Similar outcome of patients with chronic myeloid leukemia treated with imatinib on or off clinical trials

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Abstract

Introduction—Outcomes of CML-CP patients treated in clinical trials are frequently perceived to not be representative of those treated outside of clinical trials.

Materials and Methods—We investigated the outcomes of patients receiving imatinib outside of a clinical trial (off protocol) or on a clinical trial (on protocol) for CML-CP.

Results—We identified 65 patients treated with imatinib off protocol and 71 patients treated on protocol with standard-dose imatinib. The overall complete cytogenetic response (CCyR) rates were 83% and 83% for patients treated on and off protocol, respectively. CCyR rates 12 months after initiation of imatinib were not different (61% vs 66%, respectively; p=.15). Patients treated off protocol had similar rates of overall major molecular response (72% vs 73%) compared to the patients treated on protocol. The 5-year event free survival rates were 84% and 86% for off and on protocol patients, respectively. There was also no significant difference in 5-year transformation free survival (94% vs 96%) and overall survival (96% vs 90%).

Conclusion—These results suggest that patients with CML treated outside of a clinical trial may have the same excellent outcome as those treated on a clinical trial provided they are followed with the same rigor.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of hematopoietic stem cells, which accounts for 15% of adult leukemias[1]. Reciprocal translocation between long arms of chromosomes 9 and 22 results in formation of Philadelphia (Ph) chromosome that produces *BCR-ABL* fusion gene[2]. *BCR-ABL* gives rise to a chimeric protein, p210[BCR-ABL], with constitutive activation of tyrosine kinase activity, responsible for leukemogenesis[34].

For nearly 20 years, allogeneic stem cell transplantation (allo-SCT) or interferon-alpha (IFN-α)-based regimens were the mainstay of therapy for patients with chronic phase (CP)

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Disclosure of Conflicts of Interest

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CML[4]. At the end of the 1990s, imatinib (STI571), a selective *BCR-ABL* tyrosine kinase inhibitor (TKI), was initially used for CML patients who were resistant or intolerant to treatment with IFN- ☐ with excellent results achieved in patients treated after IFN- ☐ failure[5]. This led to a large multinational clinical trial, called IRIS (International Randomized Study of IFN- ☐ plus cytarabine (Ara-C) vs STI571), which randomized newly diagnosed patients with CML-CP to receive either imatinib or IFN- ☐ plus Ara-C. Imatinib was clearly superior with higher rates of complete cytogenetic response (CCyR) (76% vs 15%) and major cytogenetic response (MCyR) (87% vs 35%) at 18 months, and lower incidence of transformation to blast phase (BP) or accelerated phase (AP)[6]. Consequently, the United States Food and Drug Administration approved imatinib as the frontline therapy for patients with CML-CP. However, outcomes of CML-CP patients treated in clinical trials are frequently perceived not be representative of those treated outside of clinical trials. The latter is often referred to as "the real world" experience. Some reports have suggested that patients treated outside of clinical trials have inferior outcome[7].

Herein, we present follow-up results for 65 patients with CML-CP that treated outside of a clinical trial, and 71 patients treated on clinical trials. The objectives of this study were to compare the incidence and durability of molecular and cytogenetic responses, and determine the prognosis of CML-CP patients receiving imatinib outside of a clinical trial or on a clinical trial at a single institution.

Material and Methods

Study Group

We reviewed the medical records of all patients with CML-CP treated at The University of Texas MD Anderson Cancer Center between 2000 and 2012 to identify patients that received initial therapy with imatinib 400 mg on a clinical trial or as standard therapy outside of a clinical trial ("off protocol" group). All patients treated off protocol with 400 mg imatinib and followed at MDACC, regardless of their compliance, age, comorbidities or minimum follow-up duration, were included in this analysis. We evaluated both groups of patients ("off protocol" and "on protocol") for the following variables: age, gender, race, time interval from diagnosis to treatment, Sokal relative risk scores[8], molecular and cytogenetic analysis at 3, 6, 12, 18 months and last follow up, reason of imatinib discontinuation, transformation to AP or BP while on imatinib, loss of complete hematologic response (CHR), loss of MCyR, mortality, and cause of death. Only patients who had not received any prior therapy, or only hydroxyurea or IFN- ☐ for less than 1 month, and that initiated on 400 mg daily dose of imatinib within 6 months of diagnosis were included. Patients on the off protocol cohort could have initiated imatinib therapy before their initial visit to MD Anderson Cancer Center. We also included patients' socioeconomic characteristics into our investigation, such as median annual household income, level of education, and health insurance status. Median income data was obtained from United States Census Bureau based on the median household income by zip code. Patients' zip code information, data regarding health insurance status and level of education were obtained from initial patient history database. The study was approved by the Institutional Review Board of the MD Anderson Cancer Center with a waiver of informed consent granted.

Response Criteria

CHR required normalization of peripheral blood counts with leukocyte count $<10\times10^9$/liter, platelet count $<450\times10^9$/liter, and no immature cells such as myelocytes, promyelocytes or blasts in the peripheral, and no signs or symptoms of disease with disappearance of palpable splenomegaly. Real-time Quantitative Polymerase Chain Reaction (PCR) was used to

measure *BCR-ABL* transcripts. Molecular response was categorized as follows: no molecular response (*BCR-ABL/ABL* transcript ratio >0.1% (international scale (IS)), major molecular response (MMR) (*BCR-ABL/ABL* transcript ratio ≤0.1% (IS)), and complete molecular response (CMR) (*BCR-ABL/ABL* undetectable with minimal sensitivity of 4.5-log). Conventional cytogenetic analysis was performed by G-banding in bone marrow cells with a minimum of 20 metaphases analyzed. Cytogenetic response was categorized as follows: minor cytogenetic response (Ph Chromosome positive metaphases >35%), partial cytogenetic response (Ph Chromosome positive metaphases between 1–35%), MCyR (Ph Chromosome positive metaphases between 0–35%), and complete cytogenetic response (CCyR) (0% Ph Chromosome positive metaphases)[9].

Statistical Analysis

We evaluated the differences in subgroups by using chi-square test. For the intention-to-treat (ITT) analysis, all patients are included in the denominator, and all patients with no documented response (whether with documented lack of response or with no available sample) were considered as failure. We estimated survival probabilities by the Kaplan-Meier method, and compared differences by using the log-rank test. Event-free survival (EFS) was measured from the start of treatment to the date of any of the following events: loss of MCyR, loss of CHR, transformation to AP and BP, and death while on imatinib. Transformation-free survival (TFS) was measured from the start of treatment to the date of progression to AP/BP during therapy, last follow-up, or death from any cause. Overall survival (OS) was measured until death form any cause at any time.

Results

Patients

We identified 65 patients treated with imatinib off protocol and 71 patients treated on protocol (total 136 patients) during the period of interest. Twenty-six of 65 off protocol patients (40%) initiated imatinib in outside facilities, and their median follow up time prior to presentation to our institution was 5 months (range 1–16 months). Their characteristics are summarized in table 1. Median age at the time of CML diagnosis was 49 years in both groups, and male to female ratios were similar. Median time elapsed from diagnosis to initiation of imatinib treatment was 17 and 48 days for off protocol and on protocol groups, respectively. Sokal risk group was calculated in all patients treated on protocol, but some of the information required to calculate Sokal score was not available for 10% of the off protocol patients who had started therapy before their initial visit at MD Anderson Cancer Center. Median follow-up time was significantly longer (125 months vs 51 months) in patients treated on a clinical trial since all on protocol patients started imatinib therapy in the year 2000 while off protocol patients started imatinib after that date.

Response

Overall rates of CCyR were the same (83%) for both the off and on protocol groups (Table 2). Analyzing earlier responses, 3-month rates of MCyR were 46% for the off protocol group and 68% for the on protocol group (p=0.925) (Figure 1A). There was also no significant difference in CCyR rates at 12 months from start of imatinib therapy (66% vs 60%, respectively, p=0.150) (Figure 1B). The overall rates of MMR were similar for the off protocol and the on protocol groups (72% vs 73%, p=0.474) at any time compared to the patients treated on protocol. MMR rates at 18 months were 54% and 51%, respectively for patients treated off or on protocol (p=0.948) (Figure 1C). There was also no difference in the overall rate of CMR (32% and 39%, respectively; p=0.258).

We then compared the off and on protocol groups by performing ITT analysis. This showed no statistical difference in the rate of overall CHR (p=0.337), CCyR (p=0.997), MMR (p=0.903) and CMR (p=0.387) between off and on protocol groups. However, analyzing 3 and 6 months MCyR, on protocol patients had a better response (p=0.012 and p=0.006, respectively) (Table 3). This is due to a significant number of patient in the off protocol group, 23 patients (36%) and 22 patients (34%) at 3 and 6 month, respectively, who had no available data at the given times. In contrast, only 4 patients (6%) were considered as non-evaluable by 6 months in on protocol group (all due to discontinuation of imatinib). However, CCyR rates at 12 (p=0.499) and 18 months (p=0.513) were similar between the two groups.

Molecular response analysis at early time points was not part of routine evaluation for on protocol patients in early 2000s. For that reason, 29 patients (41%) in on protocol group were non-evaluable for MMR at 12 months, compared to 10 patients (16%) in off protocol group. At this time, ITT analysis showed better MMR rates at 12 months for off protocol group (p=0.018). However, at 18 months it did not show any MMR difference between groups (p=0.714).

Patient Disposition

At the time of last follow-up, 71% and 64% of the off and on protocol patients were still on imatinib, respectively. Among 65 patients treated off protocol, 19 patients (29%) discontinued imatinib: 8 for progressive CML, 10 because of adverse events (3 for skin rash, 2 for diarrhea, 2 for nausea, and 1 each for dizziness, muscle pain, and seizures). One patient in the off protocol group stopped imatinib to receive an allo-SCT despite being in CCyR. Among the 71 patients treated on protocol, 25 patients (36%) discontinued imatinib including 16 who discontinued because of progressive CML, 6 who discontinued therapy because of adverse events (3 with liver toxicity, 1 each for papilledema and nausea, and 1 for renal failure), 2 patients were not compliant and 1 patient elected not to receive any further therapy for CML.

Events and Survival

In the off protocol group, 4 (6%) patients lost MCyR, 3 (5%) transformed to AP (n=2) or BP (n=1), and 1 (2%) lost CHR. In the on protocol group, 12 patients (17%) lost MCyR and 4 (6%) transformed to BP. No patient died while on imatinib in either group. The 5-year EFS rates were 84% and 86% for off and on protocol patients, respectively (Table 4). There was no significant difference in 5-year TFS (94% vs 96%) and OS (96% vs 90%). Kaplan-Meier estimation of TFS, EFS and OS did not show any survival difference among off and on protocol patients (Figure 2A–2C). The causes of death for both groups included blast phase in 4 patients (n=4), and renal failure, gastrointestinal bleeding, acute myeloid leukemia, subdural hematoma, bowel perforation, and cardiac arrest, one patient each. The cause of death was not known for 6 patients.

Socioeconomic status

To determine whether patients treated in this series were comparable among groups and to the general US population, we investigated some socioeconomic characteristics. Since 80% of the study cohort (109 of 136 patients) presented to MD Anderson Cancer Center between the years 2000–2005, we obtained U.S. demographic information from the US Census Bureau for the year 2000. As shown in table 5, there was no significant difference in median income between both groups. The income for both groups was also similar to the median annual household income for the US ($42,148)[10]. Among the 136 patients treated, 113 (83%) reported their highest level of education obtained and 23 (17%) patients elected not to respond. Among the 113 patients who responded, 58% stated they had achieved at least

some college education, while the remaining 42% stated their highest degree was high school or lower. These rates were similar for patients in the off protocol and on protocol cohorts, and representative of the US general population. According to the US Census Bureau questionnaire, 52% of Americans reported their highest level of educational as some college or more. We also looked at the insurance coverage: 9% of our study group (12 of 136 patients) had no insurance coverage, which is similar to the general US population (14%).

Discussion

Despite the excellent outcome achieved by most patients with CML treated with tyrosine kinase inhibitors as initial therapy, some reports have suggested that the outcome of patients treated in clinical trials is not representative of the general population, or what some groups call "the real world" experience". In a population-based study, 49% of CML patients were reported as resistant or intolerant to imatinib at 24 months, and CCyR rates were 41% and 49% at 12 and 18 months, respectively. Authors compared their results with several imatinib clinical trials, including IRIS[10] (CCyR were 69% and 76% at 12 and 18 months, respectively), and it was concluded that imatinib may have lower efficacy in CML patients treated in community hospitals comparing to the results reported in clinical trials[7]. Other studies have reported outcomes of CML patients treated outside of a clinical trial[11–13]. Zackova et al. studied 152 CML-CP patients treated frontline with imatinib, and reported 4 year cumulative incidence of CHR and CCyR as 95.3% and 80.6%, respectively. The 4 year OS and PFS was 91.5% and 78.1%, respectively[13]. De Lavallade et al. also reported similar excellent outcomes of CML patients treated outside of a clinical trial (5 year cumulative CHR: 98.5%, CCyR: 82.7%, 5 year OS: 83.2%, PFS: 82.7%)[11].These results suggests similar outcomes as observed in IRIS trial or clinical trial in our institution[6,14]. In this report, we show that patients treated off or on clinical studies at MD Anderson Cancer Center have similar excellent outcome. These findings suggest that other factors besides management in a clinical trial might be responsible for the inferior outcome observed in some settings.

According to the national comprehensive cancer network guidelines, newly diagnosed CML-CP patients, at least, need to be evaluated for hematologic, cytogenetic and molecular responses at 3, 6 and 12 months after initiation of treatment, and that may be spaced out to every 6 months until 2 years, than yearly once they achieved stable CCyR and MMR[15]. The European Leukemia Net also recommends frequent monitoring, every 3 months until MMR is achieved and then every 6 months[16]. Appropriate monitoring of response to TKIs is critical in the management of CML patients to determine adequate response to therapy. Moreover, by monitoring properly, oncologist can detect resistant cases early, and intervene accordingly before it transforms into AP or BP and ultimately puts the patient's life in danger. Furthermore, variations in transcript levels that might suggest poor adherence to therapy can be identified and trigger patient reeducation. However, it should be recognized that there is no direct proof in our or other series that the precise timing of monitoring alters outcome in a significant number of patients. Equally as important (or more) is to minimize unnecessary dose reductions and treatment interruptions as dose intensity has been shown to correlate with favorable outcome[17]. In one recent study, authors reported significant under-monitoring of treatment response of CML-CP patients in community setting[18]. They reviewed 177 CML patients' charts, and reported decreased cytogenetic analysis over time, for those who had not achieved CCyR, from 29% at 3 months to 17% at 18 months. Among 73 patients not achieving CMR or MMR by 18 months, there was a subsequent follow-up molecular monitoring test within 6 months for only 53 (70%) patients. In that study, no progressive disease was reported among the patients followed as recommended within the first year, compared to 12% with progression among the patients not monitored per

established guidelines[15,16]. In our study group, 56 of 65 off protocol patients and 64 of 71 on protocol patients received imatinib for at least one year, and had a minimum of 3 cytogenetic and/or molecular testing performed within the first year of treatment initiation. This data suggests that at least some of the differences in outcome observed in "the real world" may be related to suboptimal monitoring of patients.

One other possible explanation for the similar outcome of the patients treated off or on protocol at our institution is that these patients might be different in ways other than those that are evident by analyzing the disease characteristics and the treatment used. To investigate whether socioeconomic factors may make our population different, we analyzed these factors in the two populations studied and compared them to the US averages as reported by the US Census Bureau. We identified no significant differences in the level of education, the median household income or the percentage of uninsured patients between off or on protocol groups either comparing them among themselves or to the general US population. Importantly, the median income data of our study group was calculated by patients' zip code with publically available figures rather than through direct information from the patient. Thus, it represents median income of the neighborhood that patients live in. However, we believe that even this information may indicate that the income of CML patients, coming to our institution may not be majorly different from that of the general U.S. population. Evidently, these factors are not the only ones that may influence outcome. Factors such as the motivation of the patients, their level of proactivity in guarding their own health, adherence to therapy and others may be as important as the ones investigated. Unfortunately, it is difficult to measure such factors. But one should consider that it is at least equally as likely that other factors such as the aforementioned adherence to a strict monitoring schedule, minimization of dose reductions and treatment interruptions, patient education at start of therapy and with each patient visit, and regular follow-up between visits by phone or e-mail communication by a dedicated CML team to address concerns, questions and adverse event management, among other factors, may favorably influence the outcome of the patients treated off protocol.

Conclusion

We conclude that patients with CML treated outside the setting of a clinical trial, may enjoy the same excellent prognosis as those treated on clinical trials provided patients are followed with the same rigor by a dedicated CML team as they are when enrolled in study protocols. Adequate and continued patient education, strict adherence to monitoring and dosing recommendations, proper interpretation of the results and recognition of indications to change or not to change therapy, and minimization of unnecessary treatment interruptions or dose reductions may play an important role in providing the best possible outcome for patients treated outside of a clinical trial in the real world. It is possible that patients with access to specialized CML center may have a better outcome due to closer adherence to these rules. Further studies are needed to investigate outcomes of CML patients treated outside of specialized leukemia centers.

Acknowledgments

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Clinical Practice Points

- Excellent outcome achieved by most patients with CML treated with TKIs as initial therapy, yet some reports have suggested that the outcome of patients treated in clinical trials may not be representative of the general population.

- We report no statistical difference in CCyR, MMR, CMR, OS, EFS and PFS between CML patients being treated on a clinical trial or outside of a clinical trial.

- Adherence to a strict monitoring schedule, minimization of dose reductions and treatment interruptions, patient education at start of therapy and with each patient visit, and regular follow-up between visits are essential for the care of CML patients.

- CML patients treated outside of a clinical trial may have the same excellent outcome as those treated on a clinical trial provided they are followed with the same rigor.
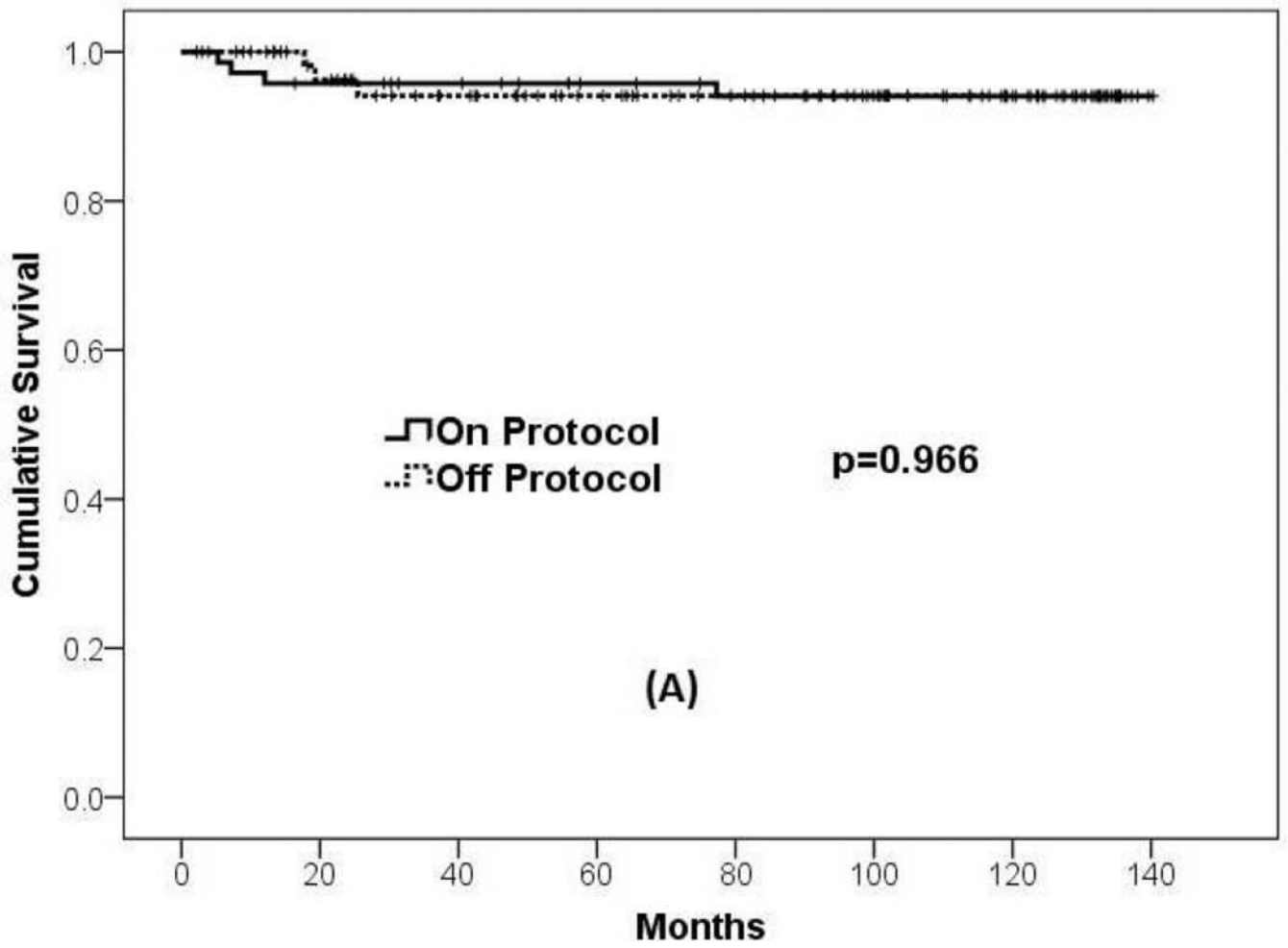
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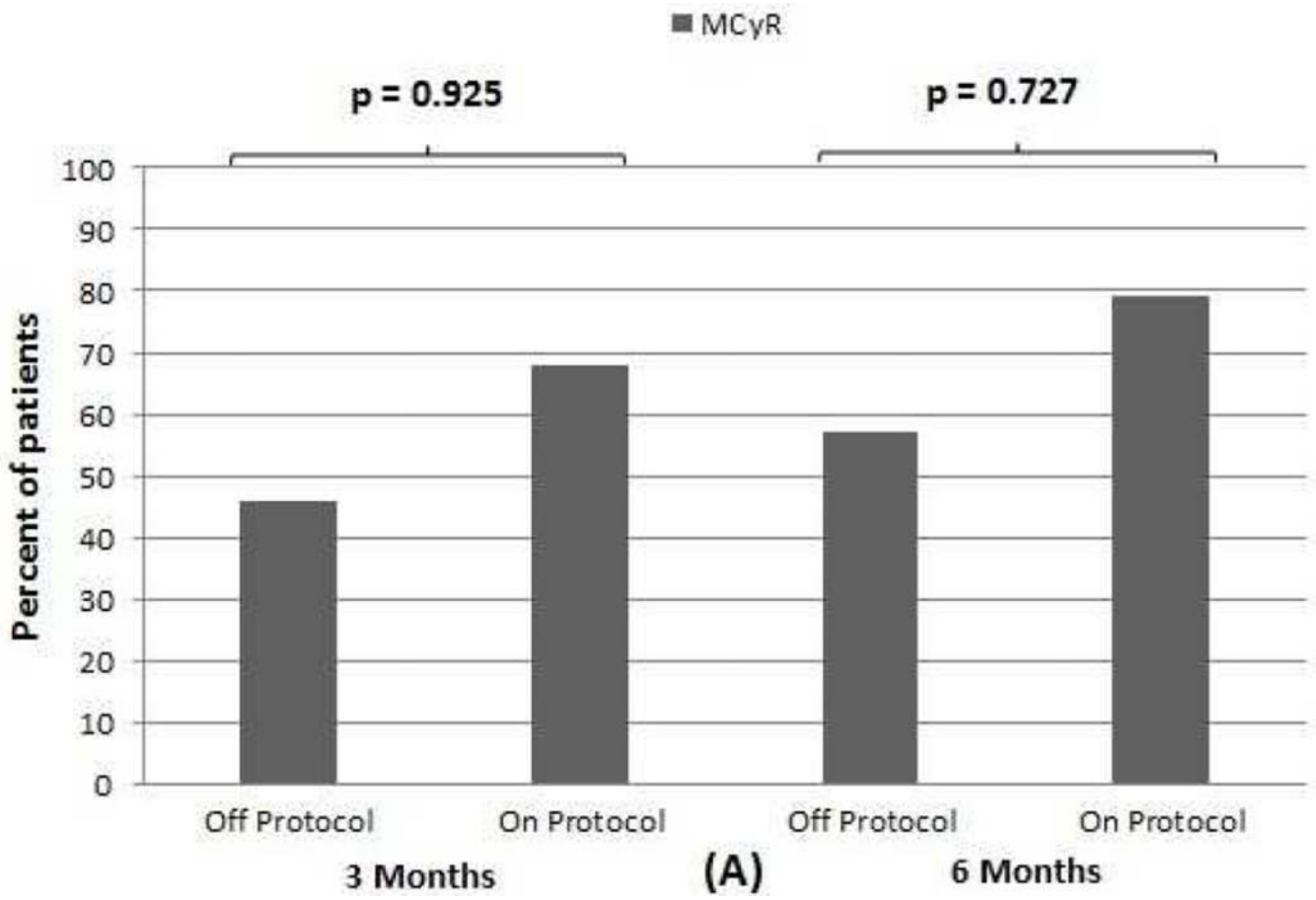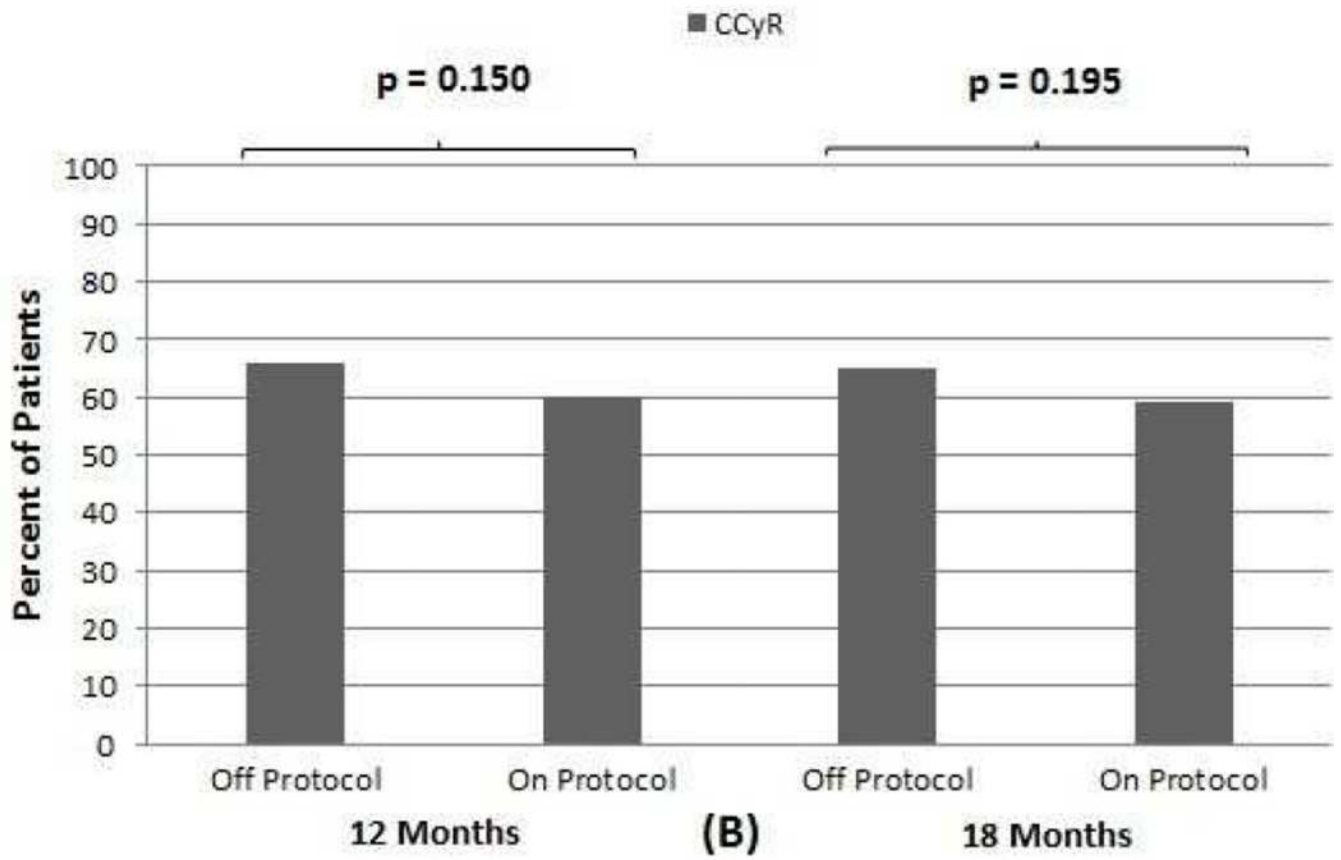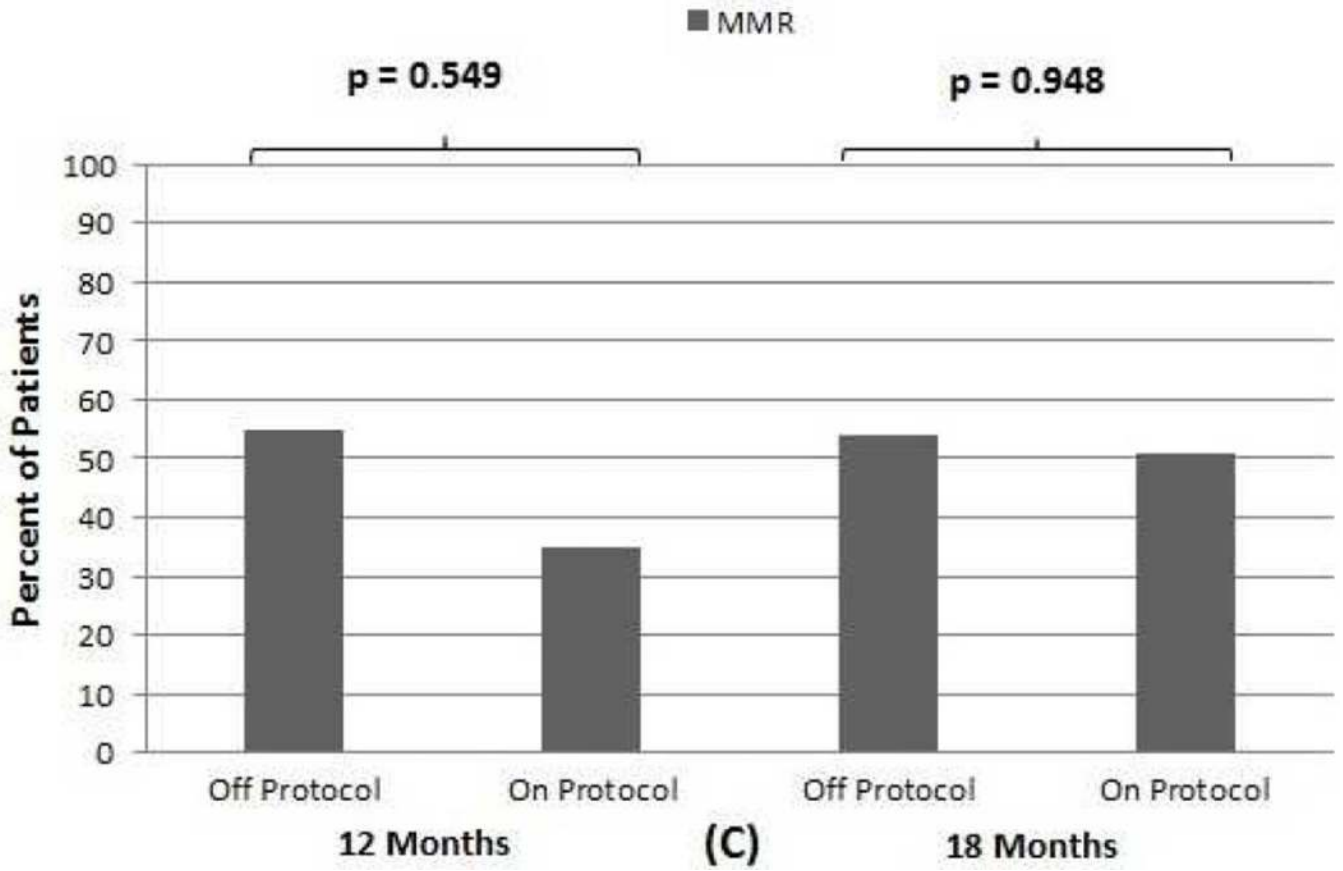
Figure 1.
Comparison of Major (A) and Complete (B) Cytogenetic Responses and Major Molecular Responses (C) among Evaluable Off or On Protocol Patients.
MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response

Cumulative Survival plot — On Protocol / Off Protocol, p=0.966 (A)
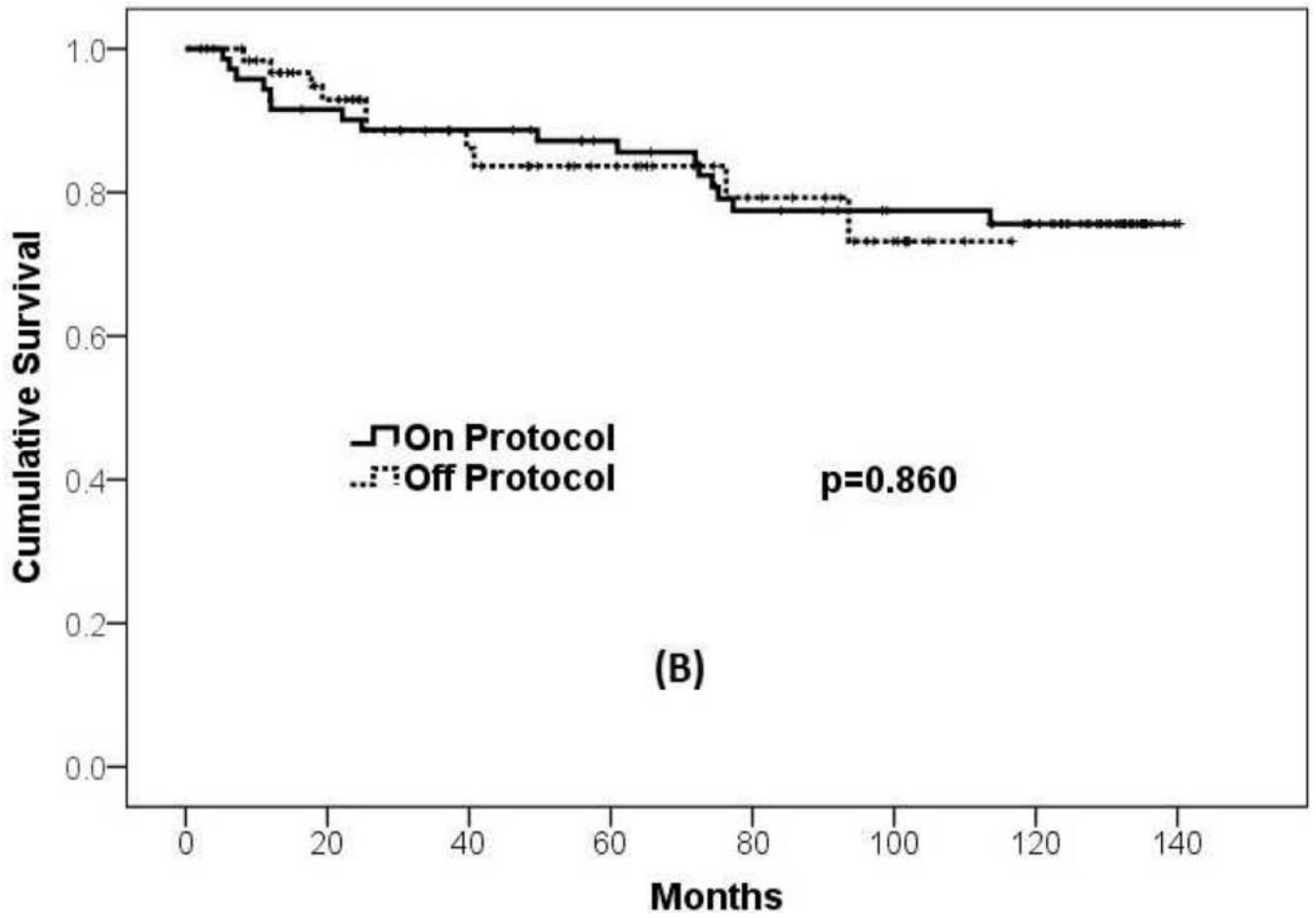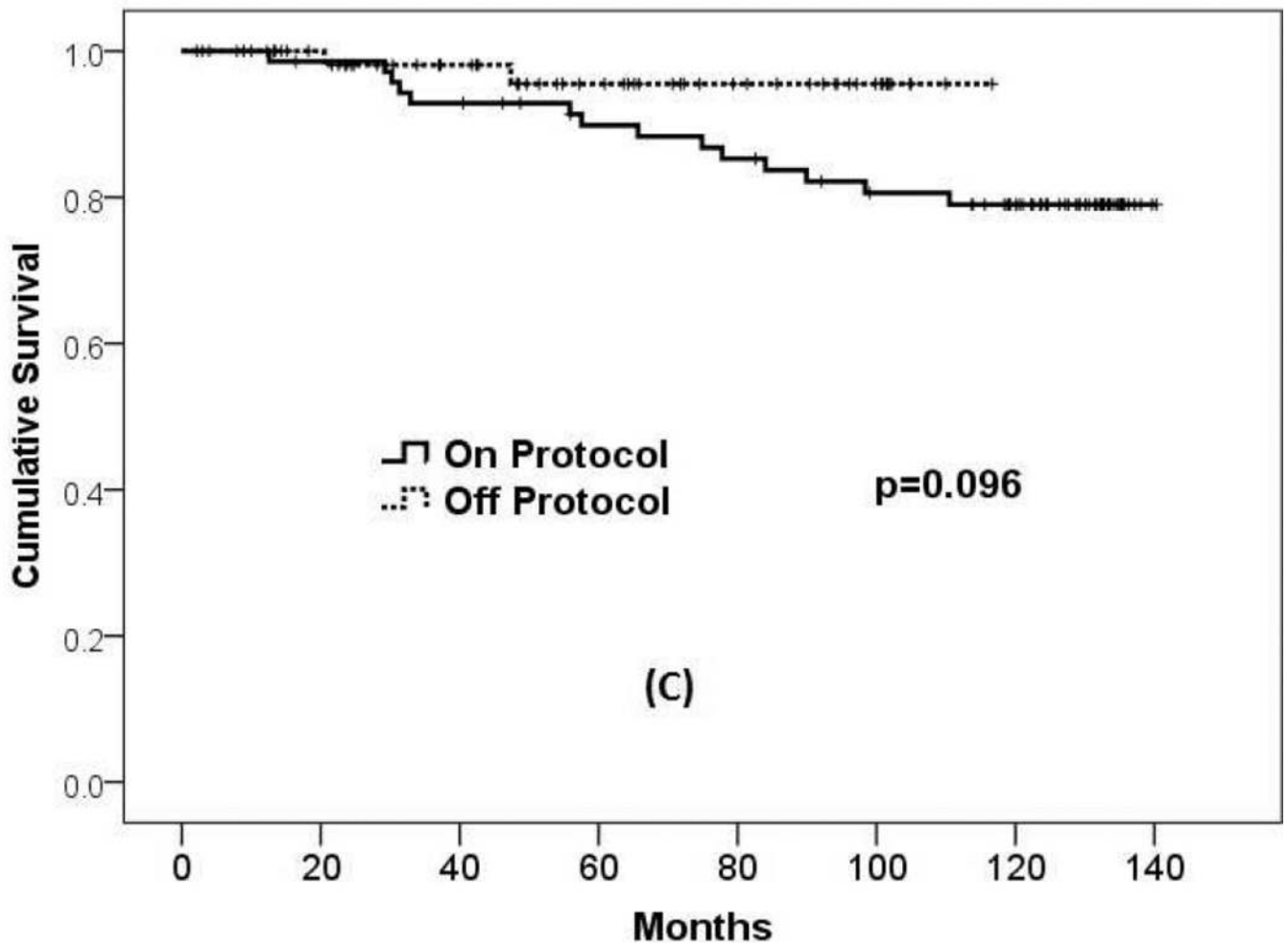
Figure 2.
Transformation Free Survival (A) Event Free Survival (B) Overall Survival (C) determined by Kaplan-Meier survival method.

Table 1

Clinical Characteristics of Patients

Characteristics	Off Protocol (n=65)	On Protocol (n=71)
Age		
Median, yr	49	49
Range, yr	15–84	15–79
≥60 yr, no. (%)	15 (23)	19 (27)
Gender, no. (%)		
Male	32 (49)	38 (54)
Female	33 (51)	33 (46)
Race, no. (%)		
White	47 (72)	55 (77)
Hispanic	12 (18)	7 (10)
African American	5 (8)	4 (6)
Other	1 (2)	5 (7)
Peripheral Blood		
Median WBC count, $\times 10^9$/L (range)	84 (3.2 – 513)	21 (1.6 – 277)
Median Hemoglobin, g/dL (range)	13(6.2 – 16)	13 (8 – 16)
Median Platelet count, $\times 10^9$/L (range)	400 (122 – 1316)	367 (103 – 1043)
Median Blasts, % (range)	0 (0 –9)	0 (0 – 2)
Median Basophils, % (range)	2 (0 – 12.4)	3 (0 – 16)
Bone Marrow		
Median Blasts, % (range)	2 (0 – 8)	1 (0 – 6)
Median Basophils, % (range)	3 (0 – 15)	2 (0 – 9)
Splenomegaly, no. (%)	21 (32)	15 (21)
Cytogenetic Clonal Evolution, no (%)	3 (4)	0 (0)
Median Interval since Diagnosis, days (range)	17 (0 – 226)	48 (0 – 377)
Sokal Risk Group, no. (%)		
Total Evaluated	58 (90)	71 (100)
Low	26 (45)	46 (64)
Intermediate	26 (45)	21 (30)
High	6 (10)	4 (6)
Median Follow Up, months (range)	51 (2 – 117)	125 (13 – 142)

Table 2

Response Rates of Evaluable Patients Treated Off or On Clinical Trials

Overall Response	No. of Patients (%)		p value
	Off Protocol	On Protocol	
CHR	65 (100)	70 (99)	0.337
CCyR	54 (83)	59 (83)	0.700
MMR	47 (72)	52 (73)	0.474
MR^4	38 (58)	45 (63)	0.296
MR$^{4.5}$	34 (52)	38 (54)	0.610
CMR	21 (32)	28 (39)	0.258

CHR: complete hematologic response; CCyR: complete cytogenetic response; MMR: major molecular response; MR^4, BCR-ABL/ABL transcript ratio ≤0.01% international scale (IS); MR$^{4.5}$, BCR-ABL/ABL transcript ratio ≤0.0032% (IS) (or ≤0.0035% at MDACC); CMR: complete molecular response

Table 3

Intention to Treat Analysis of Cytogenetic and Molecular Reponses

Response	No. of Pts (%)		p value
	Off Protocol	**On Protocol**	
3 Months			
MCyR	30 (46)	48 (68)	
No MCyR	12 (18)	20 (28)	0.012
N/A	23 (36)	3 (4)	
6 Months			
MCyR	37 (57)	56 (79)	
No MCyR	6 (9)	11 (15)	0.006
N/A	22 (34)	4 (6)	
12 Months			
CCyR	43 (66)	43 (61)	
No CCyR	10 (15)	19 (27)	0.499
N/A	12 (19)	9 (13)	
18 Months			
CCyR	42 (65)	42 (59)	
No CCyR	8 (12)	15 (21)	0.513
N/A	15 (23)	14 (20)	
12 Months			
MMR	36 (55)	25 (35)	
No MMR	19 (29)	17 (24)	0.018
N/A	10 (16)	29 (41)	
18 Months			
MMR	35 (54)	36 (51)	
No MMR	15 (23)	15 (21)	0.714
N/A	15 (23)	20 (28)	

MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; N/A: no available cytogenetic or molecular data at specified time or patient is off of imatinib

Table 4

Long Term Outcome of Patients Treated Off or On Clinical Trials

Outcome	Off Protocol	On Protocol	p=value
OS (%)			
3 Years	98	93	0.13
5 Years	96	90	
EFS (%)			
3 Years	89	89	0.87
5 Years	84	86	
TFS (%)			
3 Years	94	96	0.97
5 Years	94	96	

OS: overall survival; EFS: event free survival; TFS: transformation free survival

Etiology of Death: Blast Crises and other comorbidities (n=4), renal failure (n=1), gastrointestinal bleeding (n=1), acute myeloid leukemia (n=1), subdural hematoma (n=1), bowel perforation (n=1), cardiac arrest (n=1), no information available regarding reason of death (n=6)

Table 5

Demographic Features of the Study Cohort and General U.S. Population

Demographics	Off Protocol (n=65)	On Protocol (n=71)	Off and On Protocol (n=136)	United States[f]
Health Insurance (%)				
Insured [*]	92	90	91	86
Uninsured	8	10	9	14
Educational Attainment (%)				
Any college level or more	57	58	58	52
High School or less	43	42	42	48
Median Household Income - $				
Annual[¥]	44,606	45,735	45,203	42,148

[f] Data regarding insurance status, educational attainment and median household income of the general U.S population obtained from United States Census Bureau, American Fact Finder, year 2000

[*] Any type of health insurance coverage

[¥] Based on the median household income by zip code