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71例中高危骨髓增生异常综合征患者化学药物治疗方案选择与生存分析*

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摘要:目的 探讨中高危骨髓增生异常综合征(MDS)患者的化学药物治疗(简称化疗)方案及预后。方法 选取医院血液内科2015年1月至2020年10月收治的MDS国际预后评分系统(IPSS)危险分层为中高危的MDS患者71例,按治疗方案的不同分为接受去甲基化药物(HMA)治疗组(HMA组)和HMA联合化疗组(联合化疗组)的,回顾性分析患者的临床资料,并进行疗效评估及生存分析。结果 与HMA组比较,联合化疗组患者治疗前的IPSS危险分层更严重,骨髓原始细胞百分比更高($P < 0.05$),疗效、总生存率(OS)、无白血病生存率(LFS)无显著差异($P > 0.05$)。初诊时髓系原始细胞百分比小于分界值[4.395%,由接收者操作特征(ROC)曲线得到]的非化疗组患者的OS比化疗组更高($P = 0.0256$),在髓系原始细胞百分比 $< 10\%$ 的患者中得到相似结果。结论 部分MDS患者初诊时IPSS危险分层及骨髓原始细胞百分比比较高,其可能需要行HMA联合化疗,但对于初诊时髓系原始细胞百分比小于4.395%的患者,化疗前需谨慎评估。

关键词:中高危;骨髓增生异常综合征;髓系原始细胞;去甲基化药物;化学药物治疗;预后分析

Chemotherapy Regimen Selection and Survival Analysis of 71 Patients with Intermediate or High - Risk Myelodysplastic Syndrome

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Abstract: Objective To investigate the chemotherapy regimen and prognosis of patients with intermediate or high - risk myelodysplastic syndrome (MDS). **Methods** A total of 71 patients with International Prognosis Score System (IPSS) hazard stratification intermediate or high - risk MDS who received chemotherapy in the Department of Hematology of the hospital from

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January 2015 to October 2020 were selected, and they were divided into hypomethylating agents (HMA) treatment group (HMA group) and HMA combined with chemotherapy group (combined chemotherapy group) according to different treatment schemes. The patients' clinical data were retrospectively analyzed, and efficacy evaluation and survival analysis were performed. **Results** Before treatment, the IPSS hazard stratification and the percentage of myeloid blasts in the combined chemotherapy group were higher than those in the HMA group ($P < 0.05$), while the efficacy, overall survival rate (OS), and leukemia survival rate (LFS) between the two groups had no significant difference ($P > 0.05$). Patients whose percentage of myeloid blasts was less than the cut-off value [4.395%, according to the receiver operating characteristics (ROC) curve] at the initial diagnosis had a higher OS in the non-chemotherapy group than those in the chemotherapy group ($P = 0.0256$), and similar results were obtained in patients with myeloid blasts percentage lower than 10%. **Conclusion** The IPSS hazard stratification and the percentage of myeloid blasts in some MDS patients is high at the initial diagnosis, these patients may need HMA combined with chemotherapy. However, more caution should be taken before using chemotherapy for patients with a percentage of myeloid blasts lower than 4.395% at the initial diagnosis.

Key words: myelodysplastic syndromes; myeloid blasts; hypomethylating agents; chemotherapy; prognosis analysis

骨髓增生异常综合征(MDS)为异质性髓系克隆性造血疾病,以骨髓造血功能异常、外周血细胞减少及转化为急性髓系白血病(AML)的风险增加为特点^[1]。临床常用基于细胞遗传学特征、髓系原始细胞百分比和外周血细胞减少程度的MDS国际预后评分系统(IPSS)对MDS患者进行危险分层,并以此确定治疗方案^[2-3]。目前,中高危MDS患者的一线治疗方案为去甲基化药物(HMA),常见的HMA包括地西他滨和阿扎胞苷^[4-6]。此类药物通过调控DNA甲基化对基因进行表观遗传学修饰,增强抑癌基因的表达,从而发挥治疗作用。有研究表明,地西他滨也可通过消耗体内调节性T细胞,增强机体免疫功能对肿瘤细胞的识别及杀伤作用,从而缓解疾病^[7]。但由于HMA的作用依赖于活跃的DNA复制,因此常需多个疗程才能显效^[8],且部分患者疗效欠佳、临床预后不良。为此,本研究中分析了本院接受化学药物治疗(简称化疗)的71例中高危MDS患者的临床数据,探讨了MDS化疗方案的选择及预后。现报道如下。

1 资料与方法

1.1 一般资料

纳入标准:符合2016年世界卫生组织的MDS诊断标准;IPSS危险分层提示为中危或高危;骨髓活检、化疗方案等资料完善;已接受至少1个疗程的HMA治疗或HMA联合化疗,并能耐受。本研究经医院医学伦理委员会批准,患者签署知情同意书。

排除标准:合并其他恶性肿瘤。

病例选择与分组:选取2015年1月至2020年10月在医院血液内科住院部接受化疗的中高危MDS患者71例(中位年龄56岁),按治疗方案的不同分为HMA组(单用地西他滨/阿扎胞苷,35例)和联合化疗组(地西他滨/阿扎胞苷+其他化疗方案,36例)。

1.2 疗效判定标准及随访

疗效判定:参考《骨髓增生异常综合征中国诊断与

治疗指南(2019年版)》。完全缓解(CR),骨髓原始细胞 $\leq 5\%$ 且所有细胞系成熟正常,外周血血红蛋白(Hb) $\geq 110\text{ g/L}$ 、中性粒细胞绝对值计数(ANC) $\geq 1.0 \times 10^9/\text{L}$ 、血小板计数(PLT) $\geq 100 \times 10^9/\text{L}$,原始细胞为0;骨髓完全缓解(mCR),骨髓原始细胞 $\leq 5\%$ 且较治疗前减少 $\geq 50\%$;疾病稳定(SD),血液学指标改善(疗效维持 ≥ 8 周);治疗失败(TF),治疗期间死亡或病情进展。

随访自患者入院之日起进行,终点为2020年10月31日(或患者死亡)。记录总体生存率(OS,以开始随访至随访终点或患者死亡计算)和无白血病生存率(LFS,以开始随访至复发、转化为AML或死亡计算)。

1.3 统计学处理

采用SPSS 23.0统计学软件分析,GraPad Prism 8软件作图。计量资料以 $M(P_{25}, P_{75})$ 描述集中趋势,95%置信区间描述离散趋势,均符合正态分布,行单因素方差分析或 t 检验;计数资料以率(%)表示,行 χ^2 检验。采用Kaplan-Meier法进行生存分析,以接收者操作特征(ROC)曲线寻找Cut-off值。检验水准 $\alpha = 0.05$, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般情况

71例患者中,按IPSS分型评分分为中危-1(0.5, 1.0分)、中危-2(1.5, 2.0分)、高危(≥ 2.5 分),且存在预后不良风险因素。此外,两组患者间性别、年龄、染色体异常、基因突变、初诊时血细胞计数比较,差异无统计学意义($P < 0.05$),但两组患者初次治疗前IPSS危险分层及髓系原始细胞百分比有显著差异($P < 0.05$)。详见表1。

HMA组内,使用地西他滨、阿扎胞苷治疗的患者分别为23例、12例;联合化疗组内,使用地西他滨+CAG方案、阿扎胞苷+CAG方案、地西他滨+HAAG方案、地西他滨+HAG方案、阿扎胞苷+阿糖胞苷方案、阿扎

表1 71例接受化疗MDS患者的基线特征

Tab. 1 Baseline characteristics of 71 MDS patients who received chemotherapy

项目	HMA组(n=35)	联合化疗组(n=36)	P值
性别[例(%)]			0.286
男	19(54.29)	24(66.67)	
女	16(45.71)	12(33.33)	
年龄[例(%)]			0.061
<65岁	20(57.14)	29(80.56)	
≥65岁	15(42.86)	7(19.44)	
IPSS危险分层			0.002
[例(%)]			
中危-1	25(71.43)	10(27.78)	
中危-2	7(20.00)	24(66.67)	
高危	3(8.57)	2(5.55)	
染色体异常数			0.301
[例(%)]			
<2条	28(80.00)	32(88.89)	
≥2条	7(20.00)	4(11.11)	
基因突变数			0.556
[例(%)]			
1个	18(51.43)	16(44.44)	
>1个	17(48.57)	20(55.56)	
髓系原始细胞[M(P ₂₅ , P ₇₅), %]	3.34(2.28, 4.40)	6.31(4.47, 7.89)	0.031
血常规[M(P ₂₅ , P ₇₅)]			0.387
WBC(×10 ⁹ /L)	6.11(2.08, 10.13)	8.79(4.02, 13.55)	
Hb(g/L)	66(60, 73)	74(67, 82)	0.111
PLT(×10 ⁹ /L)	73(46, 100)	85(49, 121)	0.572

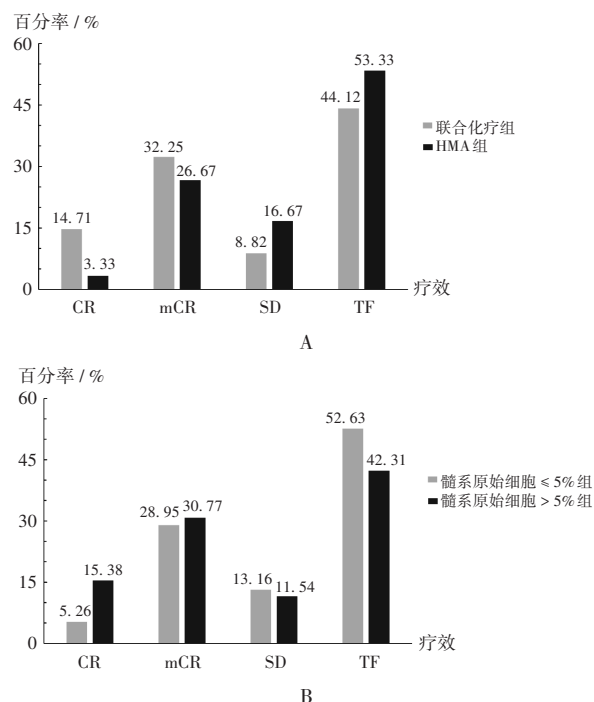
胞苷 + HAG 方案的患者分别为 23 例、4 例、3 例、3 例、2 例、1 例。

2.2 疗效判定

71 例患者中, 64 例(HMA 组 30 例、联合化疗组 34 例) 可进行疗效判定。不同治疗方案组间 ($P = 0.379$) 及以髓系原始细胞比例为 5% 为临床界值分组组间 ($P = 0.503$) 疗效无显著差异 (见图 1); 两组疗效评估提示, 性别、年龄、髓系原始细胞百分比与疗效无关 (表 2、表 3)。由表 3 可见, 联合化疗组患者髓系原始细胞百分比多超过 5%, 对该类患者多采用联合化疗, 提示治疗强度可能改善髓系原始细胞 > 5% 患者的疗效。

2.3 以髓系原始细胞百分比为临界值的生存分析

将两组患者以髓系原始细胞百分比作 ROC 曲线, 发现约登指数 (约登指数 = 灵敏度 + 特异度 - 1) 最高时, 髓系原始细胞百分比为 4.395% (见图 2)。遂以 4.395% 为分界值, 将我院该时段入院治疗的 147 例临床数据完善的 IPSS - R 危险分层为中高危的 MDS 患者纳入分析。初诊时将髓系原始细胞百分比 < 4.395% 的 69 例患者分为化疗组与非化疗组, 化疗组患者的 OS 及 LFS 小于非化疗组 (图 3 A、图 3 B); 化疗组患者中, HMA 组与联合化疗组 OS 及 LFS 无显著差异 (图 4 C、图 4 D), 含地西他滨或阿扎胞苷治疗方案组间 OS 及 LFS 无显著差异 (图 3 E、图 3 F)。在初诊时髓系原始细胞百分比 ≥ 4.395% 的 78 例患者中, 化疗与非化疗、HMA 治疗与联合化疗、含地西他滨治疗方案与阿扎胞苷治疗方案组



A. HMA 组与联合化疗组 B. 髓系原始细胞百分比 ≤ 5% 组与髓系原始细胞百分比 > 5% 组

图1 不同组间疗效

A. HMA group compared to combined chemotherapy group B. Myeloid blasts percentage ≤ 5% group compared to myeloid blasts percentage > 5% group

Fig. 1 Efficacy between different groups

表2 HMA 组组内疗效评估 (例)

Tab. 2 Efficacy evaluation in the HMA group (case)

项目		CR	mCR	SD	TF	χ^2 值	P值
性别	男	0	4	3	10	1.697	0.638
	女	1	4	2	6		
年龄	<65岁	1	6	2	9	2.344	0.504
	≥65岁	0	2	3	7		
髓系原始细胞百分比	≤5%	0	7	4	13	4.197	0.231
	>5%	1	1	1	3		

表3 联合化疗组组内疗效评估 (例)

Tab. 3 Efficacy evaluation in the combined chemotherapy group (case)

项目		CR	mCR	SD	TF	χ^2 值	P值
性别	男	4	6	3	9	2.791	0.425
	女	1	5	0	6		
年龄	<65岁	5	10	2	10	3.947	0.264
	≥65岁	0	1	1	5		
髓系原始细胞百分比	≤5%	2	4	1	7	0.442	0.931
	>5%	3	7	2	8		

间 OS 及 LFS 均无显著差异 (图 4)。在初诊时髓系原始细胞百分比 < 10% 的 135 例患者中, 化疗患者的 OS 及 LFS

显著小于非化疗患者(图5 A、图5 B);化疗患者中,不同化疗方案组间OS及LFS无显著差异(图5 C至图5 F)。注意,联合化疗组患者化疗后感染发生率为75.0%,HMA组为61.3%,两组间无显著差异。

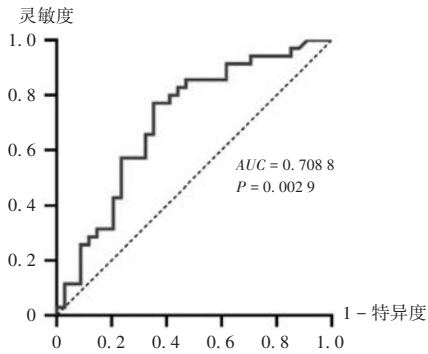


图2 两组的ROC曲线

Fig.2 ROC curve in the two groups

3 讨论

随着研究的深入开展,HMA治疗已成为中高危MDS患者一线治疗方案,但目前国内外指南对MDS患者化疗方案的选择尚无统一标准。国内指南建议对髓系原始细胞百分比 > 5% 的较高危患者行化疗或化疗桥接造血干细胞移植(HSCT)。美国国家综合癌症网络(NCCN)建议HMA用于不适合强化治疗、对其他治疗方式(如免疫抑制治疗)无反应的中高风险MDS患者或桥接HSCT,故HMA仍是针对MDS颇具治疗潜力的药物,但部分中高危MDS患者疗效不佳,针对此问题,

已有越来越多关于MDS临床试验药物和联合用药方案的文献报道,包括HMA联合其他化疗药物治疗^[9-11]。

有多项研究表明,地西他滨或阿扎胞苷与其他药物联用对不适合强化化疗的高危MDS患者有效性及耐受性良好^[12-15],HMA联合化疗可提高MDS患者的完全缓解率,此类药物联合高强度化疗可提高细胞遗传学分层欠佳的MDS患者2年OS^[16]。本研究中,联合化疗组初诊时髓系原始细胞百分比显著高于HMA组,但两组患者化疗疗效、OS、LFS无显著差异,提示强化化疗方案可能是弥补高髓系原始细胞百分比带来的预后不良风险因素之一。我院髓系原始细胞百分比 ≥ 4.395% 的患者大多采用联合化疗方案, < 4.395% 的患者大多采用HMA化疗。且髓系原始细胞百分比 < 4.395% 时,非化疗组患者OS和LFS均小于化疗组,但化疗组内不同化疗方案间OS和LFS无显著差异。故髓系原始细胞百分比对化疗方案启动和选择的影响有待更深层次的研究^[11,17],需扩大样本量及高危组人群数量以进一步探索。但部分文献表明,联合用药方案虽可一定程度上提高MDS患者缓解率,但对生存率无显著影响^[18]。此外,对低风险MDS患者使用阿扎胞苷无显著生存获益^[19]。

部分回顾性研究提示,高危MDS患者可从移植中获益^[20],故对于后期拟行序贯HSCT的MDS患者来说,

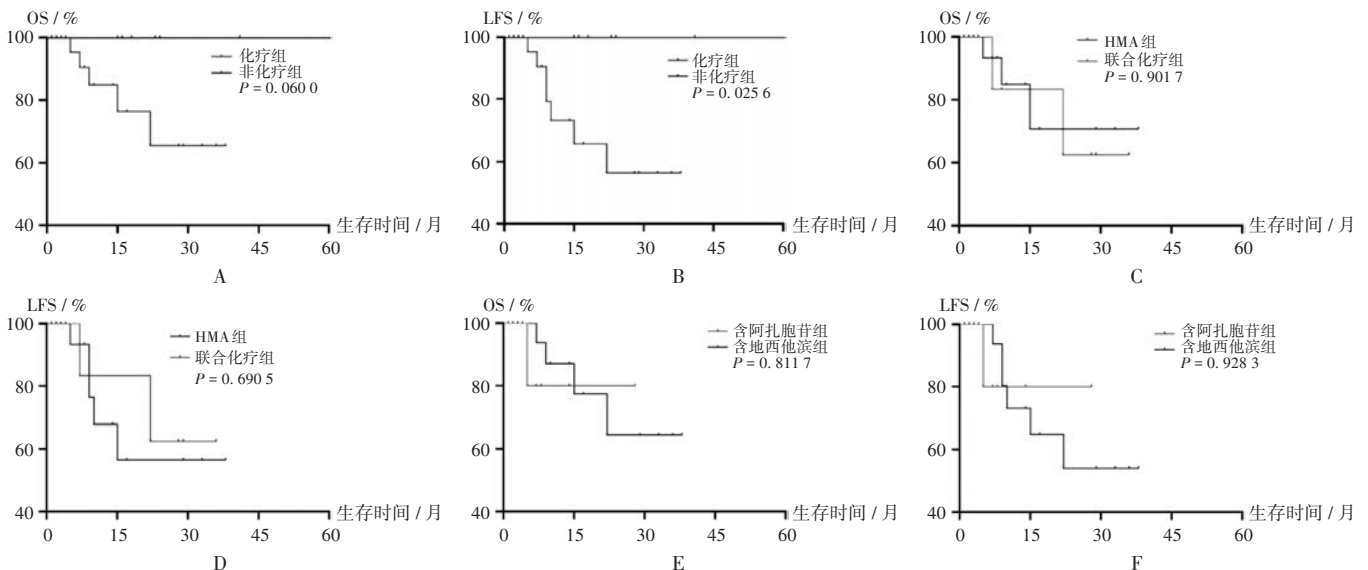
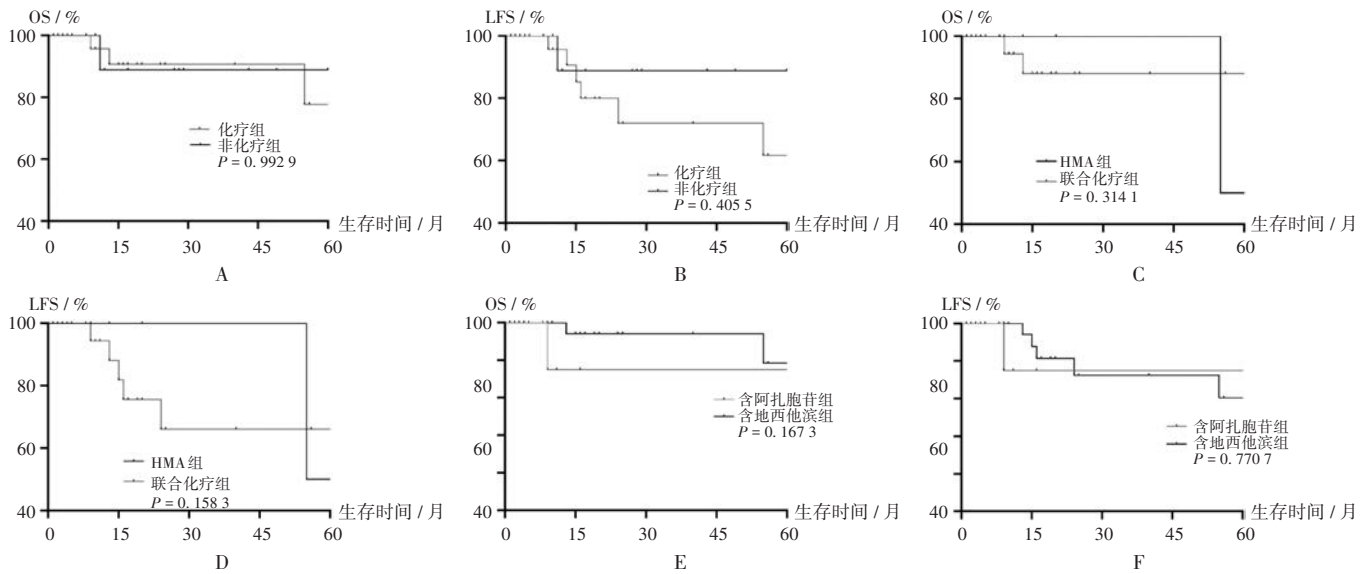


图3 69例髓系原始细胞百分比 < 4.395% 中高危MDS患者的生存分析

A. OS in chemotherapy group and non-chemotherapy group B. LFS in chemotherapy group and non-chemotherapy group C. OS in HMA group and combined chemotherapy group D. LFS in HMA group and combined chemotherapy group E. OS in treatment regimens containing azacitidine or dexamethasone F. LFS in treatment regimens containing azacitidine or dexamethasone

Fig.3 Survival analysis of 69 MDS intermediate or high-risk patients whose myeloid blasts percentage < 4.395%

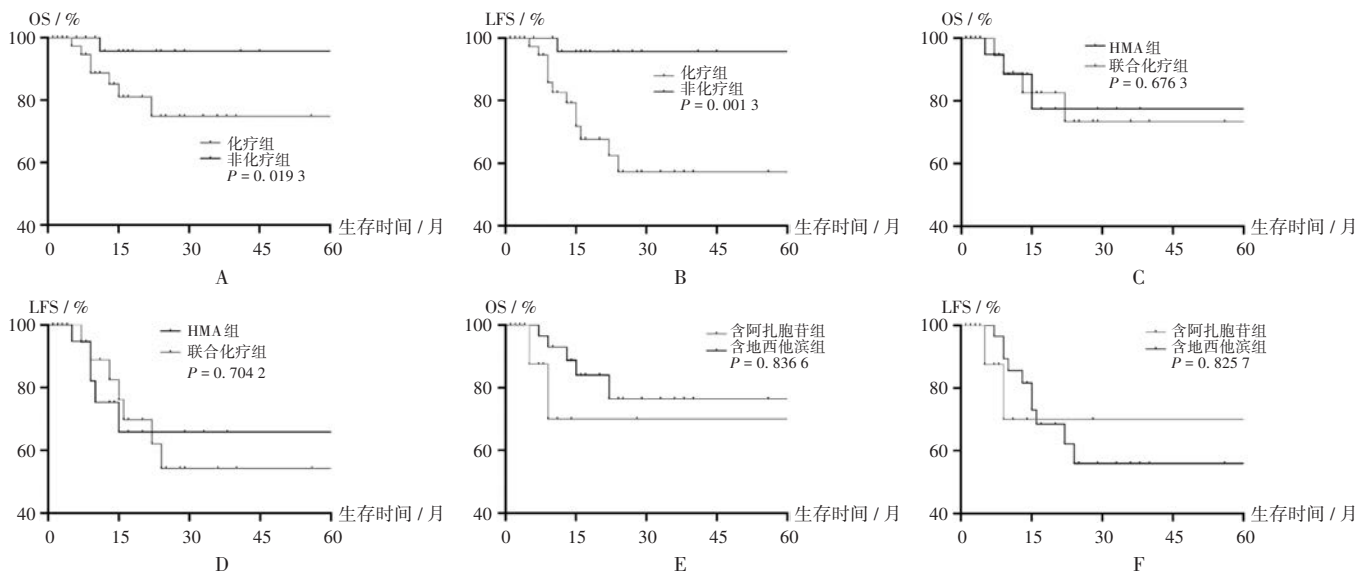


A. 化疗组与非化疗组的OS B. 化疗组与非化疗组的LFS C. HMA组与联合化疗组的OS D. HMA组与联合化疗组的LFS
E. 含阿扎胞苷的治疗方案与含地西他滨治疗方案的组间OS F. 含阿扎胞苷的治疗方案与含地西他滨治疗方案的组间LFS

图4 78例髓系原始细胞百分比≥4.395%中高危的MDS患者生存分析

A. OS in chemotherapy group and non-chemotherapy group B. LFS in chemotherapy group and non-chemotherapy group C. OS in HMA group and combined chemotherapy group D. LFS in HMA group and combined chemotherapy group E. OS in treatment regimens containing azacitidine or decitabine F. LFS in treatment regimens containing azacitidine or decitabine

Fig. 4 Survival analysis of 78 MDS intermediate or high-risk patients whose myeloid blasts percentage ≥ 4.395%



A. 化疗组与非化疗组的OS B. 化疗组与非化疗组的LFS C. HMA组与联合化疗组的OS D. HMA组与联合化疗组的LFS
E. 含阿扎胞苷治疗方案与含地西他滨治疗方案的组间OS F. 含阿扎胞苷治疗方案与含地西他滨治疗方案的组间LFS

图5 135例髓系原始细胞百分比<10%中高危的MDS患者生存分析

A. OS in chemotherapy group and non-chemotherapy group B. LFS in chemotherapy group and non-chemotherapy group C. OS in HMA group and combined chemotherapy group D. LFS in HMA group and combined chemotherapy group E. OS in treatment regimens containing azacitidine or decitabine F. LFS in treatment regimens containing azacitidine or decitabine

Fig. 5 Survival analysis of 135 intermediate or high-risk MDS patients whose myeloid blasts percentage < 10%

前期化疗方案对预后也有重要意义。目前,对HMAs在MDS患者移植前桥接治疗或移植后巩固治疗的应用存在争议,有研究提示高危MDS患者进行HSCT前应用阿扎胞苷优于强化化疗^[20],对MDS患者采用阿扎胞苷桥

接移植有效^[21]。但也有研究表明,移植前进行HMA治疗不能使MDS患者获益^[22-23]。

综上所述,虽然目前国内外对MDS患者启动化疗的时机及化疗方案选择尚无统一标准,对于IPSS危险

分层为中高危的MDS患者,髓系原始细胞百分比 \geq 4.395%时可考虑HMA联合化疗,对 $<$ 4.395%时化疗前需谨慎评估。

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