



氟马替尼治疗慢性粒细胞白血疗效及远期预后分析*

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【摘要】目的 采用倾向性评分匹配(PSM)均衡基线混杂因素,评估氟马替尼治疗慢性粒细胞白血病(CML)的临床疗效与安全性。**方法** 回顾性选取2019年1月—2025年1月195例CML患者作为研究对象,根据治疗方案分为伊马替尼组和氟马替尼组。通过PSM控制混杂因素,比较两种药物的早期治疗反应及长期生存结局[总生存期(OS)],进一步分析患者远期预后。**结果** PSM后共有61对患者完成匹配。氟马替尼一线治疗3个月时的完全血液学反应(CHR)、早期分子学缓解(EMR)率分别为96.72%、83.61%,其中EMR率高于伊马替尼治疗($P<0.001$);氟马替尼一线治疗6、9、12个月时的主要分子学反应(MMR)率分别为34.43%、50.82%、59.02%,一线治疗9、12个月时的深度分子学缓解(MR⁴)率分别为19.67%、27.87%,一线治疗3、6、12个月时的完全细胞遗传学缓解(CCyR)率分别为67.21%、85.25%、91.80%,均高于伊马替尼治疗($P<0.05$)。广义估计方程分析显示,氟马替尼组的MMR达标概率高于伊马替尼组[Wald $\chi^2=16.280$, $P<0.001$, 比值比(OR)=2.130, 95%置信区间(CI): 1.570~2.890];时间效应提示两组MMR达标概率均随治疗时间延长升高(Wald $\chi^2=48.720$, $P<0.001$);组×时间交互效应具有统计学意义(Wald $\chi^2=8.940$, $P=0.003$)。氟马替尼组患者治疗期间腹泻发生率最高(26.23%),伊马替尼组患者血小板减少症发生率最高(31.15%)。此外,伊马替尼组皮疹、水肿发生率较氟马替尼组高($P<0.05$);其他不良反应发生率差异无统计学意义($P>0.05$)。中位随访时长为43(37, 52)个月。截至随访终止时,共7例患者死亡,其中伊马替尼组4例,死亡率6.56%(4/61),氟马替尼组3例,死亡率4.92%(3/61),两组患者OS比较差异无统计学意义(log-rank $P=0.955$)。**结论** 氟马替尼相较于伊马替尼治疗CML,具有更好的短期疗效和安全性。尽管长期OS无显著改善,氟马替尼仍可以作为CML的有效一线治疗。

【关键词】 慢性粒细胞白血病 氟马替尼 伊马替尼 倾向性评分

Efficacy and Long-term Prognosis of Flumatinib in the Treatment of Chronic Myelocytic Leukemia

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[Abstract] Objective To evaluate the clinical efficacy and safety of flumatinib in the treatment of chronic myelocytic leukemia (CML) by using propensity score matching (PSM) to balance baseline confounding factors. **Methods** A retrospective cohort of 195 patients with CML treated between January 2019 and January 2025 was selected for this study. Patients were stratified into imatinib and flumatinib groups based on their treatment regimens. PSM was employed to control for confounding variables, enabling a comparative analysis of early treatment responses and long-term survival outcomes, including overall survival (OS), between the two tyrosine kinase inhibitor therapies, as well as further analysis of long-term prognosis. **Results** Through PSM, a total of 61 patient pairs were successfully matched. In the flumatinib group, the rates of complete hematologic response (CHR) and early molecular response (EMR) at 3 months of first-line treatment were 96.72% and 83.61%, respectively, with the EMR rate being significantly higher than achieved with imatinib treatment ($P<0.001$). For flumatinib, the rates of cumulative major molecular response (MMR) at 6, 9, and 12 months of first-line therapy were 34.43%, 50.82%, and 59.02%, respectively, all exceeding those observed with imatinib ($P<0.05$). The molecular response 4 (MR⁴) rates for flumatinib at 9 and 12 months of first-line treatment were 19.67% and 27.87%, respectively, also higher than those for imatinib ($P<0.05$). Additionally, the cumulative complete cytogenetic response (CCyR) rates for flumatinib at 3, 6, and 12 months of first-line treatment were 67.21%, 85.25%, and 91.28%, respectively, consistently outperforming imatinib ($P<0.05$). Generalized estimating equation analysis revealed that patients in the flumatinib group had a significantly higher probability of achieving MMR than those in the imatinib group (Wald $\chi^2=16.280$, $P<0.001$, odds ratio [OR]=2.130, 95% CI: 1.570-2.890). The time effect indicated that the probability of achieving MMR increased with the extension of treatment duration in both groups (Wald $\chi^2=48.720$, $P<0.001$). In

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addition, a statistically significant group-by-time interaction effect was observed (Wald $\chi^2 = 8.940$, $P = 0.003$). During the treatment period, the highest incidence of diarrhea was observed in the flumatinib group (26.23%), while thrombocytopenia was most prevalent in the imatinib group (31.15%). Furthermore, the imatinib group exhibited higher incidences of rash and edema compared to the flumatinib group ($P < 0.05$). No significant differences were observed in the incidence of other adverse events between the groups ($P > 0.05$). The median follow-up duration was 43 (37, 52) months. By the end of the follow-up, a total of 7 patients had died, with 4 deaths (6.56% [4/61]) in the imatinib group and 3 deaths (4.92% [3/61]) in the flumatinib group. The comparison of OS between the two groups revealed no statistically significant difference (log-rank $P = 0.955$). **Conclusion** Compared with imatinib, flumatinib demonstrates superior short-term efficacy and safety profile in the treatment of CML. Despite the lack of significant improvement in long-term OS, flumatinib can still serve as an effective first-line therapeutic option for patients with CML.

[Key words] Chronic myelocytic leukemia Flumatinib Imatinib Propensity score matching

慢性粒细胞白血病(chronic myelocytic leukemia, CML), 亦称慢性髓系白血病, 属于高发的骨髓造血干细胞异常克隆增殖类疾病, 临床上一般分为3期: 慢性期、加速期和急变期^[1]。目前CML的常见治疗方式包括药物治疗〔如酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)〕和造血干细胞移植, 但干细胞移植配型困难, 且存在较多并发症, 限制了其临床应用^[2-3]。TKI现已成为治疗CML的首选药物, 其中氟马替尼(flumatinib)作为我国自主研发的新型第二代BCR-ABL1靶向TKI, 用于新诊断的CML患者, 可显著改善其预后^[4-5]。目前已有多项临床试验及国内多中心真实世界研究验证了氟马替尼的基础疗效与安全性, 但现有同类回顾性病例研究仍存在明显不足: 多数研究未校正患者基线混杂因素, 组间基线资料不均衡易造成结果偏倚; 且现有研究多聚焦短期分子学疗效, 国人长期生存数据分析资料仍较为欠缺, 单纯常规病例总结证据等级不足, 研究结论同质化较为明显。同时临床仍存在部分患者对TKI药物反应不佳、复发进展以及向急性白血病转化等情况^[6]。因此本研究通过倾向性评分匹配法(propensity score matching, PSM)有效控制混杂因素, 规避传统回顾性研究的选择偏倚, 提升研究证据等级, 同时依托本院大样本真实病例, 探究氟马替尼治疗CML患者的临床疗效, 并进一步评估氟马替尼的安全性及长期生存率(总生存期), 旨在为CML患者的临床治疗提供借鉴。

1 资料与方法

1.1 研究对象

本研究遵循知情同意原则, 并经安徽医科大学第一附属医院临床研究伦理委员会批准(批件号: 安医一附院科研伦审-PJ 2025-09-66), 批件有效期两年。回顾性选取2019年1月—2025年1月我院收治的195例CML患者作为研究对象, 研究期间均无脱落或剔除病例。纳入标准:

①符合CML诊断标准^[7]; ②年龄>14岁; ③临床资料及随访资料完整; ④已向所有患者及家属告知本研究相关信息。排除标准: ①妊娠期或哺乳期; ②其他血液系统疾病; ③疾病分期为加速期/急变期; ④合并恶性肿瘤; ⑤治疗依从性差, 未遵医嘱。

1.2 研究方法

1.2.1 治疗方案

以患者入院后接受的一线靶向治疗方案为分组依据, 分为伊马替尼组和氟马替尼组。伊马替尼组患者接受伊马替尼治疗, 剂量为400 mg, 每日1次, 随餐口服; 氟马替尼组患者接受氟马替尼治疗, 剂量为600 mg, 每日1次, 空腹口服。治疗期间严密监测患者生命体征、外周静脉血实验室检测指标结果, 根据治疗过程中治疗反应和(或)不良反应调整剂量, 若发生严重不良反应, 须谨慎继续治疗方案。

1.2.2 疗效评价及不良反应

根据《慢性髓性白血病中国诊断与治疗指南(2020年版)》^[8]在治疗第3、6、9、12个月时进行疗效判断, 包括完全血液学反应(complete hematologic response, CHR)、早期分子学缓解(early molecular response, EMR)、主要分子学反应(major molecular response, MMR)[其中深度分子学缓解(molecular response 4, MR⁴)为MMR的亚分层指标], 以及完全细胞遗传学缓解(complete cytogenetic response, CCyR)。结合现阶段慢性髓系白血病相关真实世界研究特点, 本研究采用多时间点、多指标联合评价患者整体治疗疗效, 未单独设置单一主要结局指标; 其中9个月仅作为中期动态观察时点, 不作为主要终点。在治疗期间, 依据常见不良事件评价标准(CTCAE)5.0版, 对不良反应进行记录。

1.2.3 随访

采用门诊复查、住院复查等途径开展随访工作, 未按时定期复查的患者通过电话方式进行随访。随访截止日

期为2025年7月1日,在此期间未出现患者失访情况,中位随访时长为43(37, 52)个月。总生存期(overall survival, OS)为自开始接受TKI治疗起,至患者死亡或末次随访的时间间隔。

1.2.4 资料收集

收集患者入院时病例资料,包括:①一般资料:年龄、性别、婚姻状况、文化程度;②病理资料:疾病分期、是否伴合并症、Sokal评分、欧洲治疗与预后研究长期生存(ELTS)评分;③首次入院时实验室检查指标:血红蛋白(hemoglobin, HGB)、白细胞(white blood cell, WBC)计数、血小板(platelet, PLT)计数。

1.3 统计学方法

采用SPSS 26.0进行统计学分析,所有数据结果以双侧 $P<0.05$ 为差异有统计学意义。采用PSM法消除两组基线混杂偏倚,以一线靶向治疗方案(伊马替尼/氟马替尼)为二分类因变量,结合CML疾病特征及相关文献,将年龄、性别、疾病分期、是否伴合并症、婚姻状况、文化程度、WBC计数、HGB、PLT计数、Sokal评分、ELTS评分作为协变量,构建倾向性评分模型。匹配方式采用1:1最邻近匹配,卡钳值取0.2。Shapiro-Wilk检验评估计量数据正态性,本研究中所有计量资料均不符合正态分布,用中位数(四分位间距)表示,采用Mann Whitney U 检验;计数资料用例数(%)表示,采用卡方检验。采用广义估计方程分析不同时间点随访重复测量的MMR二分类疗效数据,设定Logit链接函数与可交换工作相关矩阵,校正同一研究对象多次观测数据的内在相关性,分析组间主效应、时间效应及分组 $\times$ 时间交互效应。采用Kaplan-Meier曲线和log-rank检验探索组间生存率差异。

2 结果

2.1 PSM匹配前后两组变量比较结果

PSM后共有61对患者完成匹配。匹配后两组患者一般资料差异均无统计学意义($P>0.05$),变量在两组分布的均衡性提升,匹配效果良好,见网络资源附件附表1和附表2。

2.2 氟马替尼治疗CML患者临床疗效

匹配后CML患者临床疗效比较发现,氟马替尼一线治疗3个月时的CHR为96.72%,与伊马替尼组相比差异无统计学意义($P>0.05$)。氟马替尼一线治疗3个月时的EMR为83.61%,一线治疗6、9、12个月时的MMR率分别为34.43%、50.82%、59.02%,一线治疗9、12个月时的MR⁴率分别为19.67%、27.87%,一线治疗3、6、12个月时的CCyR率分别为67.21%、85.25%、91.80%,均高于伊马

替尼治疗,两组差异有统计学意义($P<0.05$)。见表1。进一步采用广义估计方程分析MMR重复测量疗效指标,结果显示:氟马替尼组的MMR达标概率高于伊马替尼组[Wald $\chi^2=16.280$, $P<0.001$, 比值比(odds ratio, OR)=2.130, 95%置信区间(confidence interval, CI): 1.570 ~ 2.890];时间效应提示两组MMR达标概率均随治疗时间延长升高(Wald $\chi^2=48.720$, $P<0.001$);组 $\times$ 时间交互效应具有统计学意义(Wald $\chi^2=8.940$, $P=0.003$),提示氟马替尼组达标概率随时间升高的趋势优于伊马替尼组。

表 1 两组CML患者的临床疗效
Table 1 Clinical outcomes of the two groups of CML patients

Evaluation indicator	Imatinib group (<i>n</i> = 61)	Fumarate group (<i>n</i> = 61)	χ^2	<i>P</i>
CHR (3 months)/case (%)	57 (93.44)	59 (96.72)	0.175	0.675
EMR (3 months)/case (%)	29 (47.54)	51 (83.61)	17.574	< 0.001
MMR/case (%)				
6 months	9 (14.75)	21 (34.43)	6.365	0.012
9 months	18 (29.51)	31 (50.82)	5.764	0.016
12 months	24 (39.34)	36 (59.02)	4.723	0.030
MR ⁴ /case (%)				
6 months	2 (3.28)	6 (9.84)	1.204	0.273
9 months	4 (6.56)	12 (19.67)	4.604	0.032
12 months	7 (11.48)	17 (27.87)	5.187	0.023
CCyR/case (%)				
3 months	28 (45.90)	41 (67.21)	5.638	0.018
6 months	41 (67.21)	52 (85.25)	5.473	0.019
12 months	48 (78.69)	56 (91.80)	4.171	0.041

CHR: complete hematologic response; EMR: early molecular response; MMR: major molecular response; MR⁴: molecular response 4; CCyR: complete cytogenetic response.

2.3 氟马替尼治疗CML患者不良反应发生情况

匹配后CML患者不良反应发生情况组间比较发现,氟马替尼组患者治疗期间腹泻发生率最高(26.23%),伊马替尼组患者血小板减少症发生率最高(31.15%)。此外,伊马替尼组皮疹、水肿发生率较氟马替尼组高,差异有统计学意义($P<0.05$);其他不良反应发生率差异无统计学意义($P>0.05$)。见表2。

2.4 氟马替尼治疗CML患者预后情况分析

截至随访终止时,共7例患者死亡,其中伊马替尼组4例,死亡率6.56%(4/61),氟马替尼组3例,死亡率4.92%(3/61)。进行Kaplan-Meier生存分析,两组患者OS比较差异无统计学意义(log-rank $P>0.05$),见图1。

表 2 两组CML患者治疗不良反应发生情况

Table 2 Occurrence of adverse reactions in the two groups of CML patients during treatment

Adverse reaction	Imatinib group (n = 61)	Fumarate group (n = 61)	χ^2	P
Thrombocytopenia/case (%)	19 (31.15)	12 (19.67)	2.119	0.145
Neutropenia/case (%)	15 (24.59)	10 (16.39)	1.258	0.262
Anemia/case (%)	5 (8.20)	3 (4.92)	0.134	0.715
Vomiting/case (%)	13 (21.31)	7 (11.48)	2.153	0.142
Diarrhea/case (%)	10 (16.39)	16 (26.23)	1.760	0.185
Rash/case (%)	12 (19.67)	4 (6.56)	4.604	0.032
Edema/case (%)	18 (29.51)	4 (6.56)	10.869	< 0.001
Pain in the limbs/case (%)	10 (16.39)	5 (8.20)	1.900	0.168
Hypophosphatemia/case (%)	9 (14.75)	3 (4.92)	3.327	0.068

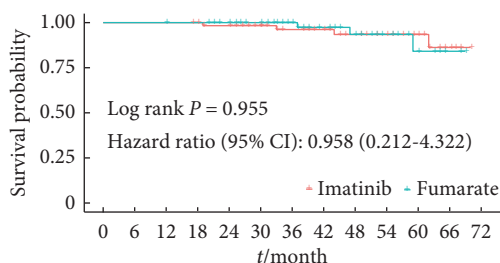


图 1 两组CML患者的总生存期

Fig 1 Overall survival in the two groups of CML patients

3 讨论

CML患者的治疗反应包括血液学、细胞遗传学和分子学反应。CCyR是疾病控制的关键节点,更深的分子学反应直接关联长期生存,因此尽快获得CCyR以及更深的分子学反应是CML患者治疗的近期目标。

本研究发现,两组患者3个月CHR无明显差异;而氟马替尼在EMR(3个月)、CCyR(3、6、12个月)及MMR(6、9、12个月)、MR⁴(9、12个月)指标上均展现出更优应答水平($P < 0.05$)。研究显示,氟马替尼相较伊马替尼的12个月MMR与CCyR更高,且出现疾病进展的患者更少,与本研究结果一致^[9-11]。基于MMR多时点重复测量数据构建广义估计方程模型,结果提示氟马替尼患者整体分子学缓解优势更强;两组MMR均随随访时间延长逐步改善,且氟马替尼组缓解效果的增长趋势优于伊马替尼组。氟马替尼作为第二代TKI,通过优化分子结构,增强了对BCR-ABL1融合蛋白的抑制能力,其作用机制更直接地阻断癌细胞增殖信号通路,诱导肿瘤细胞凋亡,因此表现出更高的短期反应率^[12-13]。从代谢组学角度而言,CML患者体内代谢紊乱程度与TKI治疗应答、缓解深度密切相关,疗效不佳者代谢异常持续存在,而深度缓解患者的代谢

谱可逐步恢复至健康水平,特异性代谢标志物还可动态评估疗效、预警病情波动^[14-15]。结合本研究疗效数据推测,氟马替尼更强的靶向抑制作用可更高效地逆转机体代谢重编程,纠正恶性代谢紊乱,这也从代谢层面解释了其整体疗效更佳的原因。截至随访终止时,共7例患者死亡,其中伊马替尼组4例,死亡率6.56%,氟马替尼组3例,死亡率4.92%,两组患者OS比较无明显差异。显示第二代TKI相较于伊马替尼更易使患者获得MMR、CCyR,但并未明显改善患者总生存期。

最常见的TKI药物相关不良反应为胃肠道反应^[16]。本研究中氟马替尼组患者治疗期间腹泻发生率最高(26.23%),与既往文献报道基本一致^[17]。伊马替尼组患者血小板减少症发生率最高(31.15%)。血液学不良事件,如中性粒细胞减少症、血小板减少症、贫血等通常仅限于第一个治疗期,可能需要暂时调整剂量,但很少是治疗改变的原因,也很少是并发症的原因^[18-19]。但血小板减少症在CML患者中可能提示骨髓抑制,且常与营养不良、肾功能不全或慢性炎症等合并症共存,此类患者可能因疾病生物学行为恶劣而预后不佳^[20-21]。伊马替尼组皮疹、水肿等与生活质量相关的不良反应发生率较氟马替尼组高。如果按处方服用,所有TKI在实现CML功能性治愈方面都有相对较高的成功率。然而,依从性是长期治疗成功的关键。不良事件的管理对于确保治疗依从性、维持疗效以及提升患者生活质量至关重要^[22-23]。各类TKI副作用存在差异,可能对伴有不同并发症的CML患者治疗效果产生影响,因此在临床治疗过程中,需加强对患者依从性的管理和教育,提高患者对规律服药重要性的认识,确保患者坚持完成治疗。

综上所述,氟马替尼相较于伊马替尼治疗CML,具有更好的12个月内短期疗效和安全性。尽管长期OS无显著改善,氟马替尼仍可以作为CML的有效一线治疗。本研究存在多项局限性:首先,本研究为单中心研究,样本量有限,且因死亡事件数少,未开展多因素独立预后因素分析。其次,研究在PSM阶段仅将病情分期作为混杂因素进行整体匹配,未进一步分层分析不同病情分期患者的治疗疗效,无法明确不同分期人群中两种药物的疗效差异^[24]。同时,研究未纳入患者染色体核型相关数据,无法探讨该指标对治疗结局的影响,未能排除其作为混杂因素干扰研究结果的可能^[25]。最后,本研究仅收集并分析了患者接受治疗期间出现的非血液学不良反应和Ⅲ级及以上血液学不良反应的发生情况,并未对Ⅰ~Ⅱ级血液学不良反应进行收集和分析。这些局限性可能会对结果产生影响,未来仍需要进行前瞻性、多中心、大样本的随

机对照试验进一步验证结果。

* * *

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