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阿扎胞苷单药或联合 HAG 方案在骨髓增生异常综合征中的临床观察 *

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摘要 目的:探究阿扎胞苷(Azacitidine, AZA)单药或联合 HAG 方案治疗骨髓增生异常综合征(Myelodysplastic syndromes, MDS)的临床疗效及安全性。**方法:**回顾性分析 49 例 MDS 患者的临床资料,根据治疗方法不同分为支持治疗组和含 AZA 组(单药或联合 HAG 方案),统计分析患者的临床疗效及不良反应情况。**结果:**支持治疗组的总有效率(Overall response rate, ORR)为 30.00% (6/20),包括 0 例完全缓解(Complete remission, CR),1 例骨髓完全缓解(Marrow complete remission, mCR),2 例部分缓解(Partial remission, PR),3 例血液学改善(Hematological improvement, HI)。含 AZA 组的 ORR 为 65.52%,包括 8 例 CR、2 例 mCR、4 例 PR、5 例 HI。其中单药组的 ORR 为 46.67%,包括 2 例 CR、1 例 mCR、2 例 PR、2 例 HI;联合组的 ORR 为 85.71%,包括 6 例 CR、1 例 mCR、2 例 PR、3 例 HI。与支持治疗组相比,含 AZA 组的完全缓解率(CR+mCR)及 ORR 显著增高,差异有统计学意义($P < 0.05$)。患者最常见的不良反应是 III-IV 级骨髓抑制(18/29)及继发感染(10/29),且随着疗程数的增加不良事件逐渐减少。含 AZA 组患者的中位总生存(Overall survival, OS)时间及中位无进展生存时间(Progression-free survival, PFS)时间显著延长($P < 0.05$)。**结论:**该小系列研究的初步结果表明,与支持治疗相比,AZA 单药或联合 HAG 方案治疗 MDS 有更高的治疗反应,可延长患者总生存期,患者有良好的耐受性,且联合治疗方案可能有更好的疗效。

关键词:阿扎胞苷;预激方案;骨髓增生异常综合征;临床观察;疗效评价

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Clinical Observation of Azacitidine or Combined with HAG Regimen in Myelodysplastic Syndrome*

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ABSTRACT Objective: To explore the clinical efficacy and safety of azacitidine(AZA) or combined with HAG regimen in the treatment of myelodysplastic syndrome (MDS). **Methods:** The clinical data of 49 patients with MDS in our hospital were retrospectively analyzed. According to different treatment methods, they were divided into supportive treatment group and AZA containing group (AZA or combined with HAG regimen). The clinical efficacy and adverse reactions of the patients were statistically analyzed. **Results:** In the supportive treatment group, the overall response rate (ORR) was 30.00%, including 0 case complete remission (CR), 1 case of bone marrow complete remission (mCR), 2 cases of partial remission (PR), 3 cases of hematological improvement (HI). The ORR of the AZA containing group was 65.52%, including 8 cases CR, 2 case mCR, 4 cases PR and 5 cases HI. The ORR of monotherapy group was 46.67%, including 2 cases CR, 1 case mCR, 2 cases PR, 2 cases HI. The ORR of combination group was 85.71%, including 6 cases CR, 1 case mCR, 2 cases PR, 3 cases HI. Compared with the supportive treatment group, the complete remission rate and ORR in the group containing AZA were significantly higher than those in the treatment group, and the difference was statistically significant($P < 0.05$). After receiving AZA containing regimen, the most common adverse reactions were grade III-IV myelosuppression (18/29) and secondary infection (10/29), and the incidence gradually decreased with the increase of treatment courses. Compared with the supportive treatment group, the median Overall survival time and median Progression-free survival time of patients with AZA were significantly longer ($P < 0.05$). **Conclusion:** The results of this small sample retrospective case study show that compared with supportive treatment, AZA or combined with

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HAG regimen has a higher response rate in the treatment of MDS patients, can prolong the overall survival time of patients, and is well tolerated. And combination therapy may have a better effect.

Key words: Azacitidine; Priming regimen; Myelodysplastic syndromes; Clinical observation; Efficacy evaluation

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前言

骨髓增生异常综合征 (Myelodysplastic syndromes, MDS) 是起源于造血干细胞的一组异质性髓系克隆性疾病, 主要发病人群为老年人, 有向急性髓系白血病(Acute myeloid leukemia, AML)转化的风险^[1,2]。异常甲基化在 MDS 的发生、发展中发挥着重要作用^[3,4]。AZA 是目前临床常用的去甲基化药物(Hypomethylating agents, HMAs)之一, 在欧美地区被广泛应用, 既往研究表明种族可影响药物疗效^[5]。由于单一的 HMAs 疗效有限^[6], 故其常与其他药物联合应用, 如各种新药(靶向药物等)^[7-9], 一方面, 这类药物较昂贵, 另一方面, 疗效也不够肯定。高三尖杉酯碱(Homoharringtonine, HHT)是我国首创推荐应用于临床的抗白血病药物^[10-12]。故在本研究中, 我们将 AZA 单药或联合 HHT 为基础的预激方案应用于 MDS-EB(较高危 MDS 的代表)患者, 以期为临床应用 AZA 提供新的经验和选择。

1 资料与方法

1.1 一般资料

回顾性分析 2017 年 11 月至 2020 年 08 月我院血液科收治的 49 例 MDS 患者的临床资料, 所有患者均参照 2016WHO 血液病诊断标准确诊为 MDS^[13]。患者治疗前均签署知情同意书。两组患者的基线特征资料详见表 1, 组间比较差异均无统计学意义($P>0.05$), 具有可比性。

1.2 治疗方案

14 例 MDS-EB 患者予 AZA 联合 HAG 方案治疗, 15 例患者予 AZA 单药方案治疗, 其余 20 例患者根据个人意愿采用对症支持治疗。具体为: 阿扎胞苷(商品名称: 维达莎; 厂家: Celgene Europe Ltd; 注册证号: H20170238; 规格: 100 mg)75 mg·m⁻²·d⁻¹× 7 d, 皮下注射, 28 天为一个疗程; HAG 方案具体为: 高三尖杉酯碱, 1mg·m⁻²·d⁻¹× 7 d, 静脉滴注; 阿糖胞苷, 10 mg·m⁻²·q12h⁻¹·d⁻¹× 7 d, 皮下注射; 粒细胞集落刺激因子 300 μg·d⁻¹× 14 d, 静脉滴注。支持治疗: 予成分血输注、促造血(促红细胞生成素、促血小板生成素)、去铁剂等支持治疗。

1.3 疗效评估

疗效评价依据 MDS 国际工作组(IWG)2006 年 MDS 疗效修订标准^[14], 不良反应按 WHO 急性及亚急性化疗药物不良反应分度标准进行判定。每个疗程前评估上一个疗程疗效, 至少使用阿扎胞苷 1 个疗程或支持治疗 1 个月后患者达到的最佳结果作为疗效的最终判断。

1.4 随访

随访截止时间为 2020 年 08 月 31 日, 随访资料来源于患者的门诊、住院资料及电话随访记录, 无失访患者。OS 定义为确诊至随访截止日期或患者死亡时间, PFS 定义为从治疗开始至疾病进展、复发或患者死亡时间。

表 1 两组患者的临床特征

Table 1 Clinical characteristics of two groups of patients

Clinical features	Supportive treatment group(n=20)	Azacitidine-containing group(n=29)
Gender (M/F)	11/9	15/14
Age	65.30± 11.87	62.55± 14.42
WHO classification(n,%)		
MDS-U	1(5.00)	1(3.45)
MDS-SLD	3(15.00)	2(6.90)
MDS-MLD	5(20.00)	4(13.79)
MDS-RS	3(15.00)	3(10.34)
MDS-EB	7(35.00)	18(62.07)
MDS-5q-	1(5.00)	1(3.45)
Pre-treatment blood cell level		
WBC(× 10 ⁹ /L)	2.96± 1.66	3.56± 2.41
HGB(g/L)	75.05± 18.64	76.53± 12.71
PLT(× 10 ⁹ /L)	73.8± 89.5	56.62± 53.04
Bone marrow primordial cell ratio(n,%)	6.0± 4.9	10.92± 5.09
Karyotype(n,%)		
Excellent	8(40.00%)	10(34.48%)
Medium	7(35.00%)	8(27.59%)
Bad	5(25.00)	11(37.93)
Mutant gene(n,%)		
NAMT3A	4(20.00)	7(24.14)
TET2	5(25.00)	6(20.69)
ASXL-1	3(15.00)	5(17.24)
TP53	2(10.00)	4(13.79)
IPSS-R classification(n,%)		
Low-risk	7(35.00)	8(27.59)
Medium-risk	4(20.00)	4(13.79)
High-risk	9(45.00)	17(58.62)
Previous history of demethylation therapy		
Yes	6(30.00)	11(37.93)
No	14(70.00)	18(62.07)
ECOG score(n,%)		
0-1	13(65.00)	17(58.62)
2	7(35.00)	12(41.38)

1.5 统计学处理

采用 SPSS 26.0 软件进行数据分析, 计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)表示, 用 t 检验; 计数资料用百分比或率表示, 用 χ^2 检验进行组间比较; 生存曲线采用 Kaplan-Meier 绘制, 组间比较采用 Log-Rank 检验; 以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 临床疗效

在 29 例接受含 AZA 治疗的患者中, 有 22 例患者完成至少 4 个疗程的 AZA 治疗, 中位疗程数为 5 个。支持治疗组的 ORR 为 30.00%。含 AZA 组的 ORR 为 65.52%, 其中单药组的 ORR 为 46.67%, 联合组的 ORR 为 85.71%。2 个疗程后的 ORR 为 7.14%, 4 个疗程后的 ORR 为 45.45% (17/22)。与支持治疗组相比, 含 AZA 组的完全缓解率及 ORR 显著增高, 差异有统计学意义 ($P < 0.005$)。详见表 2。

表 2 49 例 MDS 患者的治疗反应
Table 2 Treatment response of 49 MDS patients

Clinical effect	Supportive treatment group (n=20)	AZA containing group(n=29)		
		AZA(n=15)	AZA+HAG(n=14)	Total(n=29)
CR	0(0.00%)	2(13.33%)	6(42.86%)	8(27.59%)*
mCR	1(5.00%)	1(6.67%)	1(7.14%)	2(6.90%)
PR	2(10.00%)	2(13.33%)	2(14.29%)	4(13.79%)
HI	3(15.00%)	2(13.33%)	3(21.43%)	5(17.24%)
SD	8(40.00%)	5(33.33%)	1(7.14%)	6(20.69%)
PD	6(30.00%)	3(20.00%)	1(7.14%)	4(13.79%)
CR+mCR	1(5.00%)	3(20.00%)	7(50.00%)	10(34.48%)*
ORR	6(30.00%)	7(46.67%)	12(85.71%)	19(65.52%)*

Note: Compared with the supportive treatment group, * $P < 0.05$.

2.2 不良反应

在接受含 AZA 的方案治疗后患者主要表现为不同程度骨髓抑制及继发的感染, 且随着疗程数的增加不良事件在逐渐降

低。与单药组相比, 联合治疗组的患者更易发生骨髓抑制, 但经对症治疗后均可好转, 无因不良反应而终止治疗或死亡的病例。详见表 3、图 1。

表 3 含 AZA 方案治疗的患者不良反应情况
Table 3 Adverse reactions of patients treated with AZA regimen

Types of adverse reactions	AZA containing group(n=29)		
	AZA(n=15)	AZA+HAG(n=14)	Total(n=29)
Grade III-IV Myelosuppression	4(26.67%)	14(100.00%)	18(62.07%)
Secondary infection	3(20.00%)	7(50.00%)	10(34.48%)
Gastrointestinal reaction	2(13.33%)	6(42.86%)	8(27.59%)
Injection site erythema	4(26.67%)	2(14.29%)	6(20.69%)
Impaired liver function	1(6.67%)	3(21.43%)	4(13.79%)
Hemorrhage	1(6.67%)	1(7.14%)	2(6.90%)

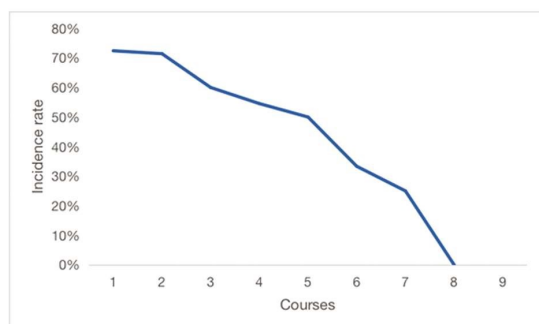


图 1 不良反应类型及发生率的分布情况

Fig.1 Distribution of types and incidence of adverse reactions

2.3 生存分析

截止随访日期, 支持治疗组有 12 例患者死亡, 含阿扎胞苷组有 11 例死亡, 两组患者的中位 OS 时间分别为 11.7 个月和 19 个月, 中位 PFS 分别为 8.9 个月、16 个月, 差异均有统计学意义 ($P < 0.05$)。如图 3、图 4。

3 讨论

AZA 主要通过 DNA、RNA 结合及抑制 DNA 甲基化这两种机制发挥抗肿瘤作用^[15]。AZA-001 和 CALBG 首次证明了 AZA 疗法对较高危 MDS 患者的疗效^[16,17]。AZA-001 试验进一

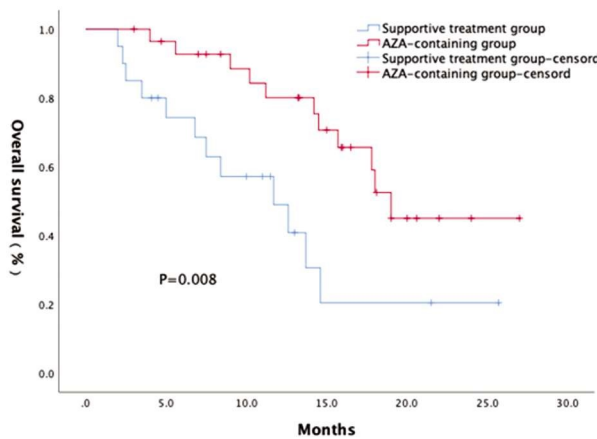


图2 两组MDS患者OS生存曲线

Fig.2 OS survival curve of MDS patients in two groups

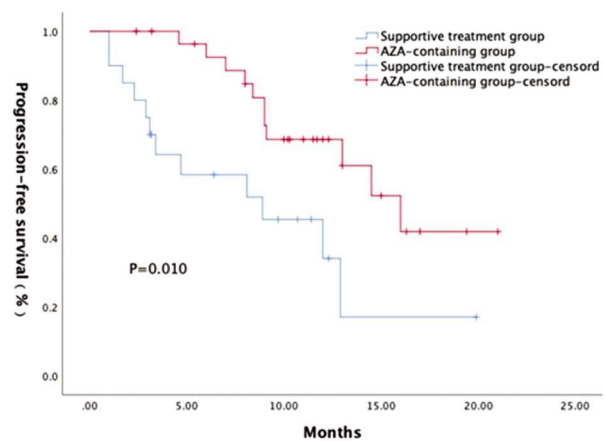


图3 两组MDS患者PFS生存曲线

Fig.3 PFS survival curve of MDS patients in two groups

步证实了 AZA 治疗 MDS 的疗效,与 CCR(常规诱导化疗,低剂量 Ara-C, BSC)相比,AZA 改善了总生存期,增加了 LT 的中位时间,且显著提高了有效率,因此可应用于中高危骨髓增生异常综合征、慢性粒单核细胞白血病及急性髓系白血病患者^[18]。但由于 2018 年 AZA 才进入中国市场,国内关于 AZA 的应用经验相对较少。

在本研究中,与支持治疗组相比,含 AZA 组的生存率及有效率均显著改善,含 AZA 组患者的中位 OS 时间为 19 个月,较 AZA-001 及我国一项 2 期临床试验报道的 OS 短^[19],这可能与本研究入组患者的中位年龄较大及入组的病例数较少有关。含 AZA 组的总有效率为 65.52%,这与姚伟等人^[20]报道的结果一致。已有研究表明,接受 AZA 治疗的 MDS 患者一般耐受性良好,且不良事件主要发生在前两个周期^[21-23]。这在本研究中也得到了证实,虽然与单药组相比,联合治疗组的更易出现骨髓抑制及感染,但经对症治疗后均可好转,提示患者耐受性良好。

CAG 预激方案是由 Yamada 等^[24]首次报道,既往研究表明 CAG 方案治疗老年 AML 和较高危 MDS 有较好的疗效,并且在过去 20 年在中国和日本得到了广泛的应用^[25]。但由于蒽环类药物的心脏毒性,一定程度上限制了其在临床中的应用,应用 HHT 代替阿克拉霉素治疗 MDS 及 AML 也取得了相似的疗效,且价格低廉,副反应少^[26]。既往有研究表明,去甲基化药物联合化疗对 AML 或高危 MDS 患者有益,有研究比较了地西他滨单药和地西他滨联合 CAG 方案治疗 MDS 或 AML 患者,提示 DAC 联合预激方案在不增加化疗相关死亡风险的前提下,能够延长生存期,提高临床疗效^[27,28]。AZA 与 DAC 同属去甲基化药物,故 AZA 联合预激方案与 DAC 联合预激方案有异曲同工之处,且在一项回顾性研究中发现阿扎胞苷治疗组比地西他滨治疗组中位生存期有显著延长^[29]。在本研究中,联合组的 ORR 为 85.71%(12/14)。而在单药组的 7 例中高危患者中,有 3 例(42.86%)疾病得到改善,这介于国内两项研究之间(ORR 分别为 66.7%、38.5%)^[20,30]。由此可见,联合方案对较高危 MDS 的治疗效果可能优于单药方案,但由于本研究纳入病例的局限性,尚需进一步的临床研究。

综上所述,与支持治疗相比,AZA 单药或联合 HAG 方案治疗 MDS 有更高的治疗反应,可延长患者生存期,患者有良好

的耐受性,且联合治疗可能有更好的疗效。

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