Published in final edited form as:

Curr Hematol Malig Rep. 2016 April ; 11(2): 80–85. doi:10.1007/s11899-016-0306-5.

Quality of life and long term therapy in patients with chronic myeloid leukemia

Kathryn E. Flynn, PhD and

Associate Professor, Department of Medicine, Center for Patient Care & Outcomes Research, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226, Office: (414) 955-8847, Fax: (414) 955-6689

Ehab Atallah, MD

Associate Professor, Department of Medicine, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226, Office: (414) 805-4600, Fax: (414) 805-6815

Kathryn E. Flynn: kflynn@mcw.edu; Ehab Atallah: eatallah@mcw.edu

Abstract

Since the development of imatinib and other tyrosine kinase inhibitors (TKIs), the prognosis for patients with chronic myeloid leukemia (CML) has markedly improved, such that most patients diagnosed with CML can now expect to live with their disease rather than die from it. However, most patients will require long term treatment, which has deleterious effects on health-related quality of life. We review recent literature on drug-related adverse effects, long term medication adherence, limitations to fertility and pregnancy, effects on cognitive function, ability to work, financial toxicity, pediatric populations, and treatment discontinuation. While patients with CML are fortunate to have excellent therapies available to control their disease, many are unable to lead normal lives, which challenges the notion that research is no longer needed in CML. Curing CML, i.e., no detectable disease and no need for daily medications, should remain the ultimate goal.

Keywords

chronic myeloid leukemias; tyrosine kinase inhibitors; therapy; quality of life

Introduction

Since the development of imatinib and other tyrosine kinase inhibitors (TKIs), the prognosis for patients with chronic myeloid leukemia (CML) has markedly improved, such that most patients diagnosed with CML can now expect to live with their disease rather than die from it. However, to achieve this, most patients will require long term—often life long—

Correspondence to: Kathryn E. Flynn, kflynn@mcw.edu.

Conflict of Interest

Kathryn E. Flynn declares no potential conflicts of interest.
Ehab Atallah reports personal fees from BMS and Pfizer.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

treatment. TKIs offer significant improvements in survival and toxicity compared to other treatments for CML but are nonetheless still associated with diminished health-related quality of life^{1, 2} While there remains a paucity of evidence-based data on long term outcomes on which to base clinical treatment decisions,³ the recent literature does include some new evidence for the effects of long term therapy on patients' lives. We review this recent literature, including drug-related adverse effects and patient-reported symptoms for each of the main treatment options, long term medication adherence, limitations to fertility and pregnancy, effects on cognitive function, ability to work, financial hardships, children and adolescents, unmet needs, and discontinuation of TKIs.

Adverse events

All treatments used for the long term treatment of patients with CML have associated side effects. Much attention is paid to the grade 3 (severe) and 4 (life-threatening) toxicities reported in clinical trials (based on the National Cancer Institute's Common Toxicity Criteria) because these may lead to drug discontinuation, hospitalization, or death. However, even grade 1 (mild) and 2 (moderate) toxicities are notable in the CML patient population because, if they are a side effect of a TKI that requires life long daily dosing, patients will likely have to live with these effects for the rest of their lives. In general, grade 1 toxicities can be relieved by rest, while grade 2 toxicities limit instrumental activities of daily living, things like preparing meals, shopping, using the telephone, and managing money. For example, a grade 2 diarrhea is 4–6 stools/day; clearly this would be disruptive to a patient's everyday life. This was demonstrated in a study by Guerin et al. (2014), in which the investigators correlated low grade adverse events with the self-reported health-related quality of life of patients enrolled on the ENESTnd trial. The ENESTnd trial was a large trial that randomized 846 patients with newly diagnosed CML to imatinib 400 mg daily, nilotinib 300 mg twice daily vs. nilotinib 400 mg twice daily. Even low grade (that is, grade 1 or 2) adverse events of the gastrointestinal system, blood and lymphatic system disorders, musculoskeletal disorders, general disorders, and psychiatric disorders were significantly correlated with patients' reports of their health-related quality of life as measured by a general measure (the SF-36) as well as a disease-specific measure (FACT-Leu).⁴

We now describe the more common grade 1 and 2 side effects associated with specific treatments, as typically a grade 3 or 4 toxicity would result in either discontinuation of the drug or dose adjustment until the adverse event resolves or is reduced to a grade 1 or 2.

Imatinib

In a study by Kalmanti et al (2015) reporting on the long term follow up of the randomized CML-study IV, 1503 patients received imatinib and 1379 received imatinib monotherapy. Of those, 406 patients received imatinib 400 mg. With a median follow up of 7 years, the 8-year probability of having at least one non-hematologic adverse reaction was 64.5%, and among patients who received imatinib 400 mg daily, 11.8% had at least one non-hematologic grade 3–4 toxicity. The most commonly reported grade 1 and 2 adverse events were edema (38%), gastrointestinal toxicity (35%), myalgia (22%), fatigue (14%), skin (18%), musculoskeletal

(18%) and constitutional (8%) symptoms. Interestingly, most adverse reactions occurred in the first 1–3 years of imatinib treatment, and no new late toxicities were observed.⁵

Dasatinib

In the 3 year follow up of the DASISION trial (DASatinib versus Imatinib Study In treatment Naive CML patients),⁶ the following grade 1 or 2 adverse events were reported: fluid retention (29%), myalgia (23%), nausea (10%), diarrhea (20%), rash (13%), headache (13%), and fatigue (9%). There was no increase in the incidence of adverse events in the first 3 years. However, in the 5 year follow up, the incidence of pleural effusions with dasatinib continued to increase with 29% of patients overall experiencing pleural effusions. Ninety percent of patients who developed a pleural effusion had a grade 1 or 2 pleural effusion. The median time to developing an effusion was 114 weeks with a range of 4–229 weeks.⁷ A grade 1 effusion is asymptomatic, while a grade 2 effusion is a symptomatic effusion requiring intervention, such as diuretics or up to two therapeutic thoracenteses. In the 6-year follow up of patients receiving dasatinib after imatinib failure/intolerance, 670 patients received dasatinib in 4 different regimens/doses. The rate of side effects did not increase after 2 years, however, patients continued to experience grade 1 or 2 side effects up to 6 years. The rates of grade 1 or 2 toxicities were: 46% with headache, 45% with musculoskeletal pain, 37% with diarrhea, 33% with fatigue, 31% with dyspnea, 29% with arthralgia, 22% with hemorrhage, 21% with abdominal pain, 21% with nausea, and 20% with pleural effusion.⁸

Bosutinib

In a recent update of the BELA trial, 500 patients with CML were randomized to either imatinib or bosutinib. For patients receiving bosutinib at 2 years, grade 1 or 2 side effects were reported by patients as follows: diarrhea by 58%, nausea by 31%, vomiting by 31%, rash by 22%, headache by 12%, fatigue by 12% and arthralgia by 7%.⁹

Nilotinib

With nilotinib, the most common grade 1 and 2 toxicities include headache (36%), nausea (31%), rash (30%), pruritus (14%), and fatigue (11%), and alopecia (7%).¹⁰ With longer term follow up at 2¹¹ and 3 years,¹² there was no worsening or increase in toxicity. However, cardiovascular toxicities are one of the long term side effects that are especially concerning. In the 5 year follow up of the ENESTnd study, the rates of cardiovascular complications were 2.1%, 6.8%, and 12.6% for imatinib 400 mg daily, nilotinib 300 mg twice daily, and nilotinib 400 mg twice daily, respectively.¹³ Cardiovascular complications include ischemic heart disease, cerebrovascular side effects, and peripheral arterial disease, with clear bearing on patients' health-related quality of life.

Stem cell treatment

While not a viable alternative to TKI therapy for many patients, one recent study in China compared patient-reported symptoms and function (using the SF-36) for patients on imatinib to those who had received hematopoietic stem cell treatment from an HLA-identical sibling donor. At 2–11 years after treatment, the 96 patients who had received stem cell treatment

had higher scores on both the role-physical functioning (3.2 points, $p=0.048$) and mental health subscales (2.3 points, $p=0.024$) than did the 126 patients who were on imatinib. Patients on imatinib had higher scores on the bodily pain (2.7 points, $p=0.015$) subscale. There were no significant differences in the other 5 subscales (physical functioning, general health, vitality, social functioning, or role-emotional functioning). It is also notable that the Physical and Mental Component Summary Scores were comparable to those in the U.S. general population (~50).¹⁴

Long-term adherence

A critical consideration for patients on long term medications is adherence to the prescribed regimen. Multiple studies have demonstrated a clear correlation between medication adherence and outcomes. In a study in Taiwan, the 4-year survival rate was 91% in adherent patients compared to 72% in non-adherent patients.¹⁵ Adherence in this study was defined using the medication possession ratio—that is, the ratio of each patients total number of days of supply of imatinib prescriptions by the prescription duration—and a cutoff of 90%. Neons et al (2009) found that only 14.2% of patients were perfectly adherent with 100% of prescribed TKI.¹⁶ More recently, Anderson et al. (2015) evaluated 124 patients with CML who were prescribed TKIs for their compliance the medication possession ration and a cutoff of 90%.¹⁷ In this study, 31% of patients met the criteria for non-adherence with their prescribed medication regimen. Surprisingly, younger patients (less than 50 years old), those not receiving any other medications, and patients on imatinib were those that were most likely to be non-adherent. In a survey of 1133 patients from 28 Italian centers, only 4% reported missing > 4 days/month of therapy. More patients (8%) missed a dose because of forgetfulness or feeling sick rather than because they felt a sense of wellness (4%).¹⁸ Finally, another Italian study of 175 pts reporting intentional and unintentional reasons for not fully adhering to imatinib found that unintentional non-adherers tended to be younger and more likely to be male, whereas those who intentionally missed doses reported worse health related quality of life and higher symptom severity.¹⁹

Another factor related to adherence is the particular dosing and dietary requirements associated with each drug, what is also known as a negative medication experience.²⁰ For example, imatinib has to be taken with a big meal, nilotinib is to be taken twice a day on an empty stomach, and dasatinib has to be taken with a full glass of water.

Medication restrictions could also pose a problem for patients. The use of proton pump inhibitors to treat GERD symptoms is generally contraindicated with TKIs. Other medications that have QT prolongation side effects have to either be discontinued or they require increased monitoring. Both of these options, whether increased monitoring or avoiding those medications, will affect a patient's health-related quality of life.

Fertility and pregnancy

Approximately 27% of patients diagnosed with CML are younger than 50 years old,²¹ and fertility and pregnancy are major factors affecting quality of life. For men, while data is limited, generally there does not seem to be a negative impact on fertility or pregnancy, at

least for those taking imatinib.^{22, 23} Even less data is available for the second generation TKIs, however they also appear to be relatively safe for men. Unfortunately, that does not appear to be the case for women taking TKIs. Several studies have shown an increased incidence of spontaneous abortions and congenital malformations among women who become pregnant while taking a TKI.^{24, 25} Based on that, the current recommendation is to discontinue TKIs for women who wish to conceive.²⁶

Apart from fertility concerns and regardless of age, sexual function is an important component of health-related quality of life for many patients (and their partners). This is an understudied area in CML. We found no published articles dedicated to sexual function in patients on long term therapy for CML; recent articles on sexual function among patients with cancer²³ or even specifically hematologic malignancies²⁴ have not presented data on CML.

Cognitive function

One year after diagnosis of CML (86% of sample) or myelodysplastic syndrome (14% of sample), two diseases that do not typically involve the central nervous system, neuropsychological assessments were given to 77 patients to evaluate how treatments may affect cognitive function. For the CML patients, these treatments included imatinib and/or stem cell treatment. The authors examined whether cognitive function was associated with changes in patient-reported symptoms and functioning. They found that simple reaction time, a component of cognitive function, was a consistent predictor of change in the SF-36 as well as another measure of overall function in day-to-day life, the Functional Living Index– Cancer.²⁷ This was a novel finding that warrants confirmation in other samples given the importance of cognitive function to daily life.

Ability to work

Health related quality of life, including the ability to work, was assessed in a phone survey of 663 patients with CML from a society registry in Brazil (the Brazilian Association of Lymphoma and Leukemia). The use of imatinib was associated with a better ability to work compared to chemotherapy ($p=0.017$) and hydroxyurea ($p=0.001$). This is important because the ability to work was also associated with higher scores on the FACT-G ($p<0.001$) and the FACT-Leu ($p<0.001$).²⁸

Financial toxicity

Financial hardship was the topic of a recent (2015) Current Hematologic Malignancy Reports. Included in one of the manuscripts²⁹ was a study from 2014 showing that “patients with higher copayments are more likely to discontinue or be nonadherent to TKIs” from a study of 1541 patients with CML, based on health plan claims.³⁰ The very high cost of TKIs is a well known problem.³¹ Even with health insurance, a 20% or even 10% copayment represents a financial burden for many and is untenable for others.

Children and adolescents

Although CML is rare in children and adolescents, this group of patients is particularly vulnerable to the long term toxicities of TKIs. Recent reports have demonstrated growth abnormalities associated in pre-pubertal children and teens receiving imatinib.^{32, 33} This growth retardation could be secondary to effects on the growth hormone/IGF-1 axis.³⁴ In addition, some case reports³⁵ and preclinical studies³⁶ have suggested a long term effect on fertility. Finally, it seems probable that this group of patients maybe more vulnerable to the long term cardiovascular side effects of TKIs given the longer duration of treatment; however, this has not been demonstrated to date. Adherence is another concern in adolescent and young adults. Younger age is a consistent predictor of poor adherence, which will affect the long term outcomes in these patients. Based on these considerations, Hijiya et al. (2015) have recently recommended that finding a way to cure those patients should remain the ultimate goal.³⁷

Unmet needs

In a large survey of patients from 28 Italian centers (n=1133), patients' overall ratings of their quality of life were 21.5% "perfect", 52% "good", and 24% "fair".¹⁸ Notably, these patients expressed the desire to talk more with their physicians about anxiety, fear of the future, psychological problems, problems at work, relationships, and sexual problems. This finding highlights a largely ignored aspect of the care of patients with CML: these patients often spend less time with their treating physicians and thus have less time to discuss management of the low grade side effects of their long term therapies. Shorter visit times make some sense; from the oncologists' perspective, the treatment of CML is as good as it gets compared to treatments received by patients with other more advanced and/or less curable cancers. But patients with CML likely do not have this perspective, and many have unmet medical needs as a result.

Discontinuation of TKIs

Several studies have demonstrated the safety and feasibility of TKI discontinuation in patients with a deep molecular response.³⁸ While data on the health-related quality of life of patients who discontinue TKIs are still limited, one unexpected effect has been noted: in one study musculoskeletal pain was reported by approximately 30% of patients after stopping TKIs.³⁹ This withdrawal syndrome was severe enough in some patients to require steroid therapy, and the symptom resolved after patients restarted a TKI. The mechanism of this musculoskeletal pain remains unclear.

Conclusions

Due to advancements in treatments, patients with CML now have a similar life expectancy to the general population. Due to the outstanding survival of patients treated with TKIs in particular, the prevalence of the disease is rapidly increasing across the world. However, with this increased survival and increased prevalence more emphasis should be placed on managing side effects to maximize the health related quality of life of patients with CML.

First, health care providers should be aware of the impact this disease and its treatments have on the health related quality of life of patients, across a broad set of symptoms and functions. Addressing the various issues that arise is paramount in improving patients' health related quality of life and maintaining patients' adherence and survival. The financial toxicity associated with this disease cannot be overemphasized, and lowering the price of drugs would alleviate some of the patient anxiety associated with the cost of treatment.

While patients with CML are fortunate to have excellent therapies available to control their disease, most do not lead normal lives due to the diminished health-related quality of life that is associated with long term treatment. This challenges the notion that research is no longer needed in CML. Curing CML, i.e. no detectable disease and no need for daily medications, should remain the ultimate goal.

Acknowledgments

Drs Flynn and Atallah were supported by grant R01 CA184798 from the National Cancer Institute. Dr Flynn was supported in part by the Research and Education Program Fund, a component of the Advancing a Healthier Wisconsin endowment at the Medical College of Wisconsin.

References

1. Saussele S, Stein M, Gil A, Kossak-Roth U, Lauseker M, Proetel U, Einsele H, Schafhausen P, Lange E, Hänel M, Spiekermann K, Söckler M, Wendtner C, Kremers S, Pfreundschuh M, Holler E, Hofmann W-K, Hochhaus A, Müller MC, Hehlmann R, Pfirrmann M. Health-Related Quality of Life Impairment in Patients with Chronic Myeloid Leukemia: Results of a German Cross-Sectional Study of Patients Registered in Prospective, Controlled Clinical Trials. *Blood*. 2015; 126:2773–2773. [PubMed: 26705340]
2. Efficace F, Baccarani M, Breccia M, Cottone F, Alimena G, Deliliers GL, Barate C, Specchia G, Di Lorenzo R, Luciano L, Turri D, Martino B, Stagno F, Dabusti M, Bergamaschi M, Leoni P, Simula MP, Levato L, Fava C, Veneri D, Sica S, Rambaldi A, Rosti G, Vignetti M, Mandelli F. Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. *Leukemia*. 2013; 27:1511–9. [PubMed: 23417029]
3. Efficace F, Cardoni A, Cottone F, Vignetti M, Mandelli F. Tyrosine-kinase inhibitors and patient-reported outcomes in chronic myeloid leukemia: a systematic review. *Leuk Res*. 2013; 37:206–13. [PubMed: 23177797]
4. Guerin A, Chen L, Ionescu-Ittu R, Marynchenko M, Nitulescu R, Hiscock R, Keir C, Wu EQ. Impact of low-grade adverse events on health-related quality of life in adult patients receiving imatinib or nilotinib for newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase. *Curr Med Res Opin*. 2014; 30:2317–28. [PubMed: 25025755]
- 5**. Kalmanti L, Saussele S, Lauseker M, Muller MC, Dietz CT, Heinrich L, Hanfstein B, Proetel U, Fabarius A, Krause SW, Rinaldetti S, Dengler J, Falge C, Oppliger-Leibundgut E, Burchert A, Neubauer A, Kanz L, Stegelmann F, Pfreundschuh M, Spiekermann K, Scheid C, Pfirrmann M, Hochhaus A, Hasford J, Hehlmann R. Safety and efficacy of imatinib in CML over a period of 10 years: data from the randomized CML-study IV. *Leukemia*. 2015; 29:1123–1132. 10 year follow up of imatinib therapy. A comprehensive analysis of imatinib therapy in CML. [PubMed: 25676422]
6. Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccarani M, Kim D-W, Bradley-Garelik MB, Mohamed H, Wildgust M, Hochhaus A. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2014; 123:494–500. [PubMed: 24311723]
7. Cortes JE, Saglio G, Baccarani M, Kantarjian HM, Mayer J, Boqué C, Shah NP, Chuah C, Casanova L, Narayanan G, Bradley-Garelik B, Manos G, Hochhaus A. Final Study Results of the Phase 3

Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056). *Blood*. 2014; 124:152–152.

- 8**. Shah NP, Guilhot F, Cortes JE, Schiffer CA, le Coutre P, Brummendorf TH, Kantarjian HM, Hochhaus A, Rousselot P, Mohamed H, Healey D, Cunningham M, Saglio G. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. *Blood*. 2014; 123:2317–2324. Long term follow up of patients on dasatinib demonstrating no increase in rate of AEs with longer follow up. [PubMed: 24569263]
9. Brummendorf TH, Cortes JE, de Souza CA, Guilhot F, Duvillie L, Pavlov D, Gogat K, Countouriotis AM, Gambacorti-Passerini C. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. *British Journal of Haematology*. 2015; 168:69–81. [PubMed: 25196702]
10. Saglio G, Kim D-W, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. *New England Journal of Medicine*. 2010; 362:2251–2259. [PubMed: 20525993]
11. Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, Goh YT, Rosti G, Nakamae H, Gallagher NJ, Hoenekopp A, Blakesley RE, Larson RA, Hughes TP. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *The lancet oncology*. 2011; 12:841–51. [PubMed: 21856226]
12. Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, Flinn IW, Kurokawa M, Moiraghi B, Yu R, Blakesley RE, Gallagher NJ, Saglio G, Kantarjian HM. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*. 2012; 26:2197–2203. [PubMed: 22699418]
13. Saglio G, Hochhaus A, Hughes TP, Clark RE, Nakamae H, Kim D-W, Jootar S, Etienne G, Flinn I, Lipton JH, Pasquini R, Moiraghi B, Kemp C, Fan X, Menssen HD, Kantarjian HM, Larson RA. ENESTnd Update: Nilotinib (NIL) Vs Imatinib (IM) In Patients (pts) With Newly Diagnosed Chronic Myeloid Leukemia In Chronic Phase (CML-CP) and The Impact Of Early Molecular Response (EMR) and Sokal Risk At Diagnosis On Long-Term Outcomes. *Blood*. 2013; 122:92.
- 14**. Mo XD, Jiang Q, Xu LP, Liu DH, Liu KY, Jiang B, Jiang H, Chen H, Chen YH, Zhang XH, Han W, Wang Y, Huang XJ. Health-related quality of life of patients with newly diagnosed chronic myeloid leukemia treated with allogeneic hematopoietic SCT versus imatinib. *Bone Marrow Transplant*. 2014; 49:576–580. Unexpected results of similar QOL between patients on TKIs and those receiving HCT. [PubMed: 24442252]
15. Chen TC, Chen LC, Huang YB, Chang CS. Imatinib adherence associated clinical outcomes of chronic myeloid leukaemia treatment in Taiwan. *Int J Clin Pharm*. 2014; 36:172–81. [PubMed: 24242992]
16. Noens L, van Lierde MA, De Bock R, Verhoef G, Zachee P, Berneman Z, Martiat P, Mineur P, Van Eygen K, MacDonald K, De Geest S, Albrecht T, Abraham I. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood*. 2009; 113:5401–11. [PubMed: 19349618]
17. Anderson KR, Chambers CR, Lam N, Yau PS, Cusano F, Savoie ML, Sheikh N. Medication adherence among adults prescribed imatinib, dasatinib, or nilotinib for the treatment of chronic myeloid leukemia. *Journal of Oncology Pharmacy Practice*. 2015; 21:19–25. [PubMed: 24503243]
18. Breccia M, Efficace F, Sica S, Abruzzese E, Cedrone M, Turri D, Gobbi M, Carella AM, Gozzini A, Usala E, Cavazzini F, Danise P, Tiribelli M, Binotto G, Pregno P, Bocchia M, Gaidano G, Crugnola M, Bonifacio M, Avanzini P, Celesti F, Guella A, Martino B, Annunziata M, Luciano L, Stagno F, Vallisa D, Pungolino E, Iurlo A, Rambaldi A, Nardiello I, Orlandi E, Gambacorti-Passerini C, Alimena G. Adherence and future discontinuation of tyrosine kinase inhibitors in chronic phase chronic myeloid leukemia. A patient-based survey on 1133 patients. *Leukemia Research*. 2015; 39:1055–1059. [PubMed: 26282944]
19. Efficace F, Rosti G, Cottone F, Breccia M, Castagnetti F, Iurlo A, Mandelli F, Baccarani M. Profiling chronic myeloid leukemia patients reporting intentional and unintentional non-adherence to lifelong therapy with tyrosine kinase inhibitors. *Leuk Res*. 2014; 38:294–8. [PubMed: 23906625]

- 20*. Hirji I, Gupta S, Goren A, Chirovsky DR, Moadel AB, Olavarria E, Victor TW, Davis CC. Chronic myeloid leukemia (CML): association of treatment satisfaction, negative medication experience and treatment restrictions with health outcomes, from the patient's perspective. *Health Qual Life Outcomes*. 2013; 11:167. Important data correlating QOL with medication experience. [PubMed: 24099272]
21. Höglund M, Sandin F, Hellström K, Björemann M, Björkholm M, Brune M, Dreimane A, Ekblom M, Lehmann S, Ljungman P, Malm C, Markevårn B, Myhr-Eriksson K, Ohm L, Olsson-Strömberg U, Sjölander A, Wadenvik H, Simonsson B, Stenke L, Richter J. Tyrosine kinase inhibitor usage, treatment outcome, and prognostic scores in CML: report from the population-based Swedish CML registry. *Blood*. 2013; 122:1284–1292. [PubMed: 23843494]
22. Breccia M, Cannella L, Montefusco E, Frustaci A, Pacilli M, Alimena G. Male patients with chronic myeloid leukemia treated with imatinib involved in healthy pregnancies: report of five cases. *Leuk Res*. 2008; 32:519–20. [PubMed: 17804066]
23. Ramasamy K, Hayden J, Lim Z, Mufti GJ, Ho AY. Successful pregnancies involving men with chronic myeloid leukaemia on imatinib therapy. *Br J Haematol*. 2007; 137:374–5. [PubMed: 17408403]
24. Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M, Rios MB, Koller C, Giles F, Keating M, Talpaz M, Cortes J. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. *J Clin Oncol*. 2006; 24:1204–8. [PubMed: 16446320]
25. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, Rosti G, Apperley JF. The effects of imatinib on pregnancy outcome. *Blood*. 2008; 111:5505–8. [PubMed: 18322153]
- 26**. Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. *Annals of hematology*. 2015; 94:167–176. Excellent review on pregnancy and outcome.
27. Chang G, Meadows ME, Smallwood JA, Antin JH, Orav EJ. Cognitive and other predictors of change in quality of life one year after treatment for chronic myelogenous leukemia or myelodysplastic syndrome. *J Neuropsychiatry Clin Neurosci*. 2014; 26:249–57. [PubMed: 24817387]
28. Hamerschlak N, de Souza C, Cornacchioni AL, Pasquini R, Tabak D, Spector N, Steagall M. Quality of life of chronic myeloid leukemia patients in Brazil: ability to work as a key factor. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2014; 22:2113–8. [PubMed: 24647489]
29. McNulty J, Khera N. Financial Hardship—an Unwanted Consequence of Cancer Treatment. *Curr Hematol Malig Rep*. 2015; 10:205–12. [PubMed: 26112652]
30. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol*. 2014; 32:306–11. [PubMed: 24366936]
31. Experts in Chronic Myeloid L. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood*. 2013; 121:4439–42. [PubMed: 23620577]
32. Millot F, Guilhot J, Baruchel A, Petit A, Leblanc T, Bertrand Y, Mazingue F, Lutz P, Verite C, Berthou C, Galambrun C, Nicolas S, Yacouben K, Chastagner P, Gandemer V, Reguerre Y, Couillaud G, Khalifeh T, Rialland F. Growth deceleration in children treated with imatinib for chronic myeloid leukaemia. *Eur J Cancer*. 2014; 50:3206–11. [PubMed: 25459396]
33. Shima H, Tokuyama M, Tanizawa A, Tono C, Hamamoto K, Muramatsu H, Watanabe A, Hotta N, Ito M, Kurosawa H, Kato K, Tsurusawa M, Horibe K, Shimada H. Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. *J Pediatr*. 2011; 159:676–81. [PubMed: 21592517]
34. Narayanan KR, Bansal D, Walia R, Sachdeva N, Bhansali A, Varma N, Marwaha RK. Growth failure in children with chronic myeloid leukemia receiving imatinib is due to disruption of GH/IGF-1 axis. *Pediatr Blood Cancer*. 2013; 60:1148–53. [PubMed: 23322583]
35. Seshadri T, Seymour JF, McArthur GA. Oligospermia in a patient receiving imatinib therapy for the hypereosinophilic syndrome. *N Engl J Med*. 2004; 351:2134–5. [PubMed: 15537917]

36. Nurmio M, Toppari J, Zaman F, Andersson AM, Paranko J, Soder O, Jahnukainen K. Inhibition of tyrosine kinases PDGFR and C-Kit by imatinib mesylate interferes with postnatal testicular development in the rat. *Int J Androl*. 2007; 30:366–76. discussion 376. [PubMed: 17705809]
37. Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood*. 2015
- 38**. Mahon FX. Discontinuation of tyrosine kinase therapy in CML. *Ann Hematol*. 2015; 94(Suppl 2):S187–93. Excellent review on the unique challenges in patients children and adolescents with CML. [PubMed: 25814085]
39. Richter J, Söderlund S, Lübking A, Dreimane A, Lotfi K, Markevörn B, Sjölander A, Saussele S, Olsson-Strömberg U, Stenke L. Musculoskeletal Pain in Patients With Chronic Myeloid Leukemia After Discontinuation of Imatinib: A Tyrosine Kinase Inhibitor Withdrawal Syndrome? *Journal of Clinical Oncology*. 2014; 32:2821–2823. [PubMed: 25071107]