Cellular Therapy and Transplantation (CTT). Vol. 6, No. 4(21), 2017
doi: 10.18620/ctt-1866-8836-2017-6-4-13-20
Submitted: 18 October 2017, accepted: 15 December 2017

Long-term survival with CML with imatinib or transplantation as first-line treatment: Comparison of outcomes from CML Studies IIIA and IV

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Summary

With introduction of the tyrosine kinase inhibitor (TKI) imatinib, the treatment strategy of CML has profoundly changed. TKIs became the first-line treatment of choice for CML competing with allogeneic hematopoietic stem cell transplantation (HCT). Variables to be considered in choosing TKIs for first-line therapy are as follows: conventional risk score; cytogenetic findings with major-route additional chromosomal aberrations (ACA) at diagnosis, and high-risk ACA in the course of CML; comorbidities; treatment costs. In cases of refractoriness to imatinib, the 2nd line treatment options are: clinical response milestones; adherence to therapy; resistance mutations; clonal evolution; therapy intolerance; drug safety; health care setting.

CML Study IV, a randomized treatment study concerning imatinib dose optimization and combined therapy with imatinib and cytarabine or interferon α included 1551 newly diagnosed patients in chronic phase. The key outcome was no superiority of survival of any treatment option. Imatinib 400 mg provides close to normal life expectancy in chronic-phase CML patients.

Survival is independent of time to response. Outcome of CML is currently more determined by disease and patients' factors, e.g., comorbidities and smoking, and by center effects than by initial treatment selection. A comparison of long-term survival after HCT or imatinib treatment showed that low risk patients had similar survival with both options. Attempts at improving treatment should focus on subgroups of refractory disease e.g. by HCT, and on non-CML determinants of survival. After progression to blast crisis, HCT did not provide a significant survival advantage, although a special study showed that most long-term survivors (72%) were patients who received a transplant. The 10-year deep molecular remission rates of 70%-80% indicate that the majority of imatinib-treated patients are candidates for treatment discontinuation.

Keywords

Chronic myeloid leukemia, tyrosine kinase inhibitors, imatinib, treatment strategy, hematopoietic stem cell transplantation, survival.

Introduction

The only curative treatment for chronic myeloid leukemia (CML) was previously allogenous hemopoietic cell transplantation (HCT) [1]. With the introduction of the tyrosine kinase inhibitor (TKI) imatinib into CML management 15 years ago and the stunning response and survival results, treatment strategy of CML has profoundly changed. TKI became the first line treatment of choice for CML.

Long term survival

Meanwhile several long-term observational and randomized studies have matured and 10-year survival outcomes are available. An overview is shown in Table 1. 5-year survival ranges around 90%, 10-year survival around 83% and 10-year relative survival compared to the general population is more than 90% [2, 3]. Similar results have been observed in population based registries [4, 5, 6]. More patients died of comorbidities than of CML [7].

Deep molecular responses are achieved in up to 80% after 5 to 10 years (Figure 1) suggesting that treatment discontinuation should be possible in these patients [8].

Table 1. Long-term survival rates of CML patients treated with TKI

Study	Dose, mg	n	Age at diagnosis, median, years	5yr survival, %	10yr survival, %	Median observation time, years
CML-IV Hehlmann et al., 2017) [3]	IM 400–800	1536	53	90	82	9.5
IRIS (Hochhaus et al., 2017) [9]	IM 400	553	50	89	83.3	10.9
GIMEMA (Palandri et al., 2009) [10]	IM 400–800	559	52	90	NA	5
Hammersmith (de Lavallade et al, 2008) [11]	IM 400	204	46.3	83	NA	3.2
PETHEMA (Cervantes et al., 2010) [12]	IM 400	210	44	97.5	NA	4.2
TOPS (Baccarani et al., 2014 [13])	IM 400 IM 800	157 319	45 48	94 (4 years) 93.4 (4 years)	NA	3.5 3.5
MDACC (Jain et al., 2015 [14])	IM 400 IM 800	70 201	48.3	NR	80 84	9.9 (min. 8)
ILTE[8] (CCR only): Gambacorti-Passerini et al., 2011 [15]	IM NR	832	51	98 (6 years)	95 (8 years)	5.8
ENESTnd (Hochhaus et al., 2016 [16])	IM 400 Nilo 600 Nilo 800	283 282 281	46 47 47	92 94 96	NA	5.5
Dasision (Cortes et al., 2016 [17])	IM 400 Dasa 100	260 259	49 46	90 91	NA	5
Median (estimate)				**91**	**83**	

NA = not available; NR = not reported; yr = year; min. = minimum; IM = imatinib; Nilo = Nilotinib; Dasa = Dasatinib; CCR = complete cytogenetic remission.

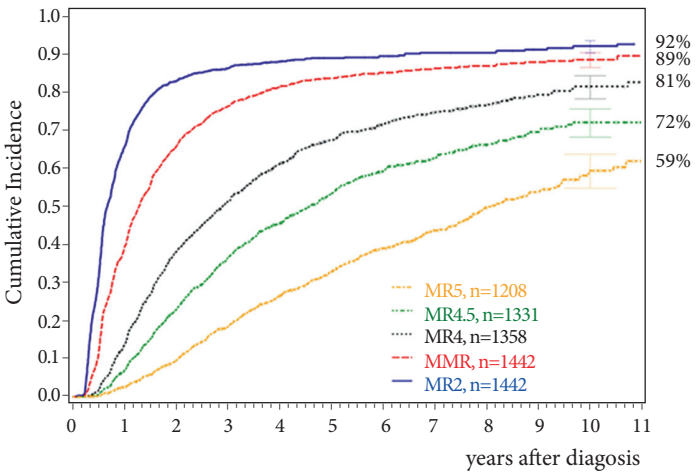

Figure 1. Molecular response achieved by imatinib [8]

First-line treatment

Current first-line options with TKI are shown in Table 2. Whereas imatinib has been proven to be safe both at 400 and the faster acting 800 mg daily even after prolonged periods of time, the also faster acting 2nd generation (2G-)TKI require risk assessment due to rare but serious, potentially life threatening adverse drug reactions. As seen from Fig. 2, no survival advantage has been observed with any treatment option [3, 16, 17]. The lower progression rate to blast crisis observed with 2G-TKI is offset by more deaths due to adverse drug reactions. Variables to be considered in choosing first-line therapy are:

– Risk score;

– Cytogenetics (major-route ACA at diagnosis, high-risk ACA in the course of CML);

– Comorbidities;

– Costs.

The impact of karyotype at diagnosis was demonstrated by Fabarius et al. [18]. Patients with major route ACA which occur in 1-2% of cases at diagnosis have a much poorer prognosis. Comorbidities do not influence progression of CML, but impact survival more than CML. Generic imatinib has become available recently. It decreases treatment costs at equal efficacy and adds to the advantages of imatinib over 2G-TKI.

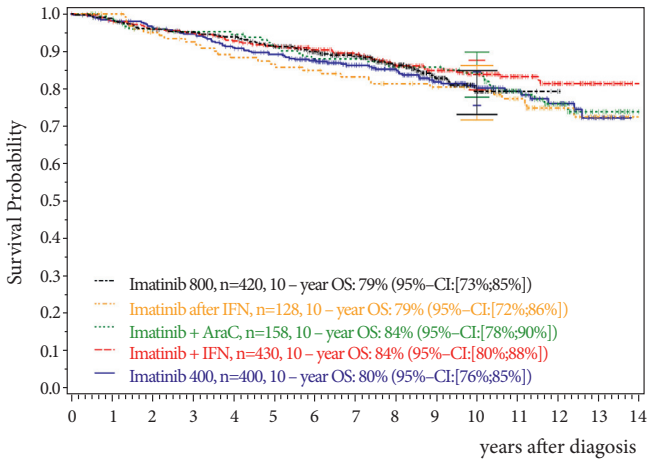

Figure 2. 10-year survival in CML study IV. [3]

Second-line therapy

2nd-line therapy is needed in cases of refractoriness to imatinib. Table 3 summarizes comparative efficacy and safety of 2nd-line treatment options. The variables to be considered for second line therapy are:

– Response milestones (Table 4);

– Adherence to therapy;

– Resistance mutations (Table 5);

– Clonal evolution;

– Intolerance;

– Drug safety;

– Health care setting.

The criteria for assessing TKI-response were proposed by the European LeukemiaNet (ELN) for newly diagnosed CML [13] and are depicted in Table 4. Before changing treatment due to resistance, non-adherence to drug-treatment has to be excluded. Non-adherence has been reported as the most frequent reason for treatment failure [19].

When changing treatment due to confirmed resistance a mutation analysis should be initiated. This can be done simultaneously with changing to the new drug. If the new drug still does not work, the mutation analysis will give a rational basis for selecting the right drug. Table 5 lists the most important mutations and there sensitivity to the currently available TKI.

Adverse TKI reactions have recently been reviewed on behalf of ELN by [20]. Table 6 gives an overview over the most frequently observed adverse TKI reactions.

Table 2. First-line therapy options: Efficacy and safety

	Imatinib 400 mg	IM 800 mg tolerability adapted	Nilotinib 2 x 300 mg	Dasatinib 100 mg
Efficacy		acts faster	acts faster, less early progressions	acts faster, less early progressions
Safety	Safe	Safe	assess risks	assess risks
Survival	82 – 86% after 10 years		91 – 94% after 5 years	

Note: No survival advantage with any therapy option.

Table 3. Second line treatment options: Efficacy and safety

	Dasatinib	Nilotinib	Bosutinib	Ponatinib	HCT
Efficacy	Nilotinib resistance mutations AP, BC	Dasatinib resistance mutations Renal failure	After failure of 2 TKI	T315I AP, BC	CE AP, BC
Safety	No pulmonary risks N.B.: infections	No CV risks N.B.: diabetes, liver disease	N.B.: GI-toxicity	No CV risks	No HCT contra-indications

Note: No survival advantage with any treatment option.

AP = Accelerated phase, BC = Blast crisis, CE = Clonal evolution, CV = Cardiovaskular, GI = Gastrointestinal, HCT = Hemopoietic cell transplantation

Table 4. ELN response milestones for newly diagnosed CML [13]

Time:	Optimal Response	Warning	Failure
3 months	BCR/ABL1 ≤10% Ph+ cells ≤35% (PCyR)	BCR/ABL1 >10% Ph+ cells 36-95%	No CHR. Ph+ cells >95%
6 months	BCR/ABL1 <1% Ph^+ cells 0% (CCyR)	BCR/ABL1 1-10% Ph+ cells 1-35%	BCR/ABL1 >10% Ph+ cells >35%
12 months	BCR/ABL1 ≤0.1% (MMR)	BCR/ABL1 0.1-1%	BCR/ABL1 >1% Ph+ cells >0%
Thereafter	Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos	-7 or del(7q) in Ph- cells	Loss of CHR or CCyR; confirmed loss of MMR. ABL1 mutations. New chromosome abnormalities

Table 5. Impact of TKI resistance mutations of the BCR/ABL kinase domain [21] (permission of reproduction granted by M. Deininger)

Mutation	IC_{50}-fold increase relative to WT (W=1)				
	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
M244V	0.9	0.9	2.0	1.2	3.2
L248R	14.6	22.9	12.5	30.2	6.2
L248V	3.5	3.5	5.1	2.8	3.4
G250E	6.9	4.3	4.4	4.6	6.0
Q252H	1.4	0.8	3.1	2.6	6.1
Y253F	3.6	1.0	1.6	3.2	3.7
Y253H	8.7	0.6	2.6	36.8	2.6
E255K	6.0	9.5	5.6	6.7	8.7
E255V	17.0	5.5	3.4	10.3	12.9
D276G	2.2	0.6	1.4	2.0	2.1
E279K	3.6	1.0	1.6	2.0	3.0
E292L	0.7	1.1	1.3	1.8	2.0
V299L	1.5	26.1	8.7	1.3	0.6
T315A	1.7	6.0	58.9	2.7	0.4
T315I	17.5	45.4	75.0	39.4	3.0
T315V	12.2	29.3	738.8	57.0	2.1
F317L	2.6	2.4	4.5	2.2	0.7
F317R	2.3	33.5	114.8	2.3	4.9
F317V	0.4	11.5	21.3	0.5	2.3
M343T	1.2	1.1	0.9	0.8	0.9
M351T	1.8	0.7	0.9	0.4	1.2
F359I	6.0	2.9	3.0	16.3	2.9
F359V	2.9	0.9	1.5	5.2	4.4
L384M	1.3	0.5	2.2	2.3	2.2
H396P	2.4	0.4	1.1	2.4	1.4
H396R	3.9	0.8	1.6	3.1	5.9
F486S	8.1	2.3	3.0	1.9	2.1
L248R + F359I	11.7	39.3	13.7	96.2	17.7

Sensitive	<2-fold difference
Moderately sensitive	2.1- to 4-fold difference
Resistant	4.1- to 10-fold difference
Highly resistant	>10-fold difference

Adapted from Redaelli S et al. *Am J Hematol.* 2012;87:E125-E128.

Table 6. Adverse TKI reactions: types and severity [20]

	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Myelosuppression	++	+	+++	+	++
Fluid retention	++	-	+++	-	-
Rash	+	++	-	-	++
Diarrhea	+	+	+	+++	+
↑ Glucose / Cholesterol	-	++	-	-	-
Vascular occlusion	-	++	+	-	+++
Renal insufficiency	+	-	(+)	?	?

CML Studies IIIA and IV

CML study IIIA is a geneticly randomized study comparing allogenous HCT with best available drug treatment. It recruited 662 patients, randomized 427 eligible patients (family donor available vs not available) and was published after a median observation time of 12.1 years [15]. The key result was equivalence of outcome for low risk patients after transplantion, if performed within one year of diagnosis, and imatinib.

CML study IV is a randomized 5-arm treatment optimization study to explore whether treatment with imatinib 400mg can be improved by doubling the dose, combining imatinib with cytarabine or interferon α (IFN) or applying imatinib after IFN failure. 1551 newly diagnosed patients in chronic phase where recruited and the study published after a median observation time of 9.5 years [3]. The key outcome was no superiority of survival of any treatment option (Fig. 2) in spite of significantly faster responses with imatinib 800 mg and the recognition of determinants of survival independent of treatment by multivariate analysis (Table 7).

Table 7. Determinants of survival by multivariate analysis (n=1252)

Variable		Hazard ratio	p-value
Therapy	IM-after-IFN-failure vs. IM 400 IM 800 vs. IM 400 IM + cytarabine vs. IM 400 IM + IFN vs. IM 400	1.334 1.033 1.170 0.933	0.256 0.875 0.519 0.727
Risk-score	Low vs. High risk Intermediate vs. High Risk	0.459 1.062	< 0.001 0.770
Center effect	Academic vs. community hospital Academic vs. office-based center	1.515 1.768	0.021 0.004
Comorbidity (Charlson index)	Per point (age not considered)	1.518	< 0.001
Gender	Male vs. female	1.199	0.240
Transcript type	b2a2 vs. b3a2 b2a2 + b3a2 vs. b3a2	1.092 1.171	0.574 0.447
Smoking habit	Smoker vs. non-smoker	1.728	0.001
Karyotype	Major-Route ACA vs. no Major-Route ACA at diagnosis	6.137	< 0.001

Note: *, age considered by Risk-score. IM = Imatinib, IFN = interferon α, ACA = additional chromosomal aberration

A comparison of long-term survival after HCT or drug treatment showed that low risk patients had similar survival with both options (Fig. 3) [22, 23].

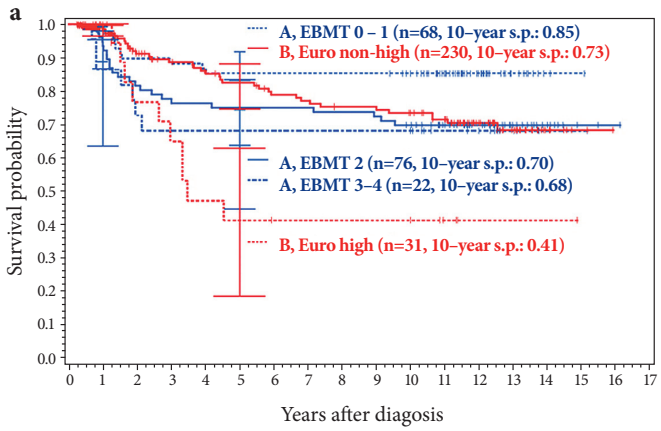

Figure 3. HCT (Group A in blue) vs. drug treatment (Group B in red) by transplant (EBMT score) – and disease- risks (EURO score) [22]

After progression to blast crisis HCT did not provide a significant survival advantage (Fig. 4), although long-term observations of 699 blast crises from the German CML studies showed that most long-term survivors (72%) were patients who received a transplant [24].

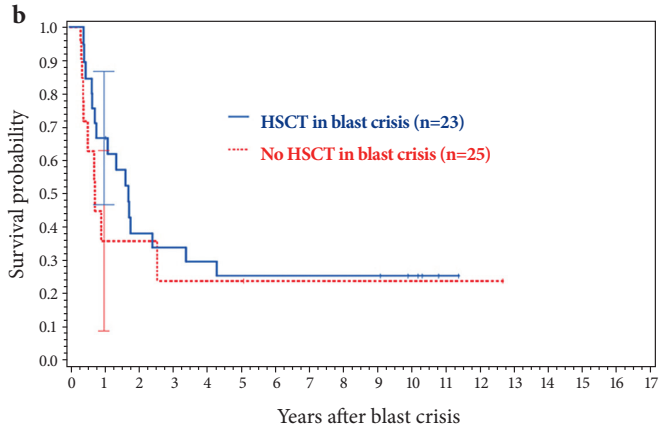

Figure 4. Effects of hematopoietic stem cell transplantation upon survival of CML patients with blast crisis [22]

Conclusion

- Imatinib 400 mg provides close to normal life expectancy in chronic-phase CML patients.
- Survival is independent of time to response.
- Outcome of CML is currently more determined by disease and patients' factors e.g. comorbidities and smoking, and by center effects than by initial treatment selection.
- In low risk patients survival after imatinib and transplantation may be similar.
- Attempts at improving treatment should focus on subgroups of refractory disease e.g. by HCT, and on non-CML determinants of survival.
- The 10-year deep molecular remission rates of 70%–80% indicate that the majority of imatinib treated patients are candidates for treatment discontinuation.

Conflict of interest

The author has no conflicts of interest to declare.

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Долгосрочная выживаемость при хроническом миелоидном лейкозе при лечении иматинибом или трансплантации гемопоэтических клеток в качестве первой линии терапии: сравнение исходов по данным исследований CML IIIA и IV

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Резюме

Стратегия лечения хронического миелолейкоза (ХМЛ) сильно изменилась после внедрения иматиниба – ингибитора тирозинкиназы (ИТК). Эти препараты стали часто применяться для первой линии лечения при ХМЛ вместо аллогенной трансплантации гемопоэтических стволовых клеток (ТГСК). При выборе ИТК в качестве терапии первой линии учитывают следующие факторы: оценка риска для больного по принятой шкале, цитогенетические маркеры со значимыми дополнительными хромосомными аномалиями (ДХА) при постановке диагноза, а также ДХА высокого риска в процессе развития ХМЛ, сопутствующие заболевания, расходы на лечение. В случаях отсутствия ответа на иматиниб, рассматриваются возможности 2-й линии терапии, с учетом показателей клинического ответа на лечение, соблюдения режима лечения, мутаций, ведущих к лекарственной устойчивости, клональной эволюции лейкоза, непереносимости данного лечения, типа лечебного учреждения.

В программе CML IV, рандомизированном исследовании, направленном на оптимизацию дозы иматиниба и эффектов сочетанной терапии иматиниба с цитарабином или интерфероном α, участвовали 1551 свежевыявленных пациентов в хронической фазе ХМЛ. Основным результатом было отсутствие какого-либо преимущества любого из применявшихся методов лечения. Иматиниб в дозе 400 мг обеспечивает близкую к норме ожидаемую продолжительность жизни у больных с ХМЛ в хронической фазе. Выживаемость пациентов независима от времени ответа. Клинические исходы ХМЛ теперь определяются скорее факторами заболевания и особенностями пациентов, например – сопутствующими заболеваниями и курением, а также подходом конкретных медицинских центров, нежели выбором тактики первичного лечения. Сравнение долгосрочной выживаемости после ТГСК или лечения иматинибом показало, что больные из группы низкого риска имели сходную выживаемость при обоих вариантах лечения. Попытки улучшения терапии, например, с применением ТГСК должны быть сосредоточены на группах рефрактерных пациентов, а также на показателях выживаемости, не связанных с ХМЛ. После прогрессии в бластный криз ТГСК не обеспечивает существенного преимущества в выживаемости, хотя специальное исследование показало, что наиболее долгоживущие пациенты (72%) были леченными посредством ТГСК. 70% – 80% частота 10-летней глубокой молекулярной ремиссии указывает на то, что большинство больных, леченых иматинибом, являя. тся кандидатами на прекращение терапии.

Ключевые слова

Хронический миелоидный лейкоз, ингибиторы тирозинкиназы, иматиниб, стратегия лечения, трансплантация гемопоэтических клеток, выживаемость.