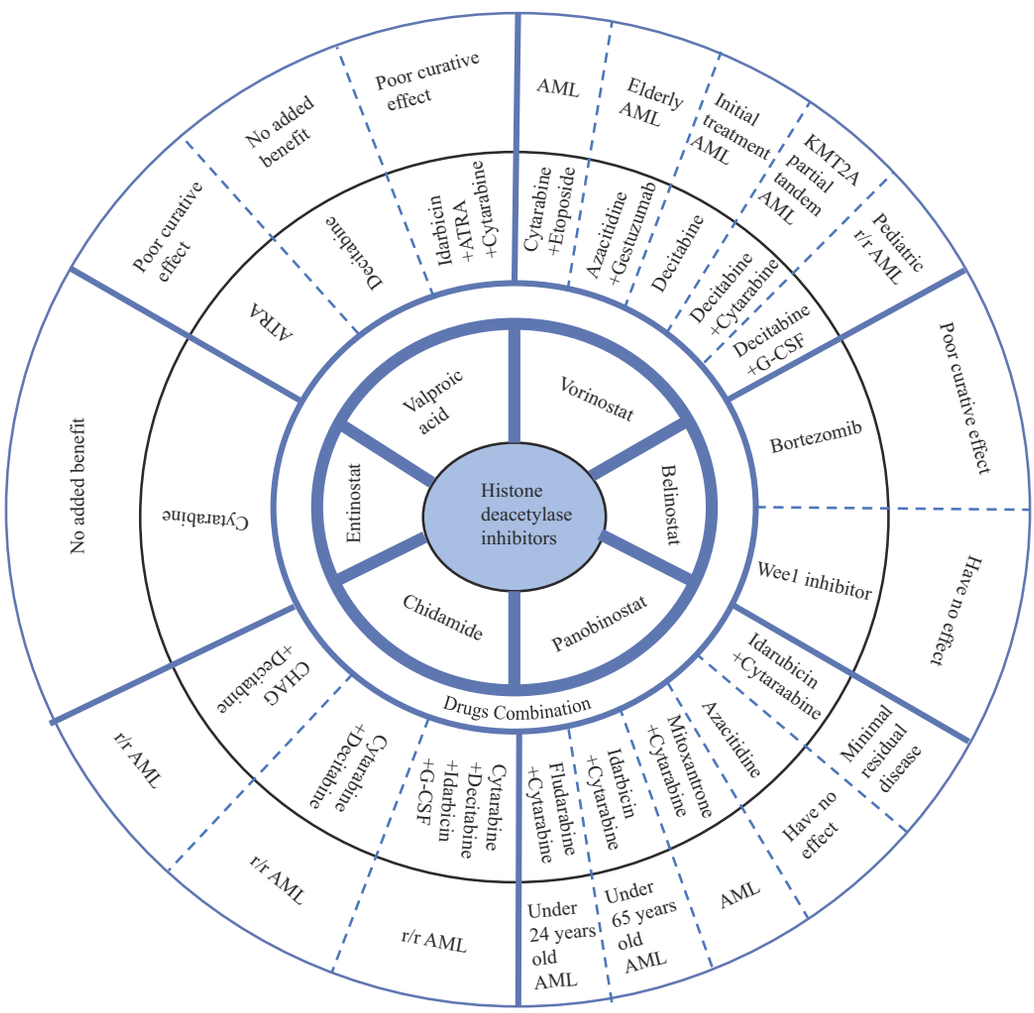
Graphical abstract



Abstract Acute myeloid leukemia (AML) is a malignant clonal disease of hematopoietic stem cells, characterized by the proliferation of abnormal primordial cells of myeloid origin in bone marrow, blood and other tissues. At present, the standard induction therapy for AML mainly includes “3+7” standard treatment

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(anthracycline combined with cytarabine), allogeneic hematopoietic stem cell transplantation (Allo-HSCT) and targeted drug therapy. However, AML cells usually express high levels of P-glycoprotein, which mediates the efflux of chemotherapeutic drugs, which makes AML cells resistant to chemotherapy, resulting in many patients who are not sensitive to chemotherapy or relapse after complete remission. And some patients can not tolerate intensive therapy or lack of donors and can not use Allo-HSCT therapy. Therefore, it is of great clinical significance to find new drugs to improve the efficacy of AML patients. Epigenetic disorders play a key role in the pathogenesis of many diseases, especially cancer. Studies have shown that most AML patients have epigenetic regulatory gene mutations, such as *DNMT3A*, *IDH* and *TET2*, and these mutations are potentially reversible, which has become one of the therapeutic targets of AML. Histone deacetylase inhibitors (HDACi) can regulate the balance between histone acetylation and deacetylation, change the expression of proto-oncogenes or tumor suppressor genes that control cancer progression from epigenetics, and play an important role in many kinds of tumor therapy. At present, HDACi has shown the ability to induce differentiation, cell cycle arrest and apoptosis of AML cells. The mechanism may be mainly related to HDACi inducing chromatin conformation opening of tumor suppressor gene by inhibiting HDAC activity, promoting oncogene damage and preventing oncogene fusion protein from recruiting HDAC. Although the preclinical outcome of HDACi is promising, it is not as effective as the conventional therapy of AML. However, the combination strategy with various anticancer drugs is in clinical trials, showing significant anti-AML activity, improving efficacy through key targeting pathways in a typical synergistic or additive way, increasing AML sensitivity to chemotherapy, reducing tumor growth and metastasis potential, inhibiting cell mitotic activity, inducing cell apoptosis, regulating bone marrow microenvironment, which provides a good choice for the treatment of AML. Especially for those AML patients who are not suitable for intensive therapy and drug resistance to chemotherapy. This review introduces the relationship between HDAC and cancer; the classification of HDAC and its function in AML; the correlation between HDAC and AML; the clinical application of five types of HDACi; preclinical research results and clinical application progress of six kinds of HDACi in AML, such as Vrinota, Belinostat, Panobinostat, Valproic acid, Entinostat, and Chidamide, the mechanism of HDACi combined with other anticancer drugs in AML indicates that the current HDACi is mainly aimed at various subtypes of pan-HDAC inhibitors, with obvious side effects, such as fatigue, thrombocytopenia, nausea, vomiting, diarrhea. In recent years, the next generation of HDACi is mainly focused on the selectivity of analogues or isomers. Finding the best combination of HDACi and other drugs and the best timing of administration to balance the efficacy and adverse reactions is a major challenge in the treatment of AML, and the continued development of selective HDACi with less side effects and more accurate location is the key point for the development of this drug in the future. It is expected to provide reference for clinical treatment of AML.

Key words acute myeloid leukemia, histone deacetylase inhibitor, histone deacetylase, epigenetics
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