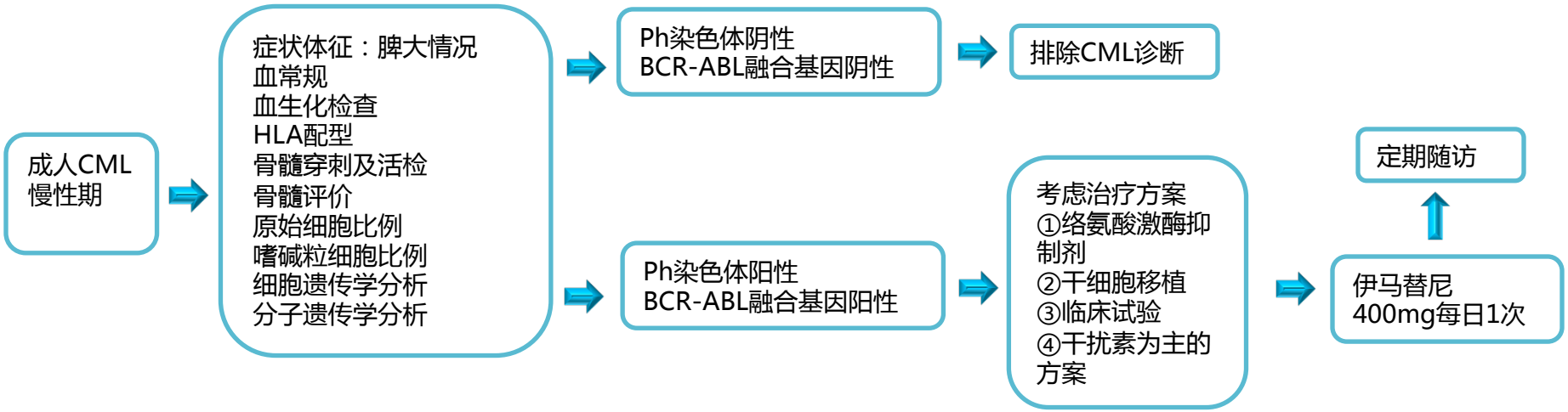
CML慢性期患者初始治疗

TKI治疗：慢性期患者首选治疗为TKI ，推荐首选伊马替尼400mg，每日１次[8-10，13-18]（图１）。



治疗期间应定期监测血液学、细胞及分子遗传学反应，参照符合中国人特点的CML患者治疗反应标准（表１）进行治疗反应评估，随时调整治疗方案（表２）。早期的分子学反应至关重要，特别是伊马替尼治疗３个月的ＢＣＲ[illegible]ＡＢＬ融合基因水平[19-20]。临床治疗反应包括最佳反应、次佳反应以及治疗失败。治疗反应次佳以及失败的患者在评价治疗依从性、患者的药物耐受性、合并用药的基础上及时行BCR-ABL激酶区突变检测，适时更换第二代TKI，如尼洛替尼或达沙替尼，有合适供者的患者可考虑行allo-HSCT[8-10,21-27]。频繁、长期的TKI治疗中断以及患者服药依从性差可能导致不良临床结果，伊马替尼耐受不佳的患者应及时更换第二代TKI 。良好的服药依从性教育以及严密监测对于获得最佳临床疗效非常重要。

表1　400mg/d伊马替尼治疗慢性髓性白血病慢性期患者治疗反应评价标准

时间	最佳反应	次佳反应	失败
3个月	达到CHR基础上至少达到mCyR（Ph^+细胞≤65%）或$BCR\text{-}ABL^{IS}$≤10%	达到CHR但未达到至少达到mCyR（Ph^+细胞65%~95%）或$BCR\text{-}ABL^{IS}$ > 10%	无任何mCyR（Ph^+细胞 > 95%）
6个月	至少达到PCyR（Ph^+细胞≤35%）或$BCR\text{-}ABL^{IS}$≤10%	达到mCyR但未达到至少达到PCyR（Ph^+细胞36%~65%）或$BCR\text{-}ABL^{IS}$ > 10%	未达到mCyR（Ph^+细胞 > 65%）
12个月	达到CCyR或$BCR\text{-}ABL^{IS}$≤1%	$BCR\text{-}ABL^{IS}$ > 1%	未达到CCyR
18个月	获得MMR（$BCR\text{-}ABL^{IS}$≤0.1%）	未获得MMR（$BCR\text{-}ABL^{IS}$ > 0.1%）	未达到CCyR
任何时间	稳定或达到MM R	丧失MM R，无伊马替尼耐药性BCR-ABL激酶区突变	丧失CHR或CCyR，出现伊马替尼或其他TKI耐药性突变，出现Ph染色体基础上其他克隆性染色体异常

表 2　400mg/d伊马替尼治疗慢性髓性白血病慢性期患者治疗调整

治疗反应	评估	治疗方案调整
最佳治疗反应		继续400mg/d伊马替尼
次佳治疗反应	评价患者依从性； 评价药物相互作用； BCR-ABL激酶突变分析	更换第二代TKI; 继续400mg/d伊马替尼
治疗失败	评价患者依从性； 评价药物相互作用； BCR-ABL激酶突变分析	更换第二代TKI; SCT评估； 临床试验
不耐受		更换第二代TKI; SCT评估； 临床试验

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Myelogenous Leukemia

Primary Treatment

Imatinib (400 mg once daily) is still recommended as a reasonable first-line therapy (category 1) for newly diagnosed patients with CP-CML. Based on the recent FDA approval of nilotinib (300 mg twice daily) and dasatinib (100 mg once daily), the guidelines have also included nilotinib or dasatinib as first-line therapy options (category 1) for newly diagnosed patients.

Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.

Baccarani M, Pileri S, Steegmann JL et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii72-7.

Chronic myeloid leukemia Treatment recommendations :
Chronic phase: First line Imatinib 400 mg, or nilotinib 300 mg × 2, or dasatinib100 mg

Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet.

Baccarani M, Cortes J, Pane F, et al. J Clin Oncol. 2009 Dec 10;27(35):6041-51.

Initial treatment was confirmed as imatinib 400 mg daily. Imatinib should be continued indefinitely in optimal responders.
The InternationalRandomizedStudyof IFNversus STI571(IRIS) estab-lished the superiority of imatinib 400 mg daily compared with IFN- and low-dose cytarabine (AraC) regarding the rateofHR,CgR, andMolR, and the study suggested a substantial advantage inPFS andOS. This advantagewas confirmed in subsequent reports.

甲磺酸伊马替尼治疗慢性粒细胞白血病慢性期100例追踪观察

江倩, 陈珊珊, 江滨等.中华血液学杂志2006年11月第27卷第11期721-6

100例Ph⁺CML第1次慢性期(多为干扰素IX治疗失败的晚慢性期)患者持续口服甲磺酸伊马替尼400mg / d(93例)或600 mg/d(7例)。研究结果显示：位追踪49.0(4.5—58.0)个月，累积获得的完全血液学缓解率为100%，主要．细胞遗传学缓解(MCyR)率为86.0%，完全细胞遗传学缓解(CCyR)率为76.0%，CCyR患者中主要分子学缓解率为68．8%，完全分子学缓解率为26.6%，预计54个月无疾病进展率和总生存率分别为90.0%和92.6%。磺酸伊马替尼明显提高Ph+CML慢性期患者的细胞遗传学和分子学疗效，改善生活质量，延长无疾病进展生存期。

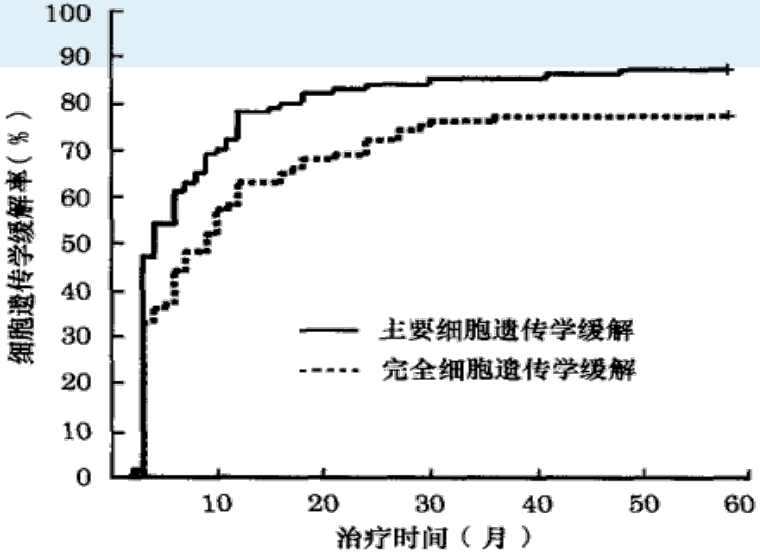


图1　100 例 CML 慢性期患者伊马替尼治疗中获得的细胞遗传学疗效

伊马替尼治疗慢性粒细胞白血病151例临床疗效及安全性观察

周励，王爱华，王黎等。中华血液学杂志2008年1月第29卷第1期13-7

151例cML患者给予伊马替尼治疗，评估其疗效、不良反应、总生存(0s)和疾病进展情况，并对相关影响因素进行分析。结果可评估的患者142例，中位伊马替尼治疗时间21.5(6～78)个月。①慢性期患者累积获得的完全血液学缓解(cHR)、主要细胞遗传学缓解(McyR)、完全细胞遗传学缓解(ccyR)和完全分子学缓解(cMoR)率分别为98.9%、82.6%、76.1%和29.3%，与加速期和急变期患者比较差异有统计学意义(P<0.0001)。②慢性期患者1年、2年和3年0s率分别为100%、(97.3±1.9)%和(95.8±2.4)%；加速期患者分别为(84.7±8.2)%、(77.0±10.4)%和(69.3±11.9)%；急变期患者分别为(62.9±8.9)%、(41.9±9.2)%和(28.5±9.1)%，三组差异有统计学意义(P<0.0001)。慢性期患者1年、2年和3年疾病无进展生存(PFs)率分别为(98.9±1.1)%、(93.9±2.7)%和(93.9±2.7)%；加速期患者分别为(68.9±10.6)%、(61.3±11.9)%和(61.3±11.9)%；急变期患者分别为(36.4±8.8)%、(25.4±8.1)%和(10.1±8.2)%，三组差异也有统计学意义(P<0．o001)。③对92例慢性期患者进行分析，初发组获得McyR和ccyR的比例显著高于干扰素治疗失败组(Jp值分别为0.015和0.010)；伊马替尼治疗12个月获得的疗效与疾病进展显著相关，获得ccyR患者疾病进展比例低于获得部分细胞遗传学缓解(PcyR)和未获得MCyR患者(P=0.0099)；根据sokal评分，低危组患者获得McyR和ccyR的比例显著高于中危和高危组患者(P值分别为0.0013和0.0024)，且与疾病进展显著相关(p=0.0467)。④伊马替尼治疗的不良反应主要为I～Ⅱ级，患者多可耐受。结论伊马替尼治疗可以使cML慢性期患者获得较高的血液学和细胞遗传学缓解率，延长患者的生存时间，但是对加速期和急变期患者疗效不理想。

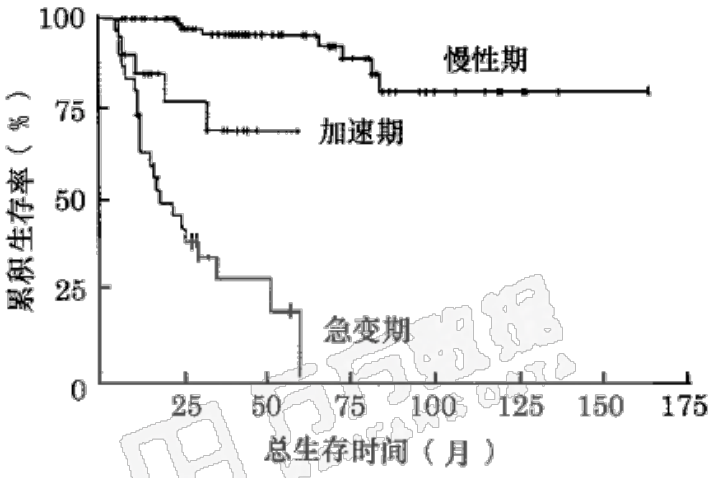


图1 CML各期患者总生存曲线

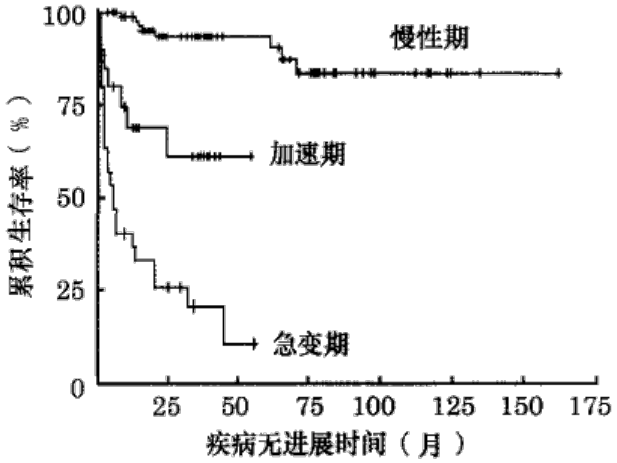


图2 CML各期患者疾病无进展生存曲线

BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia.

Schiffer CA. N Engl J Med. 2007 Jul 19;357(3):258-65.

For patients with chronic-phase CML, imatinib is initiated at a daily oral dose of 400 mg, a regi-men that begins as soon as the diagnosis is made.

First-line therapy for chronic myeloid leukemia: Past, present, and future.

Pavlovsky C, Kantarjian H, Cortes JE. Am J Hematol. 2009 May;84(5):287-93.

Standard-dose imatinib (400 mg/day in chronic phase, 600 mg/day in advanced CML) now dominates the management of this disease, producing consider-ably higher hematologic, cytogenetic, and molecular response rates than seen with previous drug thera-pies.

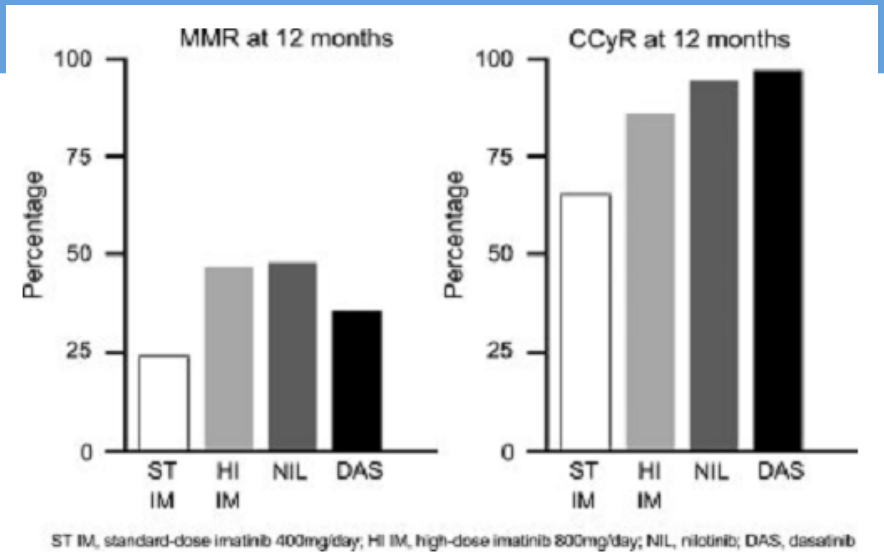


Figure 1. Summary of reported results from different studies of imatinib, nilotinib, and dasatinib in early chronic phase CML: 12 month MMR and CCyR [84,85].

Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patientswith chr onic myeloid leukemia treated with tyrosine kinase inhibitors.

Marin D, Ibrahim AR, Lucas C,et al. J Clin Oncol. 2012 Jan 20;30(3):232-8

A single measurement ofBCR-ABL1transcripts performed at 3 months is the best way to identify patients destined to fare poorly, thereby allowing early clinical intervention.

BCR-ABL1Transcript Levels at 3, 6, and 12 Months Strongly Predict for Most Relevant Clinical Outcomes

TheBCR-ABL1transcript levels at 3, 6, and 12 months signifi-cantly predicted for OS, PFS, and EFS and for the probabilities of achieving CCyR, MMR, and CMR

Table 2. RR for OS, PFS, and EFS at 8 Years and Cumulative Incidences of CCyR, MMR, and CMR According to the Transcript Level at 3, 6, and 12 Months

Outcome	RR for Transcript Level (Log)		Cutoff (%)	No. of Patients at Risk	8-Year Probability of the Outcome		8-Year Probability of the Outcome According to Risk Group		
	RR	*P*			%	*P*	No. of Patients	%	*P*
BCR-ABL1 transcript level at 3 months									
OS	0.161	< .001				< .001			
Low risk			≤ 9.84	211	93.3		N/A	N/A	
High risk			> 9.84	68	56.9		N/A	N/A	
PFS	0.162	< .001				< .001			< .001
Low risk			≤ 9.54	208	92.8		211	92.8	
High risk			> 9.54	71	57.0		68	55.5	
EFS	0.102	< .001				< .001			< .001
Low risk			≤ 9.84	211	65.1		211	65.1	
High risk			> 9.84	66	6.9		66	6.9	
CCyR	5.17	< .001				< .001			< .001
Low risk			≤ 8.58	169	99.4		180	97.9	
High risk			> 8.58	79	21.7		68	14.8	
MMR	12.98	< .001				< .001			< .001
Low risk			≤ 2.81	141	82.5		210	70.1	
High risk			> 2.81	137	21.1		68	0	
CMR	10.95	< .001				< .001			< .001
Low risk			≤ 0.61	57	84.7		211	19.3	
High risk			> 0.61	222	1.5		68	0	

Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival inchronic myeloid leukemia (CML).

Hanfstein B, Müller MC, Hehlmann R et al. Leukemia. 2012 Sep;26(9):2096-102.

At 3 months of treatment, 28% of patients failed to achieve the 10% BCR-ABL^{IS} level and had a 5-year OS of only 87%. Owing to their slow response, about one-fourth of patients were declared high-risk patients at 3 months according to our results (27% with>10% BCR-ABL^{IS}, 28% with >35% Ph+), and those reported by Marinet al.(24% with >9.84% BCR-ABL transcript level).