硼替佐米在急性白血病中的应用研究

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摘要 硼替佐米(bortezomib)是首个进入临床的蛋白酶体靶向药物, 作为一线用药治疗多发性骨髓瘤和套细胞淋巴瘤时具有显著疗效, 近年来针对硼替佐米相关机制的不断深入研究, 使得硼替佐米可作为治疗急性白血病的潜在药物。前瞻性的研究表明, 硼替佐米在与其他药物联用时能取得积极疗效, 临床应用主要聚焦于初诊、复发难治急性髓系白血病与急性淋巴细胞白血病中的治疗, 该文就硼替佐米在急性白血病中的应用研究进行综述。

关键词 硼替佐米; 急性髓系白血病; 急性淋巴性白血病; 机制和临床研究

The Application of Bortezomib in Treatment of Acute Leukemia

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Abstract Bortezomib is the first protease-targeted drug approved by the FDA, and it has significant effects in the treatment of multiple myeloma and mantle cell lymphoma. The relevant mechanism for bortezomib may become a potential treatment for acute leukemia in recent years. There is evidence that bortezomib can benefit patients when used in combination with other therapies. Clinical applications are primarily focused on the treatment of newly dignosed and relapse/refractory acute myeloid leukemia as well as acute lymphoblastic leukemia. This findings summarize the basic mechanisms and current clinical development of bortezomib.

Keywords bortezomib; acute myeloid leukemia; acute lymphocytic leukemia; mechanisms and clinical research

急性白血病(acute leukemia, AL)是起源于造血干细胞的恶性克隆性疾病, 根据疾病进展过程中白血病细胞的分化程度可分为急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)和急性髓系白血病(acute myeloid leukemia, AML)。ALL以儿童发病为主, AML则是在成人中多见[1]。目前的风险评估和导向治疗大大改善了儿童ALL预后并延长了患儿生存期, 但成人ALL的长期治愈率仍低于40%, 同时化疗强度增强也给患者带来了明显的不良反应。在过去几十年里, AML治疗主要以“3+7”方案(蒽环类药物+阿糖胞苷)为主, 生存曲线停滞不前。近年来一些新的治疗方案将原有“3+7”方案缓解率从60%~70%提高至80%以上[4-5], 但仍有许多病人会复发。AL患者的耐药/复发是影响抗白血病药物长期疗效的限制因素之一, 也是目前临床所亟需解决的重要问题, 而寻找提高AL的缓解率、生存率以及生

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存质量的靶向药物是目前AL研究的热点。在众多靶向药物中，硼替佐米作为蛋白酶体抑制剂在治疗AL研究中也备受关注。

硼替佐米作为第一代26S蛋白酶体选择性抑制剂，能与20S蛋白酶体的糜胰凝乳酶切位点b5亚基结合[6]。研究表明，硼替佐米处理能够有效抑制白血病细胞增殖[7]，另外，多个有关硼替佐米联合其他药物治疗AL的临床试验正在进行中，本文将对蛋白酶体抑制剂硼替佐米近年来在AL中的基础研究及临床应用进行综述。

1 硼替佐米在急性白血病中的基础研究

泛素–蛋白酶体系统是体内降解蛋白质合成过程中错误折叠的蛋白质和其他蛋白质的主要途径。研究表明与正常外周血细胞相比，蛋白酶体在白血病细胞中表达水平显著高于正常细胞，抑制蛋白酶体可使白血病细胞凋亡数量明显增加[8]，因此蛋白酶体抑制剂可作为AL的潜在治疗靶点。

MPAKOU等[9]研究表明，使用低剂量地西他滨联合硼替佐米能通过阻滞G_0/G_1和G_2/M细胞周期抑制DNA合成，协同抑制AML细胞增殖。在IVANOVA等[10]的研究中也发现使用α-生育酚琥珀酸酯联合硼替佐米会对ALL细胞系产生细胞毒性作用，引起ROS累积增多进而诱导ALL细胞凋亡。目前硼替佐米治疗AL的可能作用机制主要有以下几种(图1)。

1.1 蛋白酶体抑制途径

NIEWERTH等[11]发现免疫蛋白酶体比例高的细胞对硼替佐米的治疗有更好的缓解率，研究人员认为免疫蛋白酶体比例可作为硼替佐米在急性白血病中反应的潜在指标。有研究发现硼替佐米在与Obatoclax联合作用人T-ALL细胞Jurkat时，硼替佐米和Obatoclax对蛋白酶体和自噬的双重阻断导致了泛素化蛋白质的进一步积累，引起内质网应激，从而诱导细胞毒性作用[12]。研究证明肿瘤细胞对蛋白酶体抑制的敏感性与蛋白酶体亚基的表达水平相关，免疫蛋白酶体亚基比例降低会引起肿瘤细胞耐药，表明蛋白酶体亚基组成比例在白血病细胞敏感/耐药中的重要性[13-14]。

1.2 核因子κB(NF-κB)途径

硼替佐米与许多抗白血病药物作用机制类似，也与生存通路的激活有关，最常见的就是NF-κB信号通路[15]。IκB是NF-κB的细胞抑制蛋白，当它

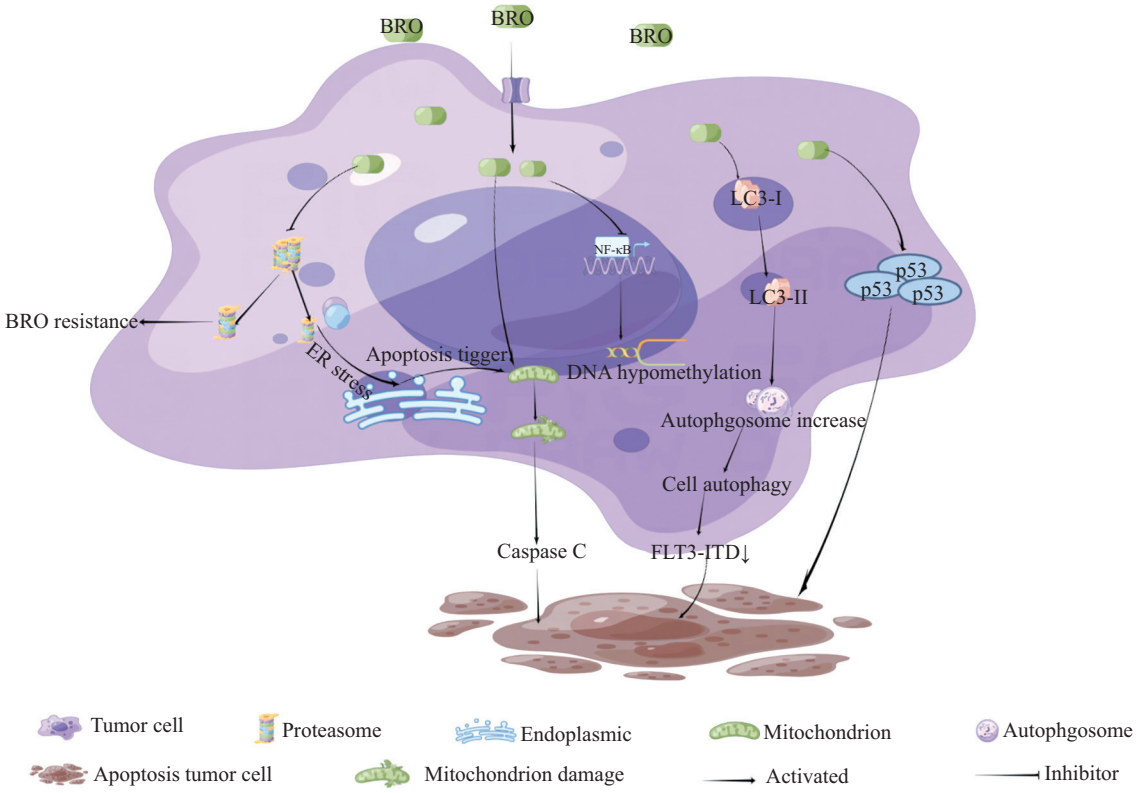

图1 硼替佐米抗白血病作用机制图

Fig.1 The anti-leukemia mechanism of bortezomib

在丝氨酸残基32和36处被磷酸化时, NF-κB会被泛素–蛋白酶体途径锁定并降解, 硼替佐米对蛋白酶体途径的抑制已被证明可以阻止IκBα的降解, 从而将NF-κB封存在细胞质中, 防止NF-κB核转位和激活*NF-κB*基因[16-17]。硼替佐米能通过干扰普遍表达的转录因子Sp1和NF-κB的相互作用, 导致整体DNA低甲基化, 进而抑制白血病细胞功能[18]。SADEGHI等[19]在实验中发现使用硼替佐米能降低NF-κB活性从而引起KG-1细胞凋亡, 表明硼替佐米具有显著的抗肿瘤作用。在ZHOU等[7]实验中使用硼替佐米作用MLL-AF9转化的AML小鼠, 发现硼替佐米抑制了AML干细胞的再生功能, 延长了小鼠总生存期, 其作用机制是细胞周期蛋白依赖性激酶6(CDK6)作为硼替佐米的靶标, 硼替佐米能通过抑制NF-κB, 继而降低CDK6的表达水平, 导致NF-κB对*CDK6*启动子的DNA结合失活从而抑制白血病干细胞的克隆增殖。

1.3 诱导细胞自噬

JIANG等[20]发现硼替佐米处理AML细胞8 h后可检测到细胞内自噬相关蛋白LC3-II上调、自噬标记物P62上调, 而细胞凋亡则发生在药物作用16 h后, 这表明硼替佐米在细胞凋亡早期即可诱导AML细胞自噬。LARRUE等[21]研究发现, 硼替佐米对含FLT3-ITD突变的AML具有靶向性, 可以通过FLT3下调导致细胞死亡, 进一步研究发现该细胞死亡途径并不主要是由半光天冬酶介导的细胞凋亡, 其中另外一种主要蛋白水解途径自噬也发挥重要作用。在硼替佐米处理含FLT3-ITD突变的AML细胞后, 细胞内LC3-I向LC3-II的转化, 自噬体数量增多, 同时FLT3-ITD可定位在自噬体中, 这表明硼替佐米能通过诱导自噬下调FLT3-ITD表达, 进而导致细胞凋亡。

1.4 线粒体凋亡途径

研究表明, 线粒体的凋亡途径在硼替佐米耐药及细胞凋亡中起着关键作用[22-23]。Bcl-2家族成员介导和控制线粒体外膜通透性从而诱导线粒体凋亡[24]。研究表明, 硼替佐米能引起Bcl-2家族促凋亡蛋白成员(如: BIK、NOXA、PUMA和BIM)的累积, 从而导致细胞凋亡[25]。MUENCHOW等[26]在研究中发现, Bcl-2抑制剂维奈克拉能通过累积BAX和NOXA蛋白, 增强肿瘤细胞对硼替佐米的敏感性, 诱导细胞线粒体外膜通透性改变, 释放细胞色素C, 导致肿瘤细胞死亡。

1.5 p53通路

TP53位于17p13.1号染色体, 编码p53抑癌蛋白, 可保护基因组的完整性并控制组织稳态, 在人类50%以上的肿瘤组织中均发现了*p53*基因的突变[27]。XUE等[28]在小鼠体内发现硼替佐米可以在正常及肿瘤组织中稳定并激活p53, 继而引起肿瘤细胞凋亡并抑制肿瘤生长。BASTIA等[29]使用硼替佐米联合组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitor, HDACI)对前体B-ALL患者的原代细胞进行处理, 发现两药联合具有协同抗白血病效应, 联合作用机制主要与细胞周期、JUN/MAPK、PI3K/AKT、p53、泛素/蛋白酶体和NF-κB通路的基因调节有关。

综上所述, 以上各项机制研究为硼替佐米与其他抗白血病药物的联合使用提供了基础, 表明硼替佐米是一种治疗AL独立于常规化疗的潜在有效药物。

2 硼替佐米在急性白血病的临床应用

多项研究表明, 硼替佐米单独治疗AML活性不高, 患者中没有观察到完全缓解(complete remission, CR)或部分缓解(partial remission, PR)[30-32]。鉴于其单药治疗作用有限, 目前需要探索其与其他药物联合使用后的疗效。以下分别对硼替佐米在AML与ALL中的临床应用情况进行综述(表1)。

2.1 硼替佐米治疗复发/难治AML

如何让复发/难治AML患者的缓解率及生存率得以提高是目前临床所面临的问题。GHADIANY等[33]在一项前瞻性非干预性研究中, 将40名接受挽救治疗的R/R AML患者随机分为FLAG(氟达拉滨、阿糖胞苷、粒细胞集落刺激因子)+EMA(依托泊苷、米托蒽醌、阿糖胞苷)组和FLAG+EMA+硼替佐米组, 两组患者平均年龄分别为48.5±8.9和50.5±9.5岁。研究结果发现FLAG+EMA+硼替佐米组和FLAG+EMA组的CR分别为30%和25%, 中位生存期分别为8.2月和7.1月 (P=0.275)。在HOLKOVA等[34]进行的一项I期传统3+3剂量递增研究中, 纳入38名患者(包括R/R AML、MDS转化AML、CML伴急变危象), 中位年龄为62岁(范围27~83岁), 在1~5天和8~12天静脉输注贝利司他, 在第 1、4、8 和11天先给予硼替佐米再输注贝利司他, 硼替佐米的起始剂量为1.0 mg/m^2; 贝利司他的起始剂量为500 mg/m^2。21天为一个周期,

表1 硼替佐米临床研究及结果

Table 1 Clinical study of bortezomib and results

文献来源 Study and year of publication	药物 Drugs	人数 Participant	年龄 Age of patients	疾病 Nature of disease	试验简介 Brief details of study	治疗结果 Results
GHADIANY M, et al, 2021	Bortezomib, fludarabine, cytarabine, etoposide, mitoxant	40	48.5±8.9 and 50.5±9.5 years old	R/R AML	A prospective non-interventional research trial dividing patients between salvage therapy plus bortezomib and salvage therapy without bortezomib	(1) CR rate was 30% and 25%, PR rate was 35% and 50%, mean survival time was 8.2 months and 7.1 months (2) DLTs observed in 15% participants per group
HOLKOVA B, et al, 2021	Belinstat, bortezomib	38	27-83 years old	R/R AML, sAML	Belinostat was administered on days 1 to 5 and 8 to 2 of each cycle of the phase I dose-escalation study. Bortezomib was administered on days 1, 4, 8 and 11 followed by belinstat infusions	(1) No abnormalities were found in the whole exome of a patient with highly refractory MLL-ENL (2) Stable disease was observed in 18 patients, which 12 patients of AML
KULKARNI U, et al, 2020	Mitoxantrone, ATO, ATRA, bortezomib	22	17.5-41.5 years old	R/R APL	An non-randomized phase II trial, mitoxantrone was given for the first 2 days of induction treatment, followed by ATO and ATRA, bortezomib consolidation therapy was given on days 2 and 5 and consisted of 4 weeks	(1) All patients were in hematological remission at the end of induction therapy, and all patients were in molecular remission after consolidation therapy. Two-year OS and EFS survival rates were 95%±4.9% and 80.2%±8.9%, respectively (2) Grade 3 toxicity was noted in 8 patients, and during a median follow-up period of 48 months (range 28-56.3), 2 patients died and 3 relapsed
SAYAR H, et al, 2019	Sorafenib, vorinostat, bortezomib	17	37-74 years old	R/R AML (FLT3-ITD)	Phase I/II study of combination of sorafenib, vorinostat and bortezomib for the treatment, and bortezomib will be given on days 1 and 8. This will be followed by 7 days of rest. Therefore each cycle will be 21 days	(1) CR and CRI was observed in 7 patients, PR was 2 (2) ALL patients was relapsed after consolidation therapy 2 cycle
APLENC R, et al, 2020	Daunorubicin, etoposide, cytarabine, bortezomib	1 097	＜30 years old	*De novo* AML	An open, multicenter randomized phase III clinical study randomized 1 097 patients under the age of 30 years with primary AML into a standard chemotherapy control group and a bortezomib plus standard chemotherapy intervention group. The intervention group was given bortezomib on days 1, 4 and 8 of each chemotherapy course	(1) The CR rates was 89% and 91% (P=0.531), respectively. Three years EFS was 44.8%±4.5% and 47.0%±4.5%, respectively Three years OS was 63.6%±4.5% and 67.2%±4.3% respectively (2) Bortezomib combination standard chemotherapy has been found to increase toxicity
ROBOZ G J, et al, 2018	Decitabine, bortezomib	163	≥60 years old	*De novo* AML	The randomized phase II trial compared decitabine alone (group A) with decitabine combined with bortezomib (group B), patients in group B also received decitabine for 10 consecutive days and were treated with bortezomib on days 1, 4, 8 and 11	CR/CRi rate was 39% (95% CI, 28-50) in group A, CR/CRi rate was 38% (95% CI, 28-50) in group B; The OS was 11.6 months (95% CI, 8.3-21.9) and 15.8 months (95% CI, 9.2-22.5), respectively

续表1

文献来源 Study and year of publication	药物 Drugs	人数 Particpant	年龄 Age of patients	疾病 Nature of disease	试验简介 Brief details of study	治疗结果 Results
HORTON T M, et al, 2019	Vincristine, doxorubicin, bortezomib, asparaginase, prednisone	135	1-31 years old	R/R ALL (B-ALL, T-ALL)	The phase II clinical trial divided relapsed patients into relapsed, very early relapsed (18 months after diagnosis) and early relapsed (18-36 months after diagnosis). Bortezomib was administered intravenously on days 1, 4, 8 and 11 in a 28-day treatment cycle for a total of three cycles	(1) CR rate was 68%±5% in pre-ALL, very early relapsed patients who achieved MRDneg and MRDpos three years EFS was 70%±14% and 3%±3% respectively, three-year OS was 70%±19% and 0% respectively; early relapsed patients who achieved MRDneg and MRDpos three years EFS was 58%±19% and 10%±9% respectively, three-year OS was 65%±17% and 19%±17% respectively (2) T-ALL also achieved good outcome(CR: 68%±10%), 75% MRD-neg patients still alive after 3 years, while three-year OS for MRDpos patients was 44%
COLUNGA-PEDRAZA J E, et al, 2020	Vincristine, doxorubicin, *L*-asparaginase, bortezomib	15	2-35 years old	R/R ALL	A retrospective analysis used bortezomib on days 1, 4, 8 and 11, dexamethasone for 21 days; intrathecal vincristine was administered on days 1, 8, 15 and 22; doxorubicin and *L*-asparaginase were infused intravenously on day 1, and intrathecal chemotherapy was administered three times to all patients	60% patients achieved CR and CRi, five-year OS was 40%
AUGUST K J, et al, 2020	Mitoxantrone dexamethasone, vincristine, bortezomib, peptonase, methotrexate	10	11 months-18.5 years old	R/R ALL	Bortezomib combined with re-induction regimen for treatment. Bortezomib was administered on days 1, 4, 8 and 11 Received mitoxantrone, dexamethasone, peptonase, vincristine, and intrathecal methotrexate over a 4-week period	(1) There are 8 patients achieved CR or CRi, MRD was not detected in 2 of the CR patients (<0.01%) (2) All 8 patients who obtained CR or CRi eventually relapsed
LA STARZA R, et al, 2019	Venetoclax, bortezomib	3	26-78 years old	ETP-ALL	Treatment with oral venetoclax (800 mg/day×28 days) and bortezomib (1.3 mg/m^2 twice weekly ×2 [case 1, case 2] or ×4 [case 3])	All patients achieved CR or PR after a month
TEACHEY D T, et al, 2022	Bortezomib, modified BFM regimens	824	＜30 years old	*De novo* T-ALL/T-LL	The randomized phase III trial divided into modified BFM regimens (group A) and modified BFM regimens combination bortezomib (group B), both of them add prednisone and peptonase to reduce prophylactic cranial radiotherapy	(1) The four-year EFS in group A and group B were 80.1%±2.3% and 83.8%±2.1% respectively, while OS were 85.7%±2.0% and 88.3%±1.8% respectively (2) Limited efficacy was observed upon treatment of bortezomib. Only 9.5% of patients in the trial group underwent prophylactic cranial radiotherapy
JAIN H, et al, 2021	Methotrexate, asparaginase, doxorubicin, vincristine, rituximab, bortezomib	35	＞14 years old	*De novo* $CD20^+Ph^-$ pre-B-ALL	An open, single-center randomized phase II trial was treated with modified BFM-90 protocol, rituximab administered intravenously on days 1, 8, 15, 22 and 28 , bortezomib administered subcutaneously on days 1, 4, 8 and 11	(1) There were 29 patients achieved CR after follow-up 21 months, EFS and OS rate were 78.8% (95% CI, 64.6-94.0) and 78.7% (95% CI, 65.8-94.0) respectively (2) There was no significant increase in toxicity with bortezomib compared to conventional chem-therapy treatment, with a 26% incidence of neuropathy

二期推荐剂量(recommended phase II dose, RP2D)使用1.3 mg/m^{2}硼替佐米和1 000 mg/m^{2}贝利司他治疗, 有18名患者疾病稳定(stable diease, SD), SD中位时间为3.8个月, 研究表明贝利司他联合硼替佐米治疗R/R AML安全, 并且对部分患者有效。KULKARNI等[35]的一项非随机、II期、单中心研究招募了22名复发急性早幼粒细胞白血病(acute promyelocytic leukemia, APL)患者, 中位年龄为26.5岁(17.5~41.5岁), 入组患者在诱导治疗的前2天给予米托蒽醌10 mg/m^2, 而后接受三氧化二砷10 mg/天静脉注射和每天维甲酸45 mg/m^{2}治疗, 在第2天和第5天予以硼替佐米1.4 mg/m^2, 巩固治疗包括4周的砷剂和维甲酸以及两次硼替佐米。在诱导治疗结束时均达到血液学缓解, 所有患者在巩固治疗后均达到分子缓解, 两年总体生存期(overall survival, OS)和无事件生存期(event-free survival, EFS)分别为95%±4.9%和80.2%±8.9%。该项研究表明, 在复发APL中, 硼替佐米联合治疗具有显著临床效果。SAYAR等[36]进行了一项索拉非尼、伏立诺他和硼替佐米联合治疗高危AML的临床I/II期研究, 该研究纳入17名R/R AML并伴有FLT3-ITD突变患者, 实验采用3+3剂量递增方案, 实验共有7名患者获得CR+CRi(CR with incomplete count recovery, CRi), 2名患者PR。该研究表明了硼替佐米联合索拉非尼、伏立诺他在治疗R/R AML伴FTL3-ITD患者方面是可耐受且有效的。有部分研究显示, 硼替佐米联合其他药物能一定程度提高复发/难治AML患者CR, 但并没有提高OS和EFS, 该结论需要更多研究提供数据支持。

2.2 硼替佐米治疗初诊AML

APLENC等[37]进行的一项开放、多中心随机III期临床研究将1 097名年龄<30岁的初诊AML患者随机分为化疗对照组(ADE; n=542)和硼替佐米试验组(ADEB; n=555)。试验组在每个化疗疗程的第1、4、8天给予1.3 mg/m^{2}硼替佐米。两组缓解率分别为89%和91%(P=0.531), 两组3年EFS分别为44.8%±4.5%和47.0%±4.5%(P=0.236), 3年OS分别为63.6%±4.5%和67.2%±4.3%(P=0.356), 联合硼替佐米对患者缓解率并无显著性改善, 而且会增加神经病变等相关毒性。ROBOZ等[38]进行的一项2期随机、多中心临床试验比较了硼替佐米与地西他滨的疗效, 将163名年龄≥60岁的AML患者随机分为地西他滨(A组, 82人)与地西他滨联合硼替佐米(B组, 81人)组。A组的患者连续10天接受20 mg/m^{2}地西他滨治疗, B组的患者在连续10天接受20 mg/m^{2}静脉注射地西他滨的基础上分别在第1、4、8和11天皮下注射1.3 mg/m^{2}硼替佐米进行治疗。两组CR/CRi分别为39%(95% CI, 28%~50%) *vs* 38%(95% CI, 28%~50%; P=0.91), 在CR/CRi患者中, OS分别为11.6个月(95% CI, 8.3%~21.9%) *vs* 15.8个月(95% CI, 9.2%~22.5%; P=0.60), 两组在缓解率、接受的治疗周期数及缓解时间方面没有统计学差异, 上述研究表明地西他滨联合硼替佐米治疗AML并不能改善患者的预后。虽然加入硼替佐米无其他药物毒性出现且较为安全, 但在CR和OS方面并没有得到提高, 使用硼替佐米治疗初诊AML仍需更多研究深入探讨。

2.3 硼替佐米治疗复发/难治ALL

研究表明, 有15%~20%的ALL儿童会出现复发, 并且复发患儿的预后很差[39]。微小残留病灶或分子残留病灶(minimal residual disease, MRD)是指肿瘤患者接受根治性治疗后, 体内仍有肿瘤细胞残留, MRD是导致疾病复发和转移的重要因素之一。HORTON等[40]开展的一项II期临床试验有125名(103名B-ALL, 22名T-ALL)复发患儿接受了硼替佐米联合VPLD方案(长春新碱、多柔比星、天冬酰胺酶、泼尼松)治疗, 复发分为极早期复发(诊断后18个月内)和早期复发(诊断后18~36个月)。在第1、4、8、11天静脉注射硼替佐米1.3 mg/m^2, 28天为一个治疗周期, 共三个周期。前体B-ALL患者CR率为68%±5%, 极早期复发MRDneg和MRDpos患者的三年EFS分别为70%±14%和3%±3%(P<0.000 1), 三年OS分别70%±19%和0%(P<0.000 3); 而早期复发后获得缓解的MRDneg和MRDpos患者的三年EFS率分别为58%±19%(P<0.000 1)和10%±9%(P<0.000 1), 三年OS分别为65%±17%和19%±17%(P=0.0014)。T-ALL患者的CR率为68%±10%(15/22名患者), 有3/4的MRDneg患者在3年后仍存活, 而MRDpos患者的3年OS仅为44%。COLUNGA等[41]回顾性分析了对15名R/R ALL患者的再诱导治疗, 患者中位年龄13岁(范围2~35岁), 在第1、4、8、11天静脉注射硼替佐米(1.3 mg/m^2); 在1~21天持续静脉注射地塞米松(10 mg/m^2); 在第1、8、15和22天静脉注射长春新碱(1.5 mg/m^2); 第1天静脉注射输注多柔比星50 mg/m^{2}或米托蒽醌10 mg/m^{2}及*L*-天冬酰胺酶6 000 U/m^2, 有60%(9/15)达到了CR/CRi, 五年OS为40%。而AUGUST等[42]在一项临床研究中

对10名R/R ALL患儿(年龄范围为11个月至18.5岁)进行了硼替佐米联合ALL R3方案(米托蒽醌、地塞米松、长春新碱、培门冬酶和鞘内注射甲氨蝶呤)的再诱导治疗。分别于第1、4、8、11天给予硼替佐米1.3 mg/m^2, 有80%(8/10)患者获得CR/CRi, 在CR患者中有2名患者获得MRD阴性(<0.01%), 提示ALL R3方案中加入硼替佐米治疗R/R ALL的儿童是一种获得有效缓解的新方案。STRAZAS等[43]对3名R/R早期前体T急性淋巴细胞白血病(ETP-ALL)患者进行口服硼替佐米[1.3 mg/m^{2}每周两次×2(病例1、病例2)或×4(病例3)]与维奈托克(800 mg/天×28天)治疗, 一个月后病例1达到CR, 另外两名患者PR, 并且研究显示硼替佐米联合维奈克拉耐受性良好。北京大学人民医院儿科的一项病例系列报告将11名ALL患儿纳入分析, 诊断中位年龄10岁(3~15), 其中包括7例T-ALL, 2例T淋巴母细胞淋巴瘤IV期, 2例B-ALL(复发/难治6例, 高危5例), 在使用硼替佐米联合化疗1个疗程后, 8例患儿(B-ALL 1例, T-ALL 7例)治疗有反应, 客观缓解率(objective response rate, ORR)为72.7%。治疗前骨髓形态未缓解3例, 部分缓解4例, 治疗后CR达到85.7%(6/7)；治疗前骨髓MRD阳性10例, 治疗后MRD比率均有下降, 并且1例MRD转阴, 中位随访时间15个月(2~29个月), 2年EFS为(45.5±15.0)%, OS为(63.6±14.5)%[44]。上述研究表明, 硼替佐米联合其他药物方案提高了患者生存率, 能够显著提高患者的MRD阴性率, 并且MRD阴性患者的预后较MRD阳性患者更佳, 因此在R/R ALL患者治疗中加入硼替佐米能在一定程度获得有效缓解, 有望提高患者OS和EFS。

2.4 硼替佐米治疗初诊ALL

ALL是儿童中最常见的肿瘤之一, 占儿童所有癌症的26%, 在成人中ALL约占AL的20%[45]。为了改善T细胞急性淋巴细胞白血病(T-ALL)患者预后, COG进行的一项III期临床试验, 将824名年龄<30岁的初诊的T-ALL患者在诱导和巩固期间随机分配为改良BFM化疗方案(A组)和硼替佐米联合改良BFM化疗方案(B组), 并在治疗方案中加入了泼尼松和培门冬酶减少预防性颅脑放疗。A组与B组的T-ALL的4年EFS和OS分别为80.1%±2.3%与83.8%±2.1%(EFS, P=0.131)和85.7%±2.0%与88.3%±1.8%(OS, P=0.085)。研究发现, 使用硼替佐米未见明显毒性, 试验组中仅有9.5%的患者进行了预防性颅脑放疗[46]。JAIN等[47]的一项单中心、II期、非随机开放研究纳入35名初诊CD20$^+$Ph$^-$前体B-ALL患者, 中位年龄20岁(范围15~52岁), 治疗使用修改后的BFM-90方案(甲氨蝶呤、门冬酰胺酶、柔红霉素、长春新碱), 在第1、8、15、22和28天静脉输注利妥昔单抗375 mg/m^2, 在第1、4、8和11天皮下给药硼替佐米1.3 mg/m^2。有29名患者达到CR(85.3%), 研究发现化疗+硼替佐米+利妥昔单抗方案可将原单独化疗方案的MRD阴性率由51.7%提升至70.9%, 随访21个月后EFS和OS率分别为78.8%(95% CI, 64.6%~94%)和78.7%(95% CI, 65.8%~94%), 与既往常规化疗治疗相比加入硼替佐米+利妥昔单抗毒性并没有显著增加毒性反应, 神经病变的发生率为26%, 表明硼替佐米联合利妥昔单抗治疗CD20$^+$Ph$^-$前体B-ALL是一种有效的方案。根据以上研究在治疗方案中加入硼替佐米治疗初诊ALL可提高MRD阴性率, 但在提高OS和EFS方面并没有显著提升。

3 正在进行的临床试验

目前有多项硼替佐米联合其他药物的治疗AL方案的临床研究正在进行, 为临床治疗探索新的方案, 最终达到提高AL的缓解率和生存期的目的(表2)。

4 总结

硼替佐米联合其他药物成为治疗AL的新选择, 为此开展大量的实验研究与临床应用。综上研究显示, 硼替佐米在治疗R/R AML时与其他抗肿瘤药物联用能够达到一定缓解并提高EFS和OS; 治疗ALL初诊患者时, 硼替佐米联合其他药物被考虑作为治疗方案; 多项研究表明, 硼替佐米与常规化疗药物、糖皮质激素、靶向药物等联用时是有效且耐受良好的方案。针对硼替佐米耐药的AL, 可以应用具有活性且毒性更低的新型蛋白酶体抑制剂, 从而克服硼替佐米耐药(如卡非佐米、伊沙佐米或马里佐米)。例如新一代的蛋白酶体抑制剂伊沙佐米(Ixazomib)具有口服见效快, 神经毒性反应更少等优点, 目前已经成为临床上一线治疗药物。在一例病例报道的研究中, 一名不符合SCT(stem cell transplantation)条件的MDS患者在阿扎胞苷和硼替佐米治疗无效后转变为AML, 后续使用伊沙佐米单药治疗后保持完全缓解[48], 并且有临床研究表明伊沙佐米联合MEC(米托蒽醌、依托

表2 硼替佐米进行中的临床试验

Table 2 Clinical trials of bortezomib and results

阶段 Phase	人数 Parti-cipant	年龄 Ages	疾病 Disease	药物 Drugs	招募状态 Recruitment status	编号 ID
I	15	18 years old and older	AML	Bortezomib, sorafenib tosylate, decitabine	Active, not recruiting	NCT01861314
II	165	60 years old and older	AML	Bortezomib, decitabine	Active, not recruiting	NCT01420926
III	1 645	Up to 29 years old	*De novo* AML	Asparaginase, cytarabine, bortezomib, daunorubicin hydrochloride, laboratory biomarker analysis, etoposide	Active, not recruiting	NCT01371981
I	22	Up to 25 years old	R/R ALL	Palbociclib, bortezomib, dexamethasone, doxorubicin	Active, recruiting	NCT04996160
II	42	15 years old and older	R/R ALL	Bortezomib, clofarabine, cyclophosphamide, dexamethasone, etoposide	Active, recruiting	NCT03136146
II	100	3 months to 21 years old	R/R ALL	Bortezomib, rituximab	Active, recruiting	NCT04224571
III	4 000	1 year old to 50 years old	ALL	dexamethasone, methylprednisolone, daunorubicin, idarubicin, bortezomib	Active, recruiting	NCT03390387
IV	56	18 years old to 50 years old	R/R ALL	Cyclophosphamide, vincristine, adriamycin, dexamethasone, bortezomib	Active, recruiting	NCT05137860

泊苷、阿糖胞苷)对30名中位年龄为58岁(范围31~70岁)的R/R AML患者进行挽救治疗时, CR+CRi达到53%, 临床缓解率高于原MEC方案预期[49], 目前多项关于伊沙佐米联合其他药物治疗AL的临床研究正在进行中。综上所述, 在可以预见的将来, 随着对硼替佐米这类蛋白酶体抑制剂的研究的不断深入, 不仅能有望提高AL患者缓解率及生存期, 而且为化疗耐药及不耐受化疗的患者提供了新的治疗策略。

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