Research Paper

The survival of patients enrolled in a global direct-to-patient cancer medicine donation program: The Glivec International Patient Assistance Program (GIPAP)

Chukwuemeka A. Umeh, Pat Garcia-Gonzalez, David Tremblay, Richard Laing

Artificial Information

Article History:
Received 8 April 2019
Revised 24 December 2019
Accepted 3 January 2020
Available online 26 January 2020

Keywords:
- Glivec International Patient Assistance Program (GIPAP)
- Chronic myeloid leukemia (CML)
- Access observatory
- CML survival rate
- Max foundation
- Novartis

Abstract

Background: The Glivec International Patient Assistance Program (GIPAP) is a unique direct-to-patient program that provides imatinib (Glivec) at no cost to eligible patients in low- and middle-income countries (LMICs) with chronic myelogenous leukemia (CML) or gastrointestinal stromal tumor (GIST). This paper analyses the output, outcome and impact of the program between 2001 and 2014 using the data collected by the Max Foundation.

Method: We extracted data on GIPAP patients’ country of residence, sex, diagnosis, date of enrollment in GIPAP, age at enrollment, case closure date, and reason for closure from The Max Foundation database covering the period 2001 to 2014. We used Kaplan-Meier method to assess the survival rate of patients in GIPAP and used the proportional hazard regression model to estimate the effect of different variables on patients’ survival.

Findings: About 63,000 GIPAP patients in 93 countries received over 71 million defined daily doses (DDD) of imatinib between 2001 and 2014. Our analysis showed that GIPAP patients had a 5-year survival rate of 89% which compares favorably to survival in high income countries despite the challenges of delivering cancer care in LMICs. Age at enrollment into the program, sex, diagnosis of CML vs non-CML, and year of enrollment were factors that influenced survival.

Interpretation: The GIPAP program has improved the survival of CML and GIST patients in LMICs, most of whom would not have had access to imatinib in the absence of the donation and therapeutic support of the program.

Funding: This work was funded as part of Access Accelerated case studies. Access Accelerated is an initiative of more than 20 global biopharmaceutical companies in partnership with the World Bank and Union of International Cancer Control that seeks to reduce barriers to prevention, treatment and care for non-communicable diseases in LMICs.

© 2020 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Chronic myeloid leukemia (CML) is a rare hematologic malignancy that globally affects between one and two per 100,000 people annually [1,2]. CML had a poor prognosis and a median survival of less than 5 years before 2001, but is now considered a chronic disease since the advent of targeted therapies such as imatinib (Glivec) [1,3]. With the introduction of imatinib, five-year cumulative relative survival ratios of CML in Swedish patients younger than 79 years increased from 0.54 between 1994 and 2000 to 0.80 between 2001 and 2008 [6]. Similarly, the five-year survival rate of CML increased from 63% with interferon therapy to 88% with the introduction of imatinib in a cancer treatment center in the United States [7]. Furthermore, imatinib has fewer side effects compared with alternative treatments [3,8].

Despite the improved outcomes for CML patients that have been treated with imatinib, the average monthly cost of $2500–$3500 USD in high income countries could limit its use in low- and middle-income countries (LMICs) [9]. This led Novartis in 2001 to establish the Glivec International Patient Assistance Program (GIPAP) to assist patients in LMICs not able to afford treatment [1,9].
The Glivec International Patient Assistance Program (GIPAP) is a global program that was established by Novartis Pharma AG in 2001 and implemented in partnership with The Max Foundation and Axios International, to provide imatinib (Glivec) at no cost to eligible patients with CML or gastrointestinal stromal tumor (GIST) [1, 10]. Eligible patients include Philadelphia chromosome-positive CML or c-kit (CD117) positive GIST patients who were not insured, not reimbursed, or could not pay for the treatment privately and were in countries that have minimal reimbursement capabilities and where regulatory approval or at least an import license for Glivec for CML/GIST had been obtained [11–13].

Using a direct-to-patient approach, GIPAP involves different levels of partners—patients, patients’ physicians, implementing partners, and Novartis. Each of the partners plays specific roles that ensure the success of the program. Novartis identified the countries where the programs would be implemented and collaborated with The Max Foundation to select qualified institutions and physicians in these countries. It also supplied the requested amount of imatinib to the cancer treating institutions and contracted with Axios International to deal with supply logistics in countries where the company lacked the necessary logistics in-country to support drug importation [1].

The Max Foundation conducted socioeconomic evaluation and verified the eligibility of patients, in addition to requesting product donation delivery from Novartis at three-month intervals based on individual patient’s physician prescription. The Max Foundation also supported patients’ adherence to medications by providing peer-to-peer support and supported by Novartis and others, also engaged in CML educational initiatives and awareness campaigns [1, 12]. Additionally, the Max Foundation and Axios International maintained databases of data from different patients and institutions involved in the program [9]. Axios International apart from managing the drug import process in some countries, supported interaction with GIPAP physicians and institutions in countries where Novartis did not have a presence to ensure that they followed correct procedures [13, 14].

The physicians in GIPAP institutions diagnosed the patients and made a request to The Max Foundation for the patients to be enrolled in the program. There were no limits to the number of patients eligible for GIPAP in any participating institution or country. Participation of physicians was voluntary, but they played an important role in the success of the program [1, 2]. The physicians’ physicians worked with the implementing partners to ensure that the patients received the appropriate doses they needed at the appropriate time. The physicians were also responsible for managing and reviewing enrolled patients quarterly. If a patient did not come for the quarterly review and attempts by The Max Foundation to locate the patient failed, such a case was considered as “closed” or non-active, and could be re-instated into the program if contact was re-established [2]. In addition, the physicians and nurses had to comply with the demanding data entry needs of the program by filling out reports for each patient quarterly that were collected and validated by The Max Foundation [1, 2]. To ensure adherence to the medication, which has been shown to correlate with improved survival, the physicians also contacted patients with appointment reminders and other necessary information [1].

Previous studies using the GIPAP data have examined institutional factors related to patient enrollment and outcomes [9], regional variations in age at diagnosis and survival of GIPAP patients [15], and three-year survival rates of GIPAP patients [2, 15]. However, none of the studies has examined the medium- to long-term survival of GIPAP patients nor estimated the number of lives saved through the program.

This paper examines the medium- to long-term survival of GIPAP patients and estimates the number of lives saved through the program using routinely collected GIPAP program data. This paper also reports the outputs and outcomes of the GIPAP program using the Boston University Access to Medicines Metrics Framework developed as part of the Access Accelerated initiative [16, 17]. The Boston University Access to Medicines Metrics Framework consists of a taxonomy of 11 global health program strategies such as medicine donation and price schemes, with the corresponding logic models designed to report inputs, activities, outputs, outcomes, and impacts of pharmaceutical industry led global health programs [16].

2. Methods

2.1. Data sources

We extracted data on patients’ country of residence, sex, diagnosis, date of enrollment in GIPAP, age at enrollment, case closure date, and reason for closure from the Max Foundation database covering the period 2001 to the end of 2014. The analysis included data from 93 countries that were involved in GIPAP between 2001 and 2014. This also includes patients enrolled in the Novartis Oncology Access (NOA) program in India who were receiving free imatinib, referred to as NOA-GIPAP patients. However, for the purposes of this paper, we will collectively refer to both the GIPAP and NOA-GIPAP patients as GIPAP patients.

2.2. Variables

We calculated the total daily doses of imatinib donated to GIPAP patients by Novartis by dividing the total volume of medicine donated in milligrams by the defined daily dose (DDD) of imatinib. Since no DDD for imatinib has been established by the World Health Organization [18], we used a DDD of 400 mg which is the modal daily dose of imatinib taken by GIPAP patients.

\[
\text{Total daily doses of imatinib donated} = \frac{\text{Volume of imatinib donated in milligrams}}{\text{defined daily dose of imatinib}}
\]

The potential number of CML patients saved by GIPAP in five years was calculated by subtracting the estimated number that survived...
after 5 years from the number expected to survive after 5 years in the absence of imatinib [7].

Potential number of CML patients saved by GIPAP in 5 years = Estimated number that survived after 5 years – Number expected to survive after 5 years in the absence of imatinib.

2.3. Statistical analysis

We did descriptive statistics using sums, means and standard deviations for continuous variables and percentages for categorical variables. We used Kaplan-Meier method to assess the survival rate of patients in GIPAP. Our event of interest was death of patient, while closure due to other reasons such as loss to follow-up, and patients that were still alive at the end of 2014, were analyzed as censored data. Additionally, we conducted a sensitivity analysis with the assumption that patients who were lost to follow-up had all died at the point they were lost to follow-up. We also systematically conducted sensitivity analyses without data from India and China (both countries contributed about 50% of GIPAP patients), to see if different results would be obtained. We used Wilcoxon and Log-Rank tests to assess whether short- (one year) or long-term differences (five to seven years) exist in survival between patients with CML diagnosis and those with non-CML (mostly gastrointestinal stromal tumor) diagnosis, and between males and females. Furthermore, we used a proportional hazard regression model to estimate the effect of sex, diagnosis (CML vs non-CML), age at enrollment in GIPAP, time in months from diagnosis to enrollment in GIPAP, and year of enrollment, on patients’ survival.

The estimated number of GIPAP CML patients that survived after five years was calculated by multiplying the five-year survival rate in GIPAP CML patients by the number of patients enrolled in the program. The number expected to survive after five years in the absence of imatinib was calculated by multiplying the 1982–1997 five-year survival rate of 650 CML patients receiving treatment in a cancer treatment center in the United States (63%) by the number of people enrolled in the program [7]. The 1982–1997 five-year survival rate was used to calculate the expected number of patients that would have survived in the absence of imatinib because it was one of the most recent published five-year survival rate of CML prior to the approval of imatinib in 2001 [7]. The graph of patients enrolled in GIPAP was performed using Microsoft Excel and SAS 9.4 software package (SAS Institute Inc., Cary, NC, USA) was used for all other statistical analysis.

2.4. Role of the funding source

The study sponsor had no role in the study design; collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the paper for publication. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

2.5. Data statement

The dataset analyzed for this publication is available on request.

3. Results

3.1. Descriptive analysis

The characteristics of the patient population is shown in Table 1. The majority of GIPAP patients were males (61%). About 85% of the patients were treated for CML, 14% for GIST and 1% for other indications such as Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL) and systemic mastocytosis. For the CML patients, 87% were in the chronic stage of the disease at diagnosis, 8% in the accelerated stage and 5% in the blast stage. The mean and median age of patients at enrollment into GIPAP were both 41 years, with a median interquartile range of 22 years, and the mean duration from disease diagnosis to enrollment in GIPAP was 10 months. The mean and median duration of patient follow-up was 41 and 30 months respectively with a median interquartile range of 51 months.

Our trend analysis of new patients ever enrolled in GIPAP in 93 countries showed a progressive increase in the number of new patients enrolled in GIPAP from 2001 to 2007, a decline in 2008 and a fairly constant number from 2009 to 2014 (Fig. 1). The total enrolled patients increased from 12 in 2001 to 63,381 in 2014.

3.1.1. Program outputs

GIPAP provided imatinib to more than 63,000 patients in 93 LMICs between 2001 and 2014. Novartis donated about 72 million DDD and 66 million treatment days of imatinib to patients enrolled in GIPAP during that time.

3.1.2. Survival rates

Our survival analysis of all GIPAP patients enrolled from 2001 to 2014 shows a one-, three, five- and seven-year survival rate of 95%, 92%, 89% and 87%, respectively (Table 2).

Our disaggregated analysis showed that the short- (p < 0.0001) and long-term (p < 0.0001) survival rates of CML patients were significantly higher than those of non-CML patients. The one-, three-, five- and seven-year survival rates for CML patients were 96%, 92%, 90% and 88% respectively compared to 95%, 90%, 86%, and 79% for GIST patients (Table 2) (Fig. 2).

The disaggregated survival analysis of CML patients in different phases of disease at diagnosis showed that those diagnosed in the chronic phase had the best survival while those diagnosed in the blast phase had the worst survival. The one-, three-, five- and seven-year survival rates for chronic phase CML patients were 97%, 95%, 92% and 90% respectively compared to 89%, 83%, 80%, and 78% for accelerated phase and 69%, 59%, 56% and 53% for blast phase (Table 3) (Fig. 3).

The proportional hazard regression showed that the risk of death in non-CML patients was 24.6% higher than in CML patients (p < 0.0001), after adjusting for sex, age at enrollment into GIPAP, time between diagnosis and enrollment into GIPAP and year of enrollment.

Similarly, the result of the proportional hazard regression of GIPAP CML patients showed that the risk of death in male patients was seven percent higher than those of female patients (p = 0.0308), after adjusting for CML phase at diagnosis, age at enrollment into

| Table 1 |
|---|
| Variable | Frequency | Percentage |
| Sex | | |
| Male | 38,432 | 60.64% |
| Female | 24,948 | 39.36% |
| Diagnosis | | |
| CML | 53,878 | 85.01% |
| GIST | 8986 | 14.18% |
| Others (e.g. Ph positive ALL; systemic mastocytosis) | 517 | 0.81% |
| Stage of CML disease | | |
| Chronic | 46,752 | 86.78% |
| Accelerated | 4522 | 8.39% |
| Blast Crisis | 2601 | 4.83% |
| Age at diagnosis (years) | | |
| Mean | 40.57 | 15.39 |
| Standard deviation | | |
| Age at enrollment into GIPAP (years) | 41.47 | 15.40 |
| Time between diagnosis and enrollment in GIPAP (months) | 10.33 | 23.83 |
| Duration of patient follow up (months) | 40.74 | 34.70 |
GIPAP, time between diagnosis and enrollment into GIPAP and year of enrollment (Table 4).

With each year increase in age at enrollment into GIPAP, the risk of death in CML patients increases by 1.7%, holding other variables constant ($p < 0.0001$). In addition, with each month increase in the time between diagnosis and enrollment into GIPAP, the risk of death in CML patients increases by 0.4%, holding other variables constant ($p < 0.0001$). For each year increase in the year of enrollment, the risk of death decreased by 3.5%, which means that those enrolled in the later years of the program had a better survival rate. The risk of death was 163% and 744% more likely in CML patients diagnosed at the accelerated or blast phase, respectively, compared to those diagnosed at the chronic phase.

The estimated five-year potential number of CML patients saved by GIPAP (see formula for calculation in the methods section) is 17,107.

### 3.1.3. Sensitivity analysis

Our sensitivity analysis based on the assumption that all the cases lost to follow-up (12,679 patients) died at the time they were lost to follow-up shows a one-, three-, five- and seven-year survival rate of 90%, 77%, 67%, and 57%, respectively (Table 5). The five-year potential number of CML patients saved by GIPAP based on this assumption will be 2757.

We also conducted sensitivity analyses without data from India and China (both countries contributed about 50% of GIPAP patients), to see if different results would be obtained. The analysis showed a one-, three-, five-
Fig. 3. Disaggregated Kaplan–Meier survival analysis of GIPAP CML patients, showing survival rate of CML patients in the chronic, accelerated and blast phases at diagnosis, 2001–2014.

Table 2
Kaplan–Meier survival analysis of GIPAP patients 2001–2014.

|                      | Number at risk: all patients | Survival rate: all patients (95% CI) | Number at risk: CML patients | Survival rate: CML patients (95% CI) | Number at risk: GIST patients | Survival rate: GIST patients (95% CI) | Number at risk: other\(^a\) patients | Survival rate: other\(^a\) patients (95% CI) |
|----------------------|-----------------------------|------------------------------------------|------------------------------|--------------------------------------|------------------------------|---------------------------------------|---------------------------------------------|---------------------------------------------|
| One year             | 47,887                      | 95.40% (95.23–95.57)                     | 41,853                       | 95.50% (95.32–95.68)                 | 5808                        | 95.25% (95.73–94.77)                  | 226                          | 85.69% (89.26–82.02)                     |
| Three year           | 28,270                      | 91.88% (91.63–92.11)                     | 25,915                       | 92.16% (91.90–92.42)                 | 2888                        | 90.48% (91.30–89.66)                  | 70                            | 72.09% (78.09–66.09)                     |
| Five year            | 17,025                      | 89.49% (89.18–89.80)                     | 15,988                       | 89.99% (89.67–90.31)                 | 1021                        | 85.59% (86.90–84.28)                  | 18                            | 56.78% (68.40–45.16)                     |
| Seven year           | 9068                        | 87.13% (86.74–87.52)                     | 8667                         | 87.79% (87.39–88.19)                 | 374                         | 78.66% (80.80–76.52)                  |                               |                                             |

\(^a\) Other patients include: hypereosinophilic syndrome/chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, myelodysplastic syndromes/myeloproliferative disorder, systemic mastocytosis, and Ph positive ALL patients.

Table 3
Disaggregated Kaplan–Meier survival analysis of GIPAP CML patients, showing survival rate of CML patients in the blast, accelerated and chronic phase at diagnosis, 2001–2014.

|                      | Number at risk: BP patients | Survival rate: BP patients (95% CI) | Number at risk: AP patients | Survival rate: AP patients (95% CI) | Number at risk: CP patients | Survival rate: CP patients (95% CI) |
|----------------------|-----------------------------|------------------------------------------|-------------------------------|--------------------------------------|-------------------------------|-------------------------------------|
| One year             | 1038                        | 68.81% (70.81–66.81)                     | 3142                         | 89.46% (90.40–88.51)                 | 37,671                        | 97.40% (97.55–97.25)                 |
| Three year           | 455                         | 58.99% (61.84–56.56)                     | 1713                         | 82.53% (83.82–81.24)                 | 23,747                        | 94.59% (94.83–94.35)                 |
| Five year            | 235                         | 56.05% (58.74–53.37)                     | 948                          | 80.03% (81.49–78.57)                 | 14,797                        | 92.44% (92.75–92.13)                 |
| Seven year           | 123                         | 53.14% (56.30–49.98)                     | 471                          | 77.52% (79.32–75.72)                 | 8013                          | 90.33% (90.73–89.93)                 |

AP: accelerated phase CML, BP: blast phase CML, CP: chronic phase CML.

Table 4
Result of the proportional hazard regression of GIPAP CML patients 2001–2014.

| Parameter                        | Parameter estimate | Standard error | Hazard ratio (95% CI) | p-value |
|----------------------------------|--------------------|----------------|-----------------------|---------|
| Age at enrollment into program   | 0.01689            | 0.00104        | 1.017 (1.019–1.015)   | <0.0001 |
| Duration between diagnosis and enrollment into program (months) | 0.00434 | 0.00040 | 1.004 (1.005–1.004) | <0.0001 |
| Enrollment year                  | -0.03529           | 0.00562        | 0.965 (0.976–0.955)   | <0.0001 |
| Sex (males vs females)           | 0.08732            | 0.03117        | 1.070 (1.137–1.006)   | 0.0308  |
| Disease phase at diagnosis (accelerated vs chronic) | 0.96526 | 0.04329 | 2.625 (2.958–2.412) | <0.0001 |
| Disease phase at diagnosis (blast vs chronic) | 2.13341 | 0.04128 | 8.444 (9.155–7.787) | <0.0001 |
five-, and seven-year survival rates of 95%, 91%, 89%, and 87% respectively which are similar to the survival rates in the main analysis.

4. Discussion

Our analysis showed a progressive linear increase in the number of new patients enrolled in GIPAP from 2001 to 2007 with a dip in 2008 [Fig. 1]. This dip in the linear trend of number of new enrollees in 2008 was because Chinese GIPAP patients left GIPAP program in 2008 to join the China patient assistance program.

Our study also found that the three and five-year survival of CML patients in GIPAP (92% and 90% respectively), unadjusted to patients’ prognosis at diagnosis, were similar to survival rates of CML patients on imatinib in other settings [19,20]. This shows that despite the limitations in providing cancer care in resource constrained settings in LMICs, GIPAP patients do as well as patients in high income countries. A 2005–2007 analysis of 13,568 GIPAP CML patients across 15 countries by Kanavos et al. [2] showed a minimum three years survival of 67% which is consistent with the survival rate in our sensitivity analysis [2]. While we calculated the “survival rate” in our main analysis, Kanavos et al. calculated the “minimum survival rate”, defined as the proportion of patients who were still active in GIPAP after three years. So patients who were lost to follow up, those who left GIPAP and were receiving imatinib through other sources or those who switched to other treatments options were regarded as “dead” for the purposes of calculating the minimum survival rate. Conversely, to calculate the survival rate, our event of interest was patients who were confirmed as dead and we made adjustments in the Kaplan-Meier survival analysis for those patients who had not died by the time they left GIPAP for any reason.

The survival of GIST patients in our study, though less than that of CML patients, was similar to the survival of patients with operable GIST who received imatinib post-surgery [21]. However, the survival was higher than the five year survival rate of 55% seen in patients diagnosed with advanced GIST who are more similar to GIST patients in GIPAP in a previous study [22]. One reason for this disparity might be due to the small sample size (147 patients) in the earlier study.

Furthermore, we observed that for each year increase in the year of enrollment, the risk of death in CML patients decreased by 3.5% after adjusting for CML phase at diagnosis, age at enrollment into GIPAP, and time between diagnosis and enrollment into GIPAP, meaning that those enrolled in the later years of the program had a better survival rate. This improvement in survival might be due to physicians improved experience with the use of imatinib and better monitoring and supportive care of GIPAP patients. The roll out of GIPAP was observed to have catalyzed the improvement of health care infrastructure and local resources needed to diagnose, monitor, and support patients in the countries where GIPAP operated [1]. The important role of The Max Foundation in monitoring and providing support to patients, caregivers and physicians cannot be underestimated.

We found that the risk of death from CML was slightly higher in males than females. This is consistent with other studies that have identified the female gender as a favorable prognostic factor in CML survival [23–25]. The reason for the improved CML survival in women is uncertain [26]. In our study, age at diagnosis, which could affect survival, were similar for males (40 years) and females (41.5 years). We do not have data on patient’s medication compliance and whether it was different for males and females which if different might explain the difference in survival. However, improved female gender survival has also been reported for some other hematological cancers such as acute myeloid leukemia [27] and acute lymphoblastic leukemia [28,29].

Additionally, our study showed that younger patients survived better than older ones. This is consistent with other studies that have shown that younger CML patients have better prognosis than older ones [30]. Old age was a major prognostic factor for CML survival prior to the introduction of imatinib but now, age only has marginal significance on survival and mainly with very old patients [31].

We estimated that the five-year potential number of CML patients saved by GIPAP is 17,107. We believe the estimated number of patients saved is a conservative estimate of the potential number of lives saved by the GIPAP program for two reasons. First, the baseline data of CML survival rate prior to the introduction of imatinib used in our calculation was from a high-income country. We expect that the baseline survival in the LMICs where GIPAP operates would be lower than what we used in our calculation. Second, the patients in GIPAP are poor patients who cannot pay for treatment privately and who do not benefit from any reimbursement or insurance scheme [12]. These are patients who without GIPAP might not be able to afford alternative cancer medications and so might have a far lower survival rate without GIPAP.

Our sensitivity analyses without data from India and China (both countries contributed about 50% of GIPAP patients), showed similar survival rates to the main analyses. This means that the survival of GIPAP patients in China and India were similar to those in the other 91 countries. This makes us to believe that the survival rate of GIPAP patients in this study can be generalized to other LMICs not included in the 93 countries if the programs are implemented in a similar fashion.

Although GIPAP has saved lives, one challenge of donation programs like GIPAP is program sustainability. Currently, it is recommended that patients on imatinib should continue indefinitely and this causes sustainability challenges [19]. To maintain sustainability, Novartis in 2009 started the NOA in countries with a growing middle class to provide imatinib at reduced prices to patients [1]. Under NOA, Novartis shares the cost of imatinib with the government (as in China), other payers, or individual patients (as in India and Philippines). In 2017, Novartis and The Max Foundation initiated the transition of the GIPAP program to CMLPath to Care™ a model where Novartis supports The Max Foundation with product donations and funding, and The Max Foundation independently distributes donations to qualified institutions for approved patients under the umbrella of its Max Access Solutions. CMLPath to Care continues to provide access to imatinib to qualified patients in 65 countries and additionally provides donations of nilotinib to qualifying patients in 39 countries as of December 2018. This new collaboration model has allowed The Max Foundation to open the partnership to other manufacturers, makers of tyrosine kinase inhibitors (TKIs) and other oral cancer medications. In 2017 Pfizer, Bristol-Myers Squibb, Takeda and Incyte had established similar collaborations with The Max Foundation under the umbrella of Max Access Solutions making available eight compounds, three of which provide second and third line treatments for CML, two provide first and second line for GIST, and others

| Table 5 |
| --- |
| Sensitivity analysis based on assumption that all the cases lost to follow-up died at the time they were lost to follow-up. |
| Number at risk: all patients | Survival rate: all patients (95% CI) | Number at risk: CML patients | Survival rate: CML patients (95% CI) | Number at risk: non-CML patients | Survival rate: non-CML patients (95% CI) |
| One year (12 months) | 47,605 | 90.05% (89.80–90.30) | 41,682 | 90.15% (89.89–90.41) | 6013 | 89.52% (88.85–90.19) |
| Three year (36 months) | 28,168 | 76.90% (76.52–77.28) | 25,825 | 77.31% (76.93–77.73) | 2343 | 73.26% (72.08–74.50) |
| Five year (60 months) | 16,940 | 66.55% (66.08–67.02) | 15,910 | 67.35% (66.86–67.84) | 1030 | 58.21% (56.48–59.94) |
| Seven year (84 months) | 9025 | 57.44% (56.88–58.00) | 8626 | 58.48% (57.89–59.07) | 399 | 45.21% (43.01–47.41) |
support patients with renal cell carcinoma, and AKL positive lung cancer. As one of the benefits of the new model, at the end of 2017, partner clinicians in 25 countries were able to prescribe and have access to all TKIs approved elsewhere for the treatment of CML.

It is important to note that there are limitations in this study. First, the data used for this analysis were routine program data that was not collected for the purposes of program evaluation and so there are gaps in the data such as absence of certain clinical and socio-demographic data of patients which limited the extent of the analysis. Secondly, there was no follow-up survival data for patients who left GIPAP for any reason such as those who transferred to other patient assistance programs. However, we dealt with this limitation by modeling time contributed by patients that were lost to follow up as censored data in the Kaplan–Meier model. Thirdly, in calculating the number of lives saved through GIPAP we assumed that all the patients receiving care through GIPAP would not have had access to imatinib in the absence of the program. Although this assumption might not be true for every single patient, we believe that for almost all patients this assumption is true because patients were enrolled into GIPAP only if they were not insured, not reimbursed, or could not pay for the treatment privately and were in countries that have minimal reimbursement capabilities.

Finally, we do not have information about the prognostic scores of GIPAP patients, such as Sokal risk score, at diagnosis [32,33]. Without adjusting for the prognosis of the patients at diagnosis, comparing the survival of GIPAP patients with survival of patients from high income countries becomes challenging. Considering that the median age of GIPAP patients at initiation of treatment (41 years) was lower than those seen in high income countries would place GIPAP patients at a lower risk score with better prognosis. In the absence of a prognostic score at diagnosis, the best conclusion we can make from our study is that the survival of GIPAP patients is excellent, and unadjusted for patients’ prognosis at time of diagnosis, compares favorably to survival in high income countries.

5. Conclusions

Glivec International Patient Assistance Program (GIPAP) has implemented a direct-to-patient drug donation model overseen by patients’ oncologists. The program outputs are about 63,000 patients in 93 countries who received over 71 million defined daily doses of imatinib between 2001 and 2014. The impact of the program on survival showed a 5-year survival rate of 89 percent which is excellent, and unadjusted for patients’ prognosis at time of diagnosis, compares favorably to survival in high income countries despite the challenges of delivering cancer care in LMICs.

Declaration of Competing Interest

David Tremblay works for Novartis Pharma AG and Pat Garcia-Gonzalez works for The Max Foundation. The Glivec International Patient Assistance Program (GIPAP) was established by Novartis Pharma AG and implemented in partnership with The Max Foundation.

Acknowledgments

We wish to thank Dr. Veronika Wirtz, Dr. Peter Rockers and Dr. Jerald Radich for reviewing the manuscript and providing very useful feedback. We also wish to thank Michael Wriggins for extracting the GIPAP data from The Max Foundation database.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100257.

References

[1] Garcia-Gonzalez P, Boulbee P, Epstein D. Novel humanitarian aid program: the glivec international patient assistance program—lessons learned from providing access to breakthrough targeted oncology treatment in low-and-middle-income countries. J Glob Oncol 2015;1(6):150–5.
[2] Kanavos P, Vardaros S, Garcia-Gonzalez P. Benefits of global partnerships to facilitate access to medicines in developing countries: a multi-country analysis of patients and patient outcomes in GIPAP. Glob Health 2020;16(1):19.
[3] Reed SD, A astrom KL, Ludmer JA, Gledening GA, Schulman KA. Cost-effectiveness of imatinib versus interferon-α plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia. Cancer 2004;101(11):2574–83.
[4] Heilmann R, Heimpel H, Hasford JF, Kolb HJ, Pralle H, Hossfeld DK, Queisser W, Loffler H, Hochhaus A, Heinze B. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukaemia. The German CML-Study Group. Blood 1994;84(12):4064–76.
[5] Gambacorti-Passerini C, Antolini L, Mahon FX, Guilhot F, Deininger M, Fava C, Nagler A, Delia Casa CM, Morra E, Abbruzzese E, D’Emilio A. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with IMATINIB. J Natl Cancer Inst 2011;103(5):553–61.
[6] Bjorkholm M, Ohn L, Eloranta S, Derolf Á, Hultcrantz M, Sjöberg J, Andersson T, Höglund M, Richter J, Landgren O, Kristinson SS. Success story of targeted therapy in chronic myeloid leukaemia: a population-based study of patients diagnosed in Sweden from 1973 to 2008. J Clin Oncol 2011;29(18):2514–20.
[7] Kantarjian HM, Talpaz M, O’Brien S, Jones D, Giles F, Garcia-Manero G, Faderl S, Ravandi F, Rios MB, Shan J, Cortes J. Survival benefit with imatinib mesylate versus interferon-α-based regimens in newly diagnosed chronic-phase chronic myelogenous leukemia. Blood 2006;108(6):1833–40.
[8] Dalziel K, Round A, Stein K, Garside R, Price A. Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. 2004. In: Proceedings of the National Health Technology Assessment Conference programme: Executive Summaries. Southampton (UK): NIHR Journals Library; 2003–. Accessed June 8, 2017 from: https://www.ncbi.nlm.nih.gov/books/NBK622271/.
[9] Tekinturhan E, Audureau E, Tavolacci MP, Garcia-Gonzalez P, Ladner J, Saba J. Improving access to care in low and middle-income countries: institutional factors related to enrollment and patient outcome in a cancer drug access program. BMC Health Serv Res 2013;13(1):304.
[10] Mellstedt H. Cancer initiatives in developing countries. Ann Oncol 2006;17(Suppl 3):v52–54.
[11] Novartis. Novartis oncology access. Accessed June 2, 2017 from https://www.novartis.com/about-us/corporate-responsibility/expanding-access-healthcare/oncology-patient-assistance-programs.
[12] The Max Foundation. Glivec international patient assistance program (GIPAP). Accessed June 2, 2017 from https://www.thenaefoundation.org/what/treatment/glivec-international-patient-assistance-program-gipap/.
[13] IPMA. Access accelerated initiative. Accessed June 8, 2017 from http://partnerships.ipema.org/partnership/access-accelerated-initiative.
[14] Axios International. Accessed September 22, 2017 from https://axiosint.com/#/home2
[15] Mendizabal AM, Garcia-Gonzalez P, Levine PH. Regional variations in age at diagnosis and overall survival among patients with chronic myeloid leukemia from low and middle income countries. Cancer Epidemiol 2013;37(3):247–54.
[16] BUSPH metrics framework. Accessed September 22, 2017 from http://sites.bsu.edu/evaluatingaccess-accessaccelerated/bushph-metrics-framework/.
[17] Access Accelerated. Access accelerated. Accessed September 22, 2017 from http://www.accessexcelerated.org/about/.
[18] World Health Organization. ATC/DDD index. Accessed September 22, 2017 from https://www.whocc.no/atc_ddd_index/.
[19] Drucker BJ, Guilhot F, O’Brien SG, Gathmann I, Kantarjian H, Gattermann N, Deininger MW, Silver RT, Goldman JM, Stone RM, Cervantes F. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355(23):2408–17.
[20] Roy L, Guilhot J, Krahne T, Guerci-Bresleri A, Drucker BJ, Larson RA, O’Brien S, Scully M, Massimini G, Guilhot F. Survival advantage from imatinib compared with the combination interferon-α plus cytarabine in chronic-phase chronic myelogenous leukaemia: historical comparison between two phase 3 trials. Blood 2006;108(5):1478–94.
[21] Joensuu H, Eriksson M, Hall KS, Hartmann JT, Pink D, Schütte J, Ramadori G, Hohenberger P, Duytsjer J, Ab-Batan SE, Schiemmer M. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307(12):1265–72.
[22] Blanke CD, Demetri GD, Von Mehren M, Heimdal K, Heinz P, Wehre E. Long-term results from a randomized phase 3 trial of standard-versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing Kit. J Clin Oncol 2008;26(4):620–5.
[23] Berger U, Maywald O, Pfeiffer M, Lahaye T, Hochhaus A, Reiter A, Hasford J, Heimpel H, Hossfeld DK, Kolb UJ, Loffler H. Gender aspects in chronic myeloid leukemia: long-term results from randomized studies. Leukemia 2005;19(6):598.
[24] Sokal JE, Baccarani M, Tura S, Fiacchini M, Cervantes F, Rozman C, Gomez GA, Galton DA, Canellos GP, Braun TJ. Prognostic discrimination among younger patients with chronic granulocytic leukemia: relevance to bone marrow transplantation. Blood 1985;66(6):1352–7.
[25] Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol 2007;25(15):1993–9.

[26] Molica S. Sex differences in incidence and outcome of chronic lymphocytic leukemia patients. Leuk Lymphoma 2006;47(8):1477–80.

[27] Bennett JM, Young ML, Andersen JW, Cassileth PA, Tallman MS, Paietta E, Wiernik PH, Rowe JM. Long-term survival in acute myeloid leukemia: the eastern cooperative oncology group experience. Cancer: Interdiscip Int J Am Cancer Soci 1997;80(S11):2205–9.

[28] Chessells JM, Richards SM, Bailey CC, Lilleyman JS, Eden OB. Gender and treatment outcome in childhood lymphoblastic leukaemia: report from the mrc ukall trials. Br J Haematol 1995;89(2):364–72.

[29] Pui CH, Boyett JM, Belling MV, Harrison PL, Rivera GK, Behm FG, Sandlund JT, Ribeiro RC, Rubnitz JE, Gajjar A, Evans WE. Sex differences in prognosis for children with acute lymphoblastic leukemia. J Clin Oncol 1999;17(3):818.

[30] Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Klun-Nelemans JC, Alimena G, Steegmann JL, Ansari H. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa writing committee for the collaborative cml prognostic factors project group. JNCI J Natl Cancer Inst 1998;90(11):850–9.

[31] Kantarjian H, O’Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, Shan J, Rios MB, Ravandi F, Faderl S, Kadia T, Borthakur G. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood 2012;119(9):1981–7.

[32] Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Klun-Nelemans JC, Alimena G, Steegmann JL, Ansari H. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa writing committee for the collaborative cml prognostic factors project group. JNCI J Natl Cancer Inst 1998;90(11):850–9.

[33] Forrest DL, Trainor S, Brinkman RR, Barnett MJ, Hogge DE, Nevill TJ, Shepherd JD, Nantel SH, Toze CL, Sutherland HJ, Song KW. Cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia are correlated with sokal risk scores and duration of therapy but not trough IMATINIB plasma levels. Leuk Res 2009;33(2):271–5.