First- and second-line strategies in chronic phase CML including hematopoietic stem cell transplantation

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Summary

The review article is dedicated to the main principles of modern therapy in chronic myeloid leukemia (CML). Current treatment options for the chronic phase (CP) CML include Imatinib at standard or high doses (400 to 800 mg/d) and second-generation tyrosine kinase inhibitors (2-G TKIs), e. g. dasatinib and nilotinib. Hematopoietic stem cell transplantation (HSCT) is generally considered second or third line. Early SCT may be an option for non-high risk patients with low transplantation risks. According to the German CML Study Group the 10-year survival in CML has continuously improved, up to 85% with imatinib introduction. Previously, the survivors after busulfan and hydroxyurea were mostly transplant recipients. CML-Study III and IIIA compared allo-SCT with the best available drug treatment. Most authors who applied TKIs in CML, used imatinib, and HSCT (in some clinical situations). According to CML-Study IV the molecular responses (MR) achieved with imatinib in MR2 situations (an analogue of complete cytogenetic remission) may reach 92% after 10 years of observations. Introduction of the 2G-TKI (dasatinib and nilotinib) is associated with more rapidly occurring and more frequent molecular responses than with imatinib at standard dose (DASISION 5-year final study results, ENESTnd 5-year update). Increased imatinib dosage to 800 mg daily provides more rapid and deep molecular responses, as shown by appropriate meta-analysis of randomized trials, being associated with a 45% higher probability of achieving MMR after 12 months with IM 800 mg or 2G-TKIs, compared to IM 400 mg ($p=0,0088$).

Second-line strategies

Switching to second-line TKI treatment and/or allogeneic HSCT is recommended in cases of intolerance or drug re-

sistance. E. g., it was concluded in the ENESTcmr Study (Hughes et al., 2014) that such transition caused more molecular responses in terms of BCR-ABL than with permanent imatinib treatment ($p=0,009$). The best approaches with drug treatment and HSCT at different phases of CML are described in some recent works (Jiang et al., 2011; Jabbour et al., 2011, Khoury et al., 2012). A good efficacy of allo-HSCT was shown in an update of the study by Saussele et al. (2014), with a median follow-up of 78,5 months (Fig. 1). The patients were stratified by risk. In 50-70% of cases unrelated donors served as a source of transplant. The patients transplanted in 1st chronic phase electively or after resistance to TKI therapy have shown a good 5-year survival (80%). Interestingly, the survival probability of the patients transplanted early in chronic phase was similar to that of patients' treatment with imatinib only.

Conclusion

- Current first-line treatment includes imatinib, dasatinib and nilotinib.
- The proportion of patients reaching MMR by 12 months is similar with optimized imatinib and second-generation TKIs.
- SCT is an option for the 2nd-line treatment.
- Long-term outcomes after early SCT in chronic phase is similar to the results obtained with imatinib.
- Early HSCT may be considered in non-high risk CP CML patients with low transplantation risk.

Keywords

chronic myeloid leukemia, chronic phase, therapy, tyrosine kinase inhibitors, hematopoietic stem cell transplantation

First-line strategies: TKI efficiency in chronic phase of CML

At present, first-line therapy options in the chronic phase of chronic myeloid leukemia (CML) include imatinib at standard or high doses (400 to 800 mg/d) and second-generation tyrosine kinase inhibitors (2 G-TKIs), i. e., dasatinib and

nilotinib, especially when the treatment milestones are not reached with imatinib. Hematopoietic stem cell transplantation (HSCT) is generally considered second or third line. More recent data show that early SCT may be an option for non-high risk patients with low transplantation risk [9]. TKI at the optimal doses provide high survival rates (Table 1).

Drug properties	Imatinib 400 mg	IM 800 mg tolerability adapted	Nilotinib 2 x 300 mg	Dasatinib 100 mg
Efficacy	Standard treatment	Acts faster	Acts faster, less early progres- sions	Acts faster, less early progres- sions
Safety	Safe	Safe	Assess risks	Assess risks
Survival	84–86% after 10 years	91–94% after 5 years	94% after 5 years	91% after 5 years

Table 1. General therapeutic characteristics of tyrosine kinase inhibitors in CML

Results of the German CML Study Group show that survival of CML has continuously improved over time from 10% after 10 years when busulfan and hydroxyurea were used to 85% with imatinib (Figure 1). Long term survivors after busul-

fan and hydroxyurea are mostly transplant recipients. CML-Study III and IIIA compare allo-SCT with best available drug treatment. Most studies on TKI in CML have used imatinib, as seen from Table 2.

Study (reference No.)	IM-dose mg	N	Age at diag- nosis, median, years	5yr survival %	8–10yr survival %	Median observation time, years
CML-IV [11]	IM 400–800	1536	53	90	86	8 (max. 13)
IRIS [6]	IM 400	553	50	89	85 (8 years)	8
GIMEMA [18]	IM 400–800	559	52	90	NA	5
Hammersmith [5]	IM 400	204	46,3	83	NA	3,2
PETHEMA [3]	IM 400	210	44	97,5	NA	4,2
TOPS [1]	IM 400 IM 800	157319	45 48	94 (4 years) 93,4 (4 years)	NA	3,5 3,5
MDACC-2014	IM 400 M 800	70 201	8.3	NR	80 84	9,9 (min. 8)
ILTE [8]	IM NR	832	51a	98 (6 years)	95 (8 years)	5,8
ENESTnd [20]	IM 400 Nilo 600	283 282	46 47	92 94	NA	5
	Nilo 800	281	47	96		
DASISION [16]	IM 400 Dasa 100	260 259	49 46	90 91	NA	5
Median (estimate)				91	84	

Notes: NR=not reported; yr=year; min.=minimum; max.=maximum; IM=imatinib; Nilo=nilotinib; Dasa=dasatinib

Notes: NR=not reported; yr=year; min.=minimum; max.=maximum; IM=imatinib; Nilo=nilotinib; Dasa=dasatinib

Table 2. Long term results with tyrosine kinase inhibitors in CML

In some clinical situations, allogeneic HSCT is applied as seen from Table 3, according to: Barrett, Ito [2].

CML phase	Clinical situation	TKI and chemotherapy	HLA typing and donor	Immediate allo-SCT
CP	First failure of imatinib, high risk	Second-line TKI	Yes	No
	First failure of nilotinib or dasatinib	Second-line TKI	Yes	Yes
	Failure to 2 TKIs	Third-line TKI	Yes	Yes
	T315I mutation	Ponatinib or omacetaxine	Yes	Yes
AP	TKI naïve	TKI 6 chemotherapy	Yes	Yes
	TKI naïve, without optimal response	Second-line TKI 6 chemotherapy	Yes	Yes
	TKI pretreated	Second-line TKI 6 chemotherapy	Yes	Yes
BP	TKI naïve or pretreated	Induction chemotherapy, TKI	Yes	Yes

Table 3. Current HSCT strategies for different CML phases

According to CML- Study IV molecular responses (MR) achieved with imatinib after 10 years of observations may reach 92% for MR2 (molecular equivalent to complete cytogenetic remission), 89% for MMR, 81% for MR4, 72% for MR4.5 and 59% for MR5.

Introduction of the 2G-TKI (dasatinib and nilotinib) is associated with more rapidly occurring and more frequent molecular responses than with imatinib at standard dose (DASISION 5-year final study results, ENESTnd 5-year update).

Increasing the imatinib dose to 800 mg also achieves faster and deeper molecular responses, as seen from comparisons of imatinib 400 and 800 mg/day [4, 7, 10, 11]. Hence, dasatinib, nilotinib and dose-optimized imatinib achieve molecular responses faster than imatinib at standard dose.

Several studies were analyzed in a systematic review and meta-analysis of randomized trials [12] comparing imatinib

400 mg/d vs. imatinib 800 mg/d [1, 4, 7, 10], and imatinib 400 mg/d vs 2G-TKI in chronic phase CML [4, 16, 19, 20].

The systematic review shows a 45% higher probability of achieving MMR after 12 months with IM 800 mg compared to IM 400 mg ($p=0.0088$). Efficacy estimated of IM 400 vs. 800 and IM 400 vs. 2G-TKI cannot be compared directly. But given the fairly similar prognostic profiles of the patients of the different trials it can be concluded that MMR rates achieved with IM 800 and 2G-TKI might be comparable.

Second-line strategies

- In the case of intolerance or resistance change of treatment to 2nd-line TKI or SCT is recommended (for criteria, see Table 4).
- Switching treatment to optimize responses is recommended, if defined milestones are missed (confirmation required).

	ELN	NCCN
3 months	Ph+ >95%	Ph+ >35% or BCR-ABL >10%
6 months	Ph+ >35% and / or BCR-ABL >10%	Ph+ >35% or BCR-ABL >10%
12 months	Ph+ >0 and / or BCR-ABL >1%	Ph+ >0 or BCR-ABL >1%

Table 4. Milestones for switching of TKI – Definition of "Failure"="Change the treatment"

Some studies tested switching of TKI to achieve time-dependent molecular targets. E.g., in the ENESTcmr Study [13], a comparison was made between imatinib treated patients in CCR switched to nilotinib ($n=104$), vs. imatinib continued ($n=103$). After 2 years 22% with nilotinib and 9% with imatinib had undetectable BCR-ABL ($p=0.0087$).

The TIDEL II Study [23], analyzed imatinib dose escalation to 800 mg or switching to nilotinib, if molecular targets were not reached. 73% of patients reached a confirmed MMR at 2 years.

Current best SCT practices in CML are based on several recent studies for the patients in chronic, accelerated, and blast phase of the disease [14, 15, 17, 21, 22].

Transplantation options

A good efficacy of allo-HSCT was shown in an update of the study by Saussele et al. [22], with a median follow-up of 78,5 months (Fig. 1). The patients were stratified by risk according to the EBMT or EURO scores. In 50-70% of cases unrelated donors served as a source of transplant.

The patients transplanted in 1st chronic phase electively or after resistance to TKI therapy have shown a good 5-year survival (80%). HSCT performed in advanced phase of the disease resulted also in high survival rates. The updated matched pair analysis has a median follow-up of 87 months. The survival probability of the patients transplanted early in chronic phase was similar to that of patients with imatinib treatment (Fig. 2).

Fig. 1. Survival probabilities in groups of CML patients treated with HSCT [22].

Figure 2. Matched pair analysis of survival in chronic phase with imatinib vs. HSCT.

Conclusions

- Current first-line treatment includes imatinib, dasatinib and nilotinib.
- MMR at 12 months is achieved faster with dose-optimized Imatinib than with IM-400.

- The proportion of patients reaching MMR by 12 months is similar to optimized imatinib and second-generation TKIs.
- SCT may be considered the 1st line in selected patients.
- SCT is an option for the 2nd-line treatment.
- Long-term outcomes after early SCT in chronic phase is similar to the results obtained with Imatinib.
- Early SCT may be considered in non-high risk patients with low transplantation risk.

Acknowledgements

The authors are much appreciated to Dr. Alexey B. Chukhlovina for valuable assistance with preparation of the manuscript.

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Стратегии первой и второй линии в лечении хронического миелоидного лейкоза (хроническая фаза), включая трансплантацию гемопоэтических клеток

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Резюме

Обзорная статья посвящена принципам современной терапии при хроническом миелоидном лейкозе (ХМЛ). В настоящее время возможности терапии в хронической фазе ХМЛ предусматривают применение иматиниба в стандартных или высоких дозах (400-800 мг/сут.) и ингибиторов тирозинкиназы (ИТК) второго поколения (дазатиниб и nilotinib). Трансплантация гемопоэтических стволовых клеток (ТГСК) рассматривается в качестве 2-й и 3-й линий лечения. ТГСК в ранние сроки может быть эффективна для больных невысокой степени риска и с низким риском исходов самой трансплантации. По данным германской группы исследований ХМЛ, 10-летняя выживаемость пациентов значительно улучшилась (до 85%) с введением иматиниба. Ранее выживаемость достигалась в основном за счет применения ТГСК. Программы исследования CML III и CML IIIA сравнивали алло-ТГСК с наилучшим доступным лекарственным лечением. Большинство авторов, применявших ИТК при ХМЛ, использовали иматиниб и, в ряде ситуаций - ТГСК. Согласно результатам CML-Study IV, молекулярные ответы (МО) с применением иматиниба для ситуаций с MP2 (цитогенетическая ремиссия) могут достигать 92% после 10 лет наблюдений. Внедрение ИТК второго поколения (дазатиниб и nilotinib) связано с большей частотой молекулярных ремиссий (DASISION, 5-летние результаты, а также ENESTnd- 5 лет). Повышение

дозы иматиниба до 800 мг также дает более скорые и глубокие молекулярные ответы, при сравнении лечения иматинибом в дозах 400 и 800 мг. Мета-анализы соответствующих рандомизированных исследований показали повышение на 45% частоты молекулярной ремиссии через 12 мес. с 800 мг иматиниба по сравнению с 400 мг иматиниба в сутки ($p=0,0088$). Предполагается также, что из анализа прогноза больных в различных исследованиях можно заключить, что частота молекулярных ремиссий сравнима при использовании иматиниба (800 мг/сут.) ИТК второго поколения.

Стратегии второй линии терапии применяются в случаях непереносимости или резистентности к препаратам. Тогда рекомендуется переход на ИТК второго ряда и/или аллогенная ТГСК. В исследовании ENESTcmr Study (Hughes et al., 2014) показано, что этот переход приводил к большему числу молекулярных ремиссий BCR-ABL, чем при постоянной терапии иматинибом ($p=0,009$). Наилучшие подходы с лекарственной терапией и применением ТГСК в различных фазах ХМЛ описаны в работах последних лет (Jiang et al., 2011; Jabbour et al., 2011, Khoury et al., 2012; Saussele et al., 2014). Так, хороший эффект от алло-ТГСК показан в работе Saussele et al., 2014, при среднем сроке наблюдения 78,5 мес. Пациентов классифицировали по степени риска. ТГСК проводили в 1-й хронической фазе элективно или при резистентности к ИТК, и показали 80%-ную выживаемость через 5 лет. Интересно, что

вероятность выживания пациентов, трансплантированных в ранней хронической фазе ХМЛ была сходной с таковой после лечения только иматинибом.

Выводы

1. Современное лечение первой линии при ХМЛ включает иматиниб, нилотиниб и дазатиниб.
2. Доля пациентов, достигающих молекулярной ремиссии к 12 мес., сходна для больных, получавших оптимизированные дозы иматиниба и ИТК 2-го поколения.
3. ТГСК является методом выбора для второй линии терапии.

4. Долгосрочные исходы после ранней ТГСК в хронической фазе сходны с результатами, полученными с иматинибом.

5. ТГСК на ранних сроках можно рассматривать при лечении пациентов с ХМЛ (хроническая фаза) невысокой степени риска.

Ключевые слова

хронический миелоидный лейкоз, хроническая фаза, терапия, ингибиторы тирозинкиназы, трансплантация гемопоэтических клеток