Impact of molecular response time achievement on survival of chronic phase chronic myelogenous leukimia patients treated by imatinib

by Putu Niken Ayu Amrita

Submission date: 04-Jul-2020 11:42PM (UTC+0800)
Submission ID: 1353383314
File name: se_chronic_myelogenous_leukimia_patients_treated_by_imatinib.pdf (390.19K)
Word count: 3302
Character count: 17745

Research Article

Impact of molecular response time achievement on survival of chronic phase chronic myelogenous leukemia patients treated by imatinib

Putu Niken Ayu Amrita, S. Ugroseno Yudho Bintoro*

ABSTRACT

Background: Chronic myelogenous leukemia (CML) is the most common myeloproliferative disorder. BCR-ABL, the CML cell, contains oncogene makes tyrosine kinase protein which causes cells to grow and reproduce out of control. Recently, a tyrosine kinase inhibitor, namely, imatinib had high efficacy in CML treatment. Importantly, quantification of BCR-ABL transcripts is the most sensitive method to monitor molecular response at deeper levels than the hematologic and cytogenetic response to achieve an excellent outcome. **Objective:** We described the molecular response, time achievement, and the impact on survival in CML patients. **Materials and Methods:** A retrospective medical record of 143 BCR-ABL positive chronic phase CML patients have been treated by imatinib 400 mg. The hematological response was determined and the molecular response was assigned by BCR-ABL quantification. The time to achieve major molecular response (MMR) was defined by ≤0.10% ratio of BCR-ABL to ABL control gene and its impact on median survival. **Results:** In our study, the median age at presentation was 45 years (range 12–73 years). Male to female ratio was 2:1. Patients achieved MMR on 12, 18, and 24 months were 8 (5.5%), 26 (18.2%), and 26 (18.2%), respectively. Patients achieved MMR in <24 months have longer median survival 83.8 (77.4–90.8) months compared to 58.9 (51.7–66.2) of those who failed to achieve it in 24 months, $P < 0.001$. **Conclusion:** Our data have shown time to MMR achievement had an impact on survival. The patients that did not achieve MMR had a poorer clinical outcome. Early recognition and prompt treatment of these patients can improve outcomes.

KEY WORDS: Imatinib, Major molecular response, Median survival

BACKGROUND

Chronic myelogenous leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation.[1] More than 95% of CML patients have a chromosomal abnormality, the Philadelphia chromosome which is a reciprocal translocation of the long arms of chromosomes 9 and 22, the t(9;22) (q34;q11). This aberrant chromosome encodes a fusion gene, BCR-ABL. The BCR-ABL fusion gene transcripts are translated into functional BCR-ABL proteins (p190, p210, or p230) which have tyrosine kinase activity.[2]

Among all myeloproliferative disorder, CML is the most common with an incidence varying from 0.6 to 2.0 cases per 100.000 inhabitants in the United States, increase with age and are higher in men than women.[3] While in Asia, they seem even less, for example, in China, an estimated number of incidents was 0.39–0.55/100,000 population, while in Thailand, the number is about 0.50/100,000 population.[4] In Indonesia, we recorded 1109 patients in 2014 and 643 patients from 2008 to 2016 were diagnosed as CML in the tertiary referral hospital in Surabaya, Indonesia.

Imatinib, a first-line tyrosine kinase inhibitor (TKI) is available in Indonesia and was expected to give revolutionary change on the CML treatment and outcome. Monitoring imatinib-treated CML patients are important to define patient response, and the molecular response is the most sensitive to judge CML course and allows detection of progression or relapse.[5] Evidence of achieving major molecular response (MMR) associated with increased progression-free survival and overall survival.[6]

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

Hematology and Medical Oncology Division, Department of Internal Medicine, Faculty of Medicine, Airlangga University – Dr. Soetomo Teaching Hospital, Surabaya Indonesia

***Corresponding author:** S. Ugroseno Yudho Bintoro, Hematology and Medical Oncology Division, Department of Internal Medicine, Faculty of Medicine, Airlangga University – Dr. Soetomo Teaching Hospital, Surabaya Indonesia. Phone: +62811320876. Fax: +62315047192. E-mail: ugrosenoyb2004@yahoo.com

Received on: 17-01-2020; Revised on: 22-02-2020; Accepted on: 26-03-2020

Most of the CML population lives in developing countries, including Indonesia, which has limited resources for monitoring strategies. For example, the ideal CML management should consist of monitoring response of hematologic, cytogenetic, and molecular responses; however, cytogenetic and molecular response analysis are not available routinely for patients in all centers and also not cover by national social insurance. Recently, GeneXpert, an automated polymerase chain reaction (PCR) system, allows rapid quantification of molecular response of CML with minimal hands-on from the technician is available. This method can overcome the challenges faced by many hematology centers in the developing country which previously have to send blood samples to diagnostic centers overseas.[7]

The aim of the study is to describe the clinical characteristics of chronic phase CML patients treated with imatinib and the impact time achievement of MMR with overall survival.

MATERIALS AND METHODS

Subjects

Retrospective medical records study of 143 CML patients in Dr. Soetomo General Hospital, a tertiary referral hospital in Surabaya Indonesia, diagnosed as Chronic Phase CML from January 2010 to December 2015. The chronic phase is important because prompt treatment will prevent development to the acceleration phase and blastic crisis phase. Ninety percent of CML patients were already at the chronic phase from initial diagnosis. We included patients with age more than 18 years old, positive qualitative of BCR-ABL transcript by reverse transcriptase-PCR, had an Eastern Co-operative Oncology Group performance status of 0–2, and signed an informed consent form. While we excluded pregnant women or nursing mother, did not receive any other chemotherapy during this study and patients with severe medical problems such as uncontrolled diabetes mellitus, hypertension, severe cardiovascular disease, or active infections were not eligible for this study. Diagnosis of CML was determined by anamnesis, physical examination, complete blood count (CBC), and the qualitative BCR-ABL transcripts by real-time (RT) PCR. Complete blood count with hematologic analyzer and peripheral blood smear were performed to determine CML disease phase by counting the immature white cells (blasts). If the immature white cells were less than 10% the patients were in chronic phase and eligible for this study.

Qualitative BCR-ABL Transcript

The method used to measure the qualitative BCR-ABL transcripts were one step multiplex reverse transcription PCR. Mononuclear cells (MNC) separated from patients' peripheral blood was used for RNA extraction. After RNA was extracted, 1 µg of RNA was used for reverse transcription to cDNA using Invitrogen kit.[8] A primer specific for e11 of the BCR gene was chosen to enable amplifying all variants in m-BCR and -BCR regions, and the specific primer for e11 was chosen to detect breakpoints in the m-bcr region. The ABL primer is specific for a3 and thus able to detect junctions in a2 and a3. In multiplex RT-PCR, the sense primers A1: 5'CAACAGTCCTTCGACAGCAG3' on BCR exon 1, B1: 5'GCTACGGAGAGGCTGAAGAA3' on BCR exon 11, and antisense primers C1: 5'CGTGATGTAGTTGCTTGGGA3' on ABL exon 3.[8]

Treatment and Molecular Monitoring Method

The treatment given was Imatinib 400 mg/day. Second generation nilotinib was used for intolerance or resistance to imatinib. Monitoring of treatment response was clinical, CBC every 2 weeks for the 1st month then continued to monthly. Monitoring the response to CML therapy is a continuum that begins at diagnosis and carries on serially throughout the entire course of treatment, as detailed in published expert consensus guidelines such as National Comprehensive Cancer Network (NCCN) 2018.

Cytogenetic examination of the Philadelphia chromosome can detect 10^9 putative leukemic cells or equal to 0.1 BCR-ABL ratios according to international scale (IS). Once a patient has achieved a CCyR, cytogenetic evaluation was less useful for monitoring residual disease. Due to the presence of the leukemia-specific *BCR-ABL* gene, CML disease status can be monitored using RT quantitative PCR (RT-qPCR) technique to quantify levels of *BCR-ABL* mRNA in peripheral blood. GeneXpert BCR-ABL monitor assay can detect lower levels of BCR-ABL transcript down to between 0.001% and 0.0001% which make this an important tool to monitor treatment efficacy.

Quantitative BCR-ABL was performed on the baseline, every 3 months to the 1st year, months 12, 18, and 24. The method used was The Xpert Cepheid Monitor Assays, with a reagent to detect BCR-ABL fusion gene resulting from two major breakpoints translocation b2as and b3a2 and the ABL transcripts as an endogenous control. This self-contained automated instrument integrates microfluidic sample preparation with RT-PCR-based, RT fluorescent signal detection.[9] MMR was defined as BCR-ABL transcripts <0.1% IS.

Statistical Analysis

The cutoff date for this analysis was June 2017. We performed an analysis of Overall Survival using Kaplan–Meier survival curve analysis and analyze its significance with log-rank (Mantel-Cox) test. Overall

survival was measured from the beginning of imatinib treatment to time of death. The prognostic score was calculated with the Sokal score (Cortes, 2008). The analyses were performed using the SPSS software, version 21.0.

RESULTS

One hundred and forty-three CML patients in the chronic phase at diagnosis were analyzed. The characteristics of patients are described in Table 1. Hydroxyurea was used in some patients (58.7%) before imatinib treatment until confirmation of the diagnosis of CML or imatinib availability. Imatinib was initiated at the median time of 3 weeks from diagnosis (0.25–6 months). The initial dose of imatinib was 400 mg/day. There were 87 males and 66 females with a median age at diagnosis of 45 years (17–73). Among 143 patients evaluated for Sokal score, 51 patients (35.7%) were low, 60 (42.0%) were intermediate, and 32 (22.4%) were high.

Hematologic and Molecular Response

Complete hematologic response achieved by 139 (97.2%) patients at median time 3 months (range 1–7 months). There were 60 of 143 patients that achieved MMR (42.0%) at median time 14 months (range 3–60). Patients achieved MMR 12 months were 8 (5.5%), while on 18 months 26 patients (18.2%) and on 24 months 26 patients (18.2%), respectively.

Survival Analysis

Patients achieved MMR in <24 months have longer estimated mean survival 83.8 (7.4–90.8) months compared to 58.9 (51.7–66.2) of those who failed to achieve it in 24 months [Figure 1]. Log-rank (Mantel-Cox) test showed a significant difference in both groups with $P = 0.007$. On 60 months after diagnosis, 90.1% subjects in MMR <24 months were still alive compared to 78% on the group who did not achieve MMR in 24 months.

Table 1: Patients' characteristics. Characteristics of chronic phase chronic myelogenous leukemia patients

Variable (n=143)	
Age at diagnosis (median- range)	45 (17–73)
Gender (male/female)	87/56 (60.8%/39.2%)
Hemoglobin (g/dL)	10.8±3.04
White blood cell × 10^9/L (median- range)	124±152
Platelets × 10^9/L (median-range)	491±374
Sokal score	
Low	51 (36%)
Intermediate	60 (42%)
High	32 (22%)
Previous treatment	
No previous treatment	59 (41.3%)
Previous hydrea	84 (58.7%)

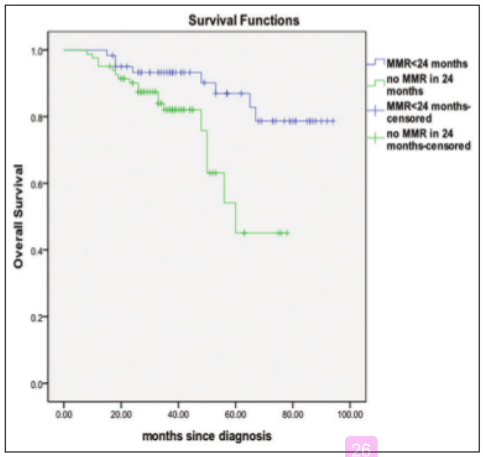

Figure 1: Overall survival for patients in major molecular response (MMR) before 24 months and those who did not achieve it in 24 months. Patients achieved MMR in <24 months have longer estimated mean survival 83.8 (7.4–90.8) months compared to 58.9 (51.7–66.2) of those who failed to achieve it in 24 months Logrank (Mantel-Cox) test showed a significant difference in both groups with $P = 0.007$. On 60 months after diagnosis, 90.1% subjects in MMR <24 months group were still alive compared to 78% on the group who did not achieve MMR in 24 months

DISCUSSION

In this study, we revealed that MMR achievement has an impact on survival. However, the achievement at 24 months by Indonesian patients was lower compared to two other studies in North America and Europe at 12 months (43% vs. 50% and 91%, respectively).[10,11] The probable reason was patient-compliant and higher Sokal prognostic score that implies a high tumor burden. Research in Egypt exhibited that patient-compliant and imatinib interruption due to drug availability can decrease progression-free survival.[12] Imatinib availability in Egypt was provided by their government as well as in Indonesia. Patients with the inferior molecular response (not achieved in 24 months) also had a poorer survival outcome as similar to other research.[11] These findings demonstrate the importance of MMR as a surrogate marker for survival. A longer follow-up time is required to achieve median survival. The molecular response by Gene Expert is important for monitoring and detecting of failure to achieve MMR. In addition, it can be used to guide the clinician to choose other TKI treatment.

Several organizations, such as the European Leukemia Net and the NCCN, provided evidence-based recommendations that define responses and milestones to monitor response to TKIs. The phase 3 IRIS trial identified that patients with 3 log or more reduction in BCR-ABL transcript levels had the best PFS. It

Table 2: Definitions of response. Definition of response based on 2013 European leukemia net recommendations for management of chronic myeloid leukemia

Response	Definition
CHR	Leucocyte count $<10\times10^9$; platelet count
MCyR	$<450\times10^9$; normal differential with no early
PCyR	forms; no splenomegaly
CCyR	0–35% Ph+ metaphase (BM)
MMR	1–35% Ph+ metaphase (BM)
CMR	0% Ph+ metaphases (BM)
	BCR-ABL 1 IS ≤0.1%
	Undetectable BCR-ABL1 (assay sensitivity ≥4.5 or 5.0 logs)
	BCR-ABL1 IS ≤0.0032 (MR 4.5)
	BCR –ABL1 IS ≤0.001 (MR 5.0)

CHR: Complete hematologic response, McyR: Major cytogenetic response, PCyR: Partial cytogenetic response, CCyR: Complete cytogenetic response, MMR: Major molecular response, CMR: Complete molecular response

defines MMR. The use of the IS encompasses different methodologies, control genes, and reagents. Table 2 shows the definitions of response.[13] The degree of molecular response at certain time points has also associated with reduced risk of progression and the Event Free Survival. MMR is also associated with the duration of a complete cytogenetic response. The impact of achieving MMR at a certain time is also important, IRIS study showed patients taking first-line imatinib who could be evaluated for MMR at 12 months, the estimated overall survival rate at 12 months was 91.1% compared to 85.3% among those without MMR at 12 months. In Surabaya, Indonesia, although in a tertiary referral hospital of the developing country, not all resources for treatment and monitoring of chronic phase CML are available. In addition, there were only 2 TKIs, imatinib, and nilotinib. Therefore, after suboptimal MMR to Imatinib, we still continue the drug. We also could not perform cytogenetic examination routinely. Thus, we use the MMR as our target milestone for treatment response. A good correlation exists between bone marrow cytogenetics and transcript level in peripheral blood, with a BCR-ABL1 IS ≤10% equivalent to major cytogenetic response and IS ≤1% equivalent to a complete cytogenetic response.[14]

The median age in our study was a decade younger compared to European (55 years) and American (66 years) studies.[15] It may be caused by Indonesia's population pyramid tends to be young and growing. Other reasons remain elusive. Most of our patients come as an asymptomatic patient with high white blood cell count (mean 124 ± 152 × 10^9/L) compared to western data that 40% of the patient are asymptomatic,[16] suggesting a high tumor burden at the beginning which can affect treatment response and survival.

A retrospective study with higher prone to subject selection bias and misclassification bias become the limitation of this study. In addition, we did not perform cytogenetic examination due to a lack of facilities in our center and only record the event (death) monthly on a patient scheduled to the outpatient department. The subjects group who succeed in achieving Major Molecular Response before 24 months did not reach median survival yet. On 60 months after diagnosis, 90.1% subjects in this group were still alive compared to 78% on the group who did not achieve MMR in 24 months. A longer follows up time needed to achieve a median survival.

CONCLUSION

This study demonstrates the importance of achieving MMR as a surrogate marker for survival, preferably sooner and stable. Patients who did not achieve MMR in 24 months had poorer clinical outcome. Early recognition and prompt treatment of these patients can improve outcomes.

AUTHORS' CONTRIBUTIONS

This study was designed, directed, and coordinated by U.Y.B. U.Y.B as the principal investigator, provided conceptual, technical guidance for all aspects of the project. The manuscript was written by P.N.A and M.M and commented on by all authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study protocol was approved by the ethical committee of DR. Soetomo Teaching Hospital, Surabaya, Indonesia.

REFERENCES

1. Champlin R, Golde D. Chronic myelogenous leukemia: Recent advances. Blood 1985;65:1039-47.
2. Goldman JM, Melo JV. Chronic myeloid leukemia-advances in biology and new approaches to treatment. N Engl J Med 2003;349:1451-64.
3. Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukaemia (CML). Best Pract Res Clin Haematol 2009;22:295-302.
4. Au WY, Caguioa PB, Chuah C, Hsu SC, Jootar S, Kim DW, *et al*. Chronic myeloid leukemia in Asia. Int J Hematol 2009;89:14-23.
5. Renault IZ, Scholl V, Hassan R, Capelletti P, Lima Md, Cortes J. The significance of major and stable molecular responses in chronic myeloid leukemia in the tyrosine kinase inhibitor era. Rev Bras Hematol Hemoter 2011;33:455-60.
6. Hughes TP, Hochhaus A, Branford S, Müller MC, Kaeda JS, Foroni L, *et al*. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: An analysis from the international randomized study of interferon and STI571 (IRIS). Blood 2010;116:3758-65.
7. Radich JP. Chronic myeloid leukemia: Global impact from a local laboratory. Cancer 2017;123:2594-6.
8. Goh HG, Hwang JY, Kim SH, Lee YH, Kim YL, Kim DW. Comprehensive analysis of BCR-ABL transcript types in Korean CML patients using a newly developed multiplex RT-PCR. Transl Res 2006;148:249-56.

9. Jobbagy Z, van Atta R, Murphy KM, Eshleman JR, Gocke CD. Evaluation of the cepheid GeneXpert BCR-ABL assay. J Mol Diagn 2007;9:220-7.
10. Press RD. Major molecular response in CML patients treated with tyrosine kinase inhibitors: The paradigm for monitoring targeted cancer therapy. Oncologist 2010;15:744-9.
11. Sobh M, Labussiere H, Gilis L, Barraco F, Etienne M, Le Borgne O, *et al*. Impact of major molecular response on overall survival and its time of achievement on complete molecular response incidence in chronic myeloid leukemia patients treated by tyrosine kinase inhibitors in first chronic phase. Am Soc Hematol 2013;122:2721.
12. Edesa WA, Abdel-malek RR. Impact of imatinib interruption and duration of prior hydroxyurea on the treatment outcome in patients with chronic myeloid leukemia: Single institution experience. J Egypt Natl Cancer Inst 2015;27:69-75.
13. Assouline S, Lipton J. Monitoring response and resistance to treatment in chronic myeloid leukemia. Curr Oncol 2011;18:e71-83.
14. Ross D, Branford S, Moore S, Hughes T. Limited clinical value of regular bone marrow cytogenetic analysis in imatinib-treated chronic phase CML patients monitored by RQ-PCR for BCR-ABL. Leukemia 2006;20:664-70.
15. Tardieu S, Brun-Strang C, Berthaud P, Michallet M, Guilhot F, Rousselot P, *et al*. Management of chronic myeloid leukemia in France: A multicentered cross-sectional study on 538 patients. Pharmacoepidemiol Drug Saf 2005;14:545-53.
16. Gratwohl A, Hermans J, Goldman J, Arcese W, Carreras E, Devergie A, *et al*. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Lancet 1998;352:1087-92.

Source of support: Data collection, analysis, and interpretation, writing manuscript and publication were funded by authors; Conflicts of interest: None Declared

Impact of molecular response time achievement on survival of chronic phase chronic myelogenous leukimia patients treated by imatinib

ORIGINALITY REPORT

25%	17%	22%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Jorge Cortes, Alfonso Quintás-Cardama, Hagop M. Kantarjian. "Monitoring molecular response in chronic myeloid leukemia", Cancer, 2011 Publication	2%
2	Elias Jabbour, Jorge E. Cortes, Hagop M. Kantarjian. "Molecular monitoring in chronic myeloid leukemia", Cancer, 2008 Publication	2%
3	A. Mukhopadhyay, S. Dasgupta, S. Mukhopadhyay, C. K. Bose, S. Sarkar, F. Gharami, S. Koner, J. Basak, U. K. Roy. "Imatinib Mesylate Therapy in Patients of Chronic Myeloid Leukemia with Philadelphia Chromosome Positive: An Experience from Eastern India", Indian Journal of Hematology and Blood Transfusion, 2011 Publication	2%
4	Mauricette Michallet, Mohamad Sobh, Helene Labussiere, Lila Gilis et al. "Impact Of Major	1%

	Molecular Response On Overall Survival and Its Time Of Achievement On Complete Molecular Response Incidence In Chronic Myeloid Leukemia Patients Treated By Tyrosine Kinase Inhibitors In First Chronic Phase", Blood, 2013 Publication	
5	Vigil, C.E.. "Interpretation of cytogenetic and molecular results in patients treated for CML", Blood Reviews, 201105 Publication	1%
6	Fruehauf S., Steiger S., Topaly J., Ho A.. "Pulmonary artery hypertension during interferon-α therapy for chronic myelogenous leukemia", Annals of Hematology, 2001 Publication	1%
7	www.nejm.org Internet Source	1%
8	repub.eur.nl Internet Source	1%
9	jprsolutions.info Internet Source	1%
10	Rao, Kamakshi V, Andrea Iannucci, and Elias Jabbour. "Current and Future Clinical Strategies in the Management of Chronic Myeloid Leukemia", Pharmacotherapy The Journal of Human Pharmacology and Drug Therapy, 2010. Publication	1%

11	digital.library.adelaide.edu.au Internet Source	1%
12	www.mmh.org.tw Internet Source	1%
13	bmcpulmmed.biomedcentral.com Internet Source	1%
14	www.nature.com Internet Source	1%
15	Zsolt Jobbagy, Reuel van Atta, Kathleen M. Murphy, James R. Eshleman, Christopher D. Gocke. "Evaluation of the Cepheid GeneXpert BCR-ABL Assay", The Journal of Molecular Diagnostics, 2007 Publication	1%
16	"60th Annual Conference of Indian Society of Hematology & Blood Transfusion (ISHBT) October 2019", Indian Journal of Hematology and Blood Transfusion, 2019 Publication	<1%
17	healthallianceinternational.org Internet Source	<1%
18	www.journal.unair.ac.id Internet Source	<1%
19	Froylan Calderon de Anda, Ana Lucia Rosario, Omer Durak, Tracy Tran et al. "Autism spectrum	<1%

disorder susceptibility gene TAOK2 affects basal dendrite formation in the neocortex", Nature Neuroscience, 2012
Publication

20	Shinsuke Noguchi, Chiaki Nakaseko, Kaichi Nishiwaki, Hitoshi Ogasawara et al. "Switching to nilotinib is associated with deeper molecular responses in chronic myeloid leukemia chronic phase with major molecular responses to imatinib: STAT1 trial in Japan", International Journal of Hematology, 2018 Publication	<1%
21	www.omicsonline.org Internet Source	<1%
22	fk.unair.ac.id Internet Source	<1%
23	mdanderson.influuent.utsystem.edu Internet Source	<1%
24	ijcto.org Internet Source	<1%
25	www.researchsquare.com Internet Source	<1%
26	David T. Yeung, Michael P. Osborn, Deborah L. White, Susan Branford et al. "TIDEL-II: first-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent	<1%

	molecular targets", Blood, 2015 Publication	
27	www.repository.uhblibrary.co.uk Internet Source	<1%
28	"Chronic Myeloid Leukemia", Springer Science and Business Media LLC, 2016 Publication	<1%
29	services.rmh.med.sa Internet Source	<1%
30	Jong-Hun Kang, Hyun-Gyung Goh, Sang-Ho Chae, Sung-Yong Kim, Dong-Wook Kim, Chi-Bom Chae. "Genotyping of Chimerical BCR-ABL1 RNA in Chronic Myeloid Leukemia by Integrated DNA Chip", The Journal of Molecular Diagnostics, 2012 Publication	<1%
31	mgend.med.kyoto-u.ac.jp Internet Source	<1%
32	www.apjcpcontrol.org Internet Source	<1%
33	E Elonen. "Comparison between four and eight cycles of intensive chemotherapy in adult acute myeloid leukemia: a randomized trial of the Finnish Leukemia Group", Leukemia, 07/24/1998 Publication	<1%

34	Korkmaz, Serdal, Mehmet Sinan Dal, Ilhami Berber, Deniz Goren Sahin, Mehmet Hilmi Dogu, Orhan Ayyildiz, Ilknur Nizam, Murat Albayrak, Ramazan Esen, Sinem Namdaroglu, Mehmet Sencan, Olga Meltem Akay, Sibel Hacioglu, Rahsan Yildirim, Ali Eser, Anil Tombak, Cigdem Pala, and Osman Ilhan. "Clinical characteristics and therapeutic outcomes of elderly patients with chronic myeloid leukemia: A retrospective multicenter study : Elderly patients with chronic myeloid leukemia", Geriatrics and Gerontology International, 2014. Publication	<1%
35	epdf.tips Internet Source	<1%
36	T Pavey, M Hoyle, O Ciani, L Crathorne et al. "Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses.", Health Technology Assessment, 2012 Publication	<1%
37	Mariana Serpa, Sabri S Sanabani, Pedro Enrique Dorliac-Llacer, Monika Conchon et al. "Molecular measurement of BCR-ABL transcript variations in chronic myeloid leukemia patients in cytogenetic remission", BMC Hematology,	<1%

2010
Publication

38	Carolina Pavlovsky, Isabel Giere, Beatriz Moiraghi, Miguel A. Pavlovsky et al. "Molecular Monitoring of Imatinib in Chronic Myeloid Leukemia Patients in Complete Cytogenetic Remission: Does Achievement of a Stable Major Molecular Response at any Time Point Identify a Privileged Group of Patients? A Multicenter Experience in Argentina and Uruguay", Clinical Lymphoma Myeloma and Leukemia, 2011 Publication	<1%
39	Dan Jones. "Chronic Myelogenous Leukemia", Molecular Pathology Library, 2010 Publication	<1%
40	Elias Jabbour, Jorge Cortes, Francis Giles, Susan O'Brien, Hagop Kantarjian. "The clinical challenge of imatinib resistance in chronic myeloid leukemia: emerging strategies with new targeted agents", Targeted Oncology, 2006 Publication	<1%
41	dare.ubvu.vu.nl Internet Source	<1%
42	Tiribelli, Mario, and Marta Medeot. "Overcoming therapy failure in elderly patients with chronic myeloid leukemia", International Journal of Hematologic Oncology, 2014.	<1%

	Publication	
43	www.neliti.com Internet Source	<1%
44	tel.archives-ouvertes.fr Internet Source	<1%
45	Francis J Giles. "Molecular Monitoring of BCR-ABL Transcripts—Standardization Needed to Properly Use, and Further Investigate the Value of, a Critical Surrogate Marker for Success in Therapy of Chronic Myeloid Leukemia", Oncology & Hematology Review (US), 2011 Publication	<1%
46	Gabriele Gugliotta, Fausto Castagnetti, Miriam Fogli, Michele Cavo, Michele Baccarani, Gianantonio Rosti. "Impact of comorbidities on the treatment of chronic myeloid leukemia with tyrosine-kinase inhibitors", Expert Review of Hematology, 2014 Publication	<1%
47	www.cancer.gov Internet Source	<1%
48	www.ahrq.gov Internet Source	<1%
49	Haneen Banjar, Damith Ranasinghe, Fred Brown, David Adelson et al. "Modelling Predictors of Molecular Response to Frontline	<1%

Imatinib for Patients with Chronic Myeloid Leukaemia", PLOS ONE, 2017
Publication

---

50 Chen, Huan, Kai-yan Liu, Lan-ping Xu, Dai-hong Liu, Yu-hong Chen, Xiang-yu Zhao, Wei Han, Xiao-hui Zhang, Yu Wang, Yuan-yuan Zhang, Ya-zhen Qin, Yan-rong Liu, and Xiao-jun Huang. "Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphobla stic leukemia", Journal of Hematology & Oncology, 2012.
Publication

<1%

---

51 Yusuf Baran, Saydam. "Cumulative clinical experience from a decade of use: imatinib as first-line treatment of chronic myeloid leukemia", Journal of Blood Medicine, 2012
Publication

<1%

---

52 Tim P. Hughes. "Frequency of Major Molecular Responses to Imatinib or Interferon Alfa plus Cytarabine in Newly Diagnosed Chronic Myeloid Leukemia", New England Journal of Medicine, 10/09/2003
Publication

<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Impact of molecular response time achievement on survival of chronic phase chronic myelogenous leukimia patients treated by imatinib

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5