伊马替尼一线治疗慢性髓系白血病的预后相关因素分析*

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摘要 目的:评价生物学因素和治疗相关因素在伊马替尼一线治疗慢性髓系白血病(CML)中的预后价值。方法:回顾性分析 72 例 CML 慢性期(CML-CP)患者的临床资料,包括性别、年龄、外周血白细胞计数、血小板计数、嗜碱性粒细胞比例、血红蛋白、脾肋下长度、附加染色体(ACAs)、血清乳酸脱氢酶(LDH)水平、伊马替尼治疗第 3 个月和第 6 个月的分子学反应。采用 Kaplan-Meier 方法分析上述因素对长期生存(OS)率及无事件生存(EFS)率的影响,Cox 比例风险模型评估独立预后因素。结果:中位随访期为 61(4~96)个月,5 年中位 OS 率 88.89%,5 年中位 EFS 率 41.67%。单因素分析显示,各组内 OS 率比较,外周血嗜碱性粒细胞比例 <3% 的患者明显高于外周血嗜碱性粒细胞比例 ≥3% 的患者(97.1% *vs* 84.2%,$P<0.05$);不存在 ACAs 患者明显高于存在 ACAs 患者(97.6% *vs* 28.3%,$P<0.05$);LDH <1 000 U/L 患者明显高于 LDH ≥1 000 U/L 患者(96.2% vs 84.8%,$P<0.05$)。各因素组内 EFS 率比较显示,脾肋下长度 <7 cm 患者明显高于脾肋下长度 ≥7 cm 患者(41.8% *vs* 27.0%,$P<0.05$);不存在 ACAs 患者明显高于存在 ACAs 患者(38.4% *vs* 10.4%,$P<0.01$);第 3 个月早期分子学反应(EMR)≤0.1 患者明显高于 EMR >0.1 患者(45.1% *vs* 16.8%,$P<0.01$);第 6 个月 EMR <0.1、0.1~0.01、>0.1 的 3 组患者 EFS 率分别为 57.0%、31.8%、15.4%(均 $P<0.05$)。多因素分析显示存在 ACAs [$OR=5.821$,95% $CI(2.015,16.819)$,$P<0.01$] 及治疗第 6 个月的 EMR[$OR=4.850$,95% $CI(2.887,8.148)$,$P<0.01$] 对 EFS 率具有独立的预后价值。结论:外周血嗜碱性粒细胞比例、ACAs、LDH 可能影响伊马替尼一线治疗 CML 患者的 OS 率,脾大小、ACAs、第 3、6 个月的 EMR 均会影响患者的 EFS 率。ACAs 和第 6 个月的 EMR 对患者 EFS 率有独立的预后价值。

关键词 伊马替尼; 慢性髓性白血病; 预后

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Prognostic related factors in chronic myeloid leukemia with imatinib as first line treatment *ZHANG Chun-jia, ZHENG Xiao-ling, ZHENG Dan-tian, XIA Wei-lin*, SU Xiu-lian. Jieyang People's Hospital, Jieyang 552000, China*

Abstract Objective: To assess the prognostic value of the biological features and therapy related factors in chronic myeloid leukemia(CML) with imatinib as the first line treatment. Methods: A retrospective analysis was performed on 72 cases of CML chronic phase (CML-CP). The data of biological features including sex, age, counts of peripheral white blood cells, platelet count, proportion of peripheral basophilia cells, hemoglobin, proportion of peripheral blast cells, lactic dehydrogenase (LDH), spleen length below the costal margin and additional cytogenetic abnormalities (ACAs), and the data of therapy related factors including the early molecular response (EMR) at 3rd and 6th month after the imatinib treatment were collected. The effects of the factors above on the overall survival (OS) rate and event-free survival (EFS) rate were analyzed by Kaplan-Meier analysis, univariate analysis by Log-rank test and multivariate analysis by COX regression model. Results: During a median follow-up period of 61 (4-96) months, the 5-year OS rate was 88.89%, and 5-year EFS rate was 41.67%. Univariate analysis indicated that the OS rate in the patients with proportion of peripheral blast cells <3% was significantly higher than in those ≥3% (97.1% *vs.* 84.2%, $P<0.05$). The OS rate in the patients without ACAs was significantly higher than in those with ACAs (97.6% *vs.* 28.3%, $P<0.05$). The OS rate in the patients with LDH <1000 U/L was significantly higher than in those with LDH ≥1000 U/L (96.2% *vs.* 84.8%, $P<0.05$). The EFS rate in patients with spleen length below the costal margin <7 cm was significantly higher than in those with ≥7 cm (41.8% *vs.* 27.0%, $P<0.05$), that in the patients without ACAs was significantly higher than in those with ACAs (38.4% *vs.* 10.4%, $P<0.01$),

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that in the patients with the 3rd-month EMR ≤0.1 was significantly higher than in those with the 3rd-month EMR >0.1 (45.1% *vs.* 16.8%, $P<0.01$). The EFS rate in the patients with EMR <0.1, 0.1-0.01 and >0.1 at 6th month was 57.0%, 31.8% and 15.4% respectively (all $P<0.05$). The multivariate analysis showed that patients with ACAs [$OR=5.821$, 95% CI (2.015, 16.819), $P<0.01$] and worse EMR at the 6th month [$OR=4.850$, 95% CI (2.887, 8.148)] were independent poor prognostic factors. Conclusion: Proportion of peripheral blast cells, ACAs and LDH may influence the OS rate of patients with CML with imatinib as first-line treatment, and the size of spleen, ACAs, the EMR at 3rd and 6th month can affect the EFS rate. ACAs and the EMR at 6th month had independent prognostic value.

Key words Imatinib; Chronic myeloid leukemia; Prognostic related factors

慢性髓系白血病(chronic myeloid leukemia, CML)是一种具有特征性的融合基因(BCR/ABL)和/或 Ph 染色体的髓系克隆性恶性肿瘤[1],抑制其致病基因 BCR/ABL 融合蛋白的第 1 代酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)甲磺酸伊马替尼作为一线治疗药物使 CML 患者 10 年生存率达 85% ~90%[2]。目前 CML 治疗目标也进入了无治疗缓解(treatment-free remission, TFR)时代[3~5]。关于 CML 预后因素目前 EUTOS[6]系统只保留了嗜碱性粒细胞比例及脾肋下长度。近年来国内外研究发现治疗早期分子学反应(early molecular response, EMR)也是重要的预后因素[7,8],认为第 3、6 个月的 EMR 是判断患者是否需调整用药方案的指标[5,8~10]。另外,也有研究认为年龄[11]、血清 TGF-α 及 IL-6 水平[12]对 CML 的疗效和预后有评估作用,但目前仍存无统一的预后标准[13,14]。

资料与方法

一般资料 回顾性分析 2012 年 1 月 1 日 ~ 2020 年 2 月 29 日揭阳市人民医院诊断为 CML 的患者的临床资料。纳入标准:①确诊 CML 慢性期(CML-chronic phase, CML-CP),符合中国慢性髓系白血病诊断与治疗指南(2016 年版)诊断标准[5];②以第一代 TKI 伊马替尼作为一线治疗方案,初始治疗剂量为 400 mg,1 次/d;③具有完整的初诊资料及治疗后中位第 3、6 个月的国际标准化 BCR/ABL 分子转录水平结果。随访资料来源于住院和门诊病历,随访截止日期为 2020 年 2 月 29 日。

研究因素 生物学因素:年龄、白细胞计数、血红蛋白水平、血小板计数、外周血是否可见原始细胞、外周血嗜碱性粒细胞[15](该临界值参照 EURO 积分)、脾是否明显增大[16]、是否存在附加染色体(additional cytogenetic abnormalities, ACAs)。

治疗相关因素:治疗第 3、6 个月的 EMR(3m-EMR 和 6m-EMR),采用国际标准化实时荧光定量聚合酶链式反应(RQ-PCR)进行 BCR-ABL 分子转录水平检测,符合中国慢性髓系白血病诊疗规范(2014 年版)[17]的监测标准,以 BCR-ABLIS 表示。

评估指标 统计各因素各分组的长期生存(overall survival, OS)率及无事件生存(event-free survival, EFS)率并进行比较。无事件生存间期定义为从患者确诊 CML 并开始口服伊马替尼到任何事故发生,包括:①至少每 3 个月一次的分子转录水平监测发现较上一次的水平增加 10% 或以上;②发生对当前 TKI 耐药的激酶突变;③转变为加速期或急变期,符合中国慢性髓系白血病诊断与治疗指南(2016 年版)分期标准[5]。

统计学处理 采用 SPSS 21.0 统计学软件,计数资料以百分数(%)表示,生存分析采用 Kaplan-Meier 方法,各组生存之间的比较采用 log-rank 检验,Cox 比例风险模型用于评估独立预后因素,以 $P<0.05$ 为差异有统计学意义。

结 果

一般临床特征 入组 72 例(男 39,女 33)CML 患者,中位年龄 45(10 ~ 81)岁,中位白细胞计数(WBC)153.13(102.17 ~ 714.93) $\times 10^9$/L,中位嗜碱性粒细胞比例 6.05(1.2 ~ 10)%,中位血红蛋白(Hb)100.5(41 ~ 166) g/L,中位血小板计数(PLT)422.5(118 ~ 982) $\times 10^9$/L,脾肋下中位长度 6.85(0 ~ 13) cm,中位外周血原始细胞比例 4(0 ~ 6)%,中位乳酸脱氢酶(LDH)751(383 ~ 2140) U/L,5 例(6.94%)患者出现 ACAs 异常,其中有 3 例存在复杂染色体,包括 t(9;22;17)(34;q11;q21),t(2;9;22)(q33;q34;q11),der(7;9)(q10;q10)及 +22,der(22);1 例患者存在 -8 异常,1 例患者存在 -16 异常。

治疗第 3 个月 BCR/ABLIS ≤10% 者50 例;>10% 者 22 例;治疗第 6 个月 BCR/ABLIS <1% 者 27 例;1% ~10% 者 22 例;>10% 者 17 例。

单因素分析 截止 2020 年 2 月 29 日,入组 72 例患者,伊马替尼治疗后中位观察期为 61(4 ~

96)个月,死亡 8 例,存活 64 例,中位 5 年 OS 率 88.89%,其中,5 例存在 ACAs 患者 4 例死亡,1 例存活;有 42 例患者至少出现一次疾病相关事件,30 例患者未发生疾病相关事件,中位 5 年 EFS 率 41.67%,其中,5 例存在 ACAs 患者均出现进展事件,包括急变、激酶突变。

各因素组内 OS 率及 EFS 率比较 外周血嗜碱性粒细胞比例 <3% 的患者 OS 率明显高于外周血嗜碱性粒细胞比例≥3% 的患者;不存在 ACAs 患者 OS 率明显高于存在 ACAs 患者;LDH <1 000 U/L 患者 OS 率明显高于 LDH≥1000U/L 患者。各因素组内 EFS 率比较显示,脾肋下长度 <7 cm 患者 EFS 率明显高于脾肋下长度≥7 cm 患者;不存在 ACAs 患者 EFS 率明显高于存在 ACAs 患者;第 3 个月 BCR-ABLIS≤0.1的患者 EFS 率明显高于 BCR-ABLIS >0.1 的患者;第6 个月 BCR-ABLIS <0.1、0.1 ~0.01、或 >0.1的 3 组患者 EFS 率分别为 57.0% 、31.8%、15.4%(均P <0.01),见表 1。

表 1 单因素分析(%)

因素	例	OS 率	EFS 率
年龄(岁)			
<45	34	93.7 ±4.3	37.1 ±3.5
≥45	38	84.9 ±7.0	33.4 ±4.6
性别			
男	39	38.3 ±24.3	36.7 ±5.0
女	33	41.8 ±24.9	35.2 ±3.7
WBC($\times10^9$/L)			
<150	32	88.8 ±5.9	36.4 ±5.2
≥150	40	91.3 ±5.2	35.2 ±3.4
嗜碱性粒细胞(%)			
<3	38	97.1 ±2.8*	38.9 ±4.9
≥3	34	84.2 ±6.6	32.7 ±3.6
PLT($\times10^9$/L)			
<350	25	95.5 ±4.3	38.3 ±4.1
≥350	47	77.1 ±5.8	33.8 ±3.9
Hb(g/L)			
<100	49	90.1 ±5.4	32.3 ±3.1
≥100	23	77.9 ±4.7	42.0 ±5.7
脾肋下长度(cm)			
<7	41	96.7 ±4.0	41.8 ±4.3*
≥7	31	74.0 ±8.2	27.0 ±3.2
ACAs			
无	67	97.6 ±3.1*	38.4 ±3.3*
有	5	28.3 ±7.3	10.4 ±3.1
外周血原始细胞比例			
无	51	84.7 ±4.0	34.9 ±4.1
有	21	86.7 ±7.7	39.7 ±4.6
LDH(U/L)			
<1 000	35	96.2 ±3.6*	41.0 ±4.8
≥1 000	37	84.8 ±6.5	30.6 ±3.6
3 个月 EMR			
≤0.1	50	95.7 ±4.0	45.1 ±4.0*
>0.1	22	74.9 ±11.2	16.8 ±2.5
6 个月 EMR			
<0.01	28	100.5 ±3.4	57.0 ±7.7*
0.01 ~0.1	27	79.2 ±6.2	31.8 ±3.4
>0.1	17	50.0 ±4.3	15.4 ±3.3

注:各因素组内比较,*P <0.05

多因素分析 将上述共 12 个因素引入 Cox 比例风险模型进行多因素分析,显示存在 ACAs 及治疗第 6 个月的 EMR 对 EFS 具有独立的预后价值,存在 ACAs 达到获得 EFS 的风险是不存在 ACAs 的 5.821 倍,95% 可信区间为[(2.015,16.819),P <0.01],治疗第 6 个月分子转录水平越高风险越大,>0.1 是 <0.01 的 4.850 倍,95% 可信区间为[(2.887,8.148),P <0.01],其他因素对 EFS 率及 OS 率无独立的预后价值(均 P >0.05),见表 2。

表 2 Cox 比例风险模型的预后因素

因素	EFS 率	
	OR(95% *CI*)	*P* 值
年龄	1.416(0.683,2.935)	0.350
性别	0.870(0.412,1.836)	0.715
WBC	0.783(0.410,1.496)	0.459
嗜碱性粒细胞比例	1.453(0.660,3.202)	0.354
PLT	0.771(0.358,1.662)	0.507
Hb	0.844(0.376,1.891)	0.680
脾肋下长度	0.971(0.372,2.534)	0.954
ACAs	5.821(2.015,16.819)	0.001
外周原始细胞比例	0.858(0.389,1.892)	0.704
LDH	0.938(0.447,1.971)	0.867
3 个月 EMR	0.845(0.202,3.434)	0.818
6 个月 EMR	4.850(2.887,8.148)	0.000

讨 论

本研究 72 例患者,5 年中位 OS 率达到 88.89%,5 年的中位 EFS 率仅为 41.67%,但发生急变或加速的患者仅 12 例,无进展生存率为 83.33%(60/72),与国内外临床研究数据相似[18~21]。大部分患者主要在治疗过程中出现激酶突变及分子转录水平较前一次升高,在更改新一代的 TKI 后仍可获得长期生存,意大利一项纳入 556 例 CML-CP 患者的临床研究显示[20],>6 年的中位治疗期中,只有

65% 的患者仍然用伊马替尼治疗,说明能长期用一代 TKI 治疗的患者比例并不高,而本研究中,中位 5 年治疗期仅 41.67% 患者仍用伊马替尼,考虑可能第一代 TKI 并不是获得长期 EFS 理想选择。

前面提到 EUTOS[8] 预后积分包含了外周血嗜碱性粒细胞比例及脾肋下长度两个因素,本研究单因素分析结果显示嗜碱性粒细胞比例对 EFS 率有预后作用,而脾肋下长度对 OS 率有预后作用,但多因素分析显示两者均不是 EFS 率或 OS 率的独立预后因素,考虑这两个因素在 TKI 治疗时代仍然有较明确的预后提示,但需结合其他因素。

既往认为的可能会影响患者预后的不良因素,如年龄、外周血白细胞计数、血小板计数、外周血原始粒细胞 <3% 等在单因素或多因素分析中差异无统计学意义,不影响患者的预后。大部分 CML 患者初诊时出现不同程度贫血,血红蛋白浓度是否是一个潜在的预后因素,本研究中 Hb < 100 g/L 和 ≥ 100 g/L患者的 OS 率及 EFS 率比较,差异无统计学意义。

近年研究认为 EMR 至关重要,特别是 TKI 治疗 3 个月的 BCR-ABL 融合基因水平[21,22],Marin 等[23] 甚至认为第 3 个月的 EMR 是预测深度缓解的唯一指标。本研究结果显示第 3、6 个月的 EMR 对 EFS 率均有影响,但对于 OS 率无影响,考虑可能大部分患者在出现上述 CML 相关事件,如监测分子水平时发生较前升高、激酶突变甚至疾病进展时,及时更换了新一代的 TKI,从而明显改善了 OS 率,故可认为即使出现不理想的 EMR,在及时更换了新一代的 TKI 后,仍可以获得理想的 OS。

附加遗传学是指 Ph 染色体之外的遗传学异常,大约有 5% CML 患者初诊时存在 ACAs[24],与本研究 6.94% 数据相近。有研究[25] 认为 ACAs 的患者可能对甲磺酸存在天然耐药,故对第一代 TKI 甲磺酸伊马替尼治疗反应欠佳,亦有认为该类患者更容易发生急变[26],欧洲白血病协会[27] 将 ACAs 定义为“警告”级别,建议该类患者在治疗过程中要密切监测。本研究显示 ACAs 影响患者的 EFS 率和 OS 率,多因素分析显示 ACAs 是 EFS 率的独立预后不良因素,强烈提示 ACAs 为 CML 不良预后因素。本文认为对于存在 ACAs 患者需进行更密切的分子学监测,比如每月 1 次,而不是常规 3 个月1 次,甚至可考虑从第二代 TKI 开始治疗。但由于病例数仅为 5 例,结果尚欠缺说服力,有待后续增加样本量。

CML 患者获得无治疗长期生存,是目前 CML 治疗的远期目标,也是该领域的前沿研究重点。持续的深度缓解是目前国际上较为认可的停药标准之一[28,29]。研究显示新一代的 TKI 作为 CML 患者的一线治疗,可使患者更快获得深度缓解[30,31],但是二、三代 TKI 药物价格仍高,并且存在严重不良事件的风险,如顽固性胸腔积液、心肺血管事件、急性胰腺炎等[32,33],所以目前我国依然将一代 TKI 作为 CML 的一线选择。

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