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The Clinical Significance of Achieving Different Levels of Cytogenetic Response in Patients with Chronic Phase Chronic Myeloid Leukemia After Failure to Frontline Therapy: Is Complete Cytogenetic Response the Only Desirable Endpoint?

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Abstract

Background—Complete cytogenetic response (CCyR) is the gold standard for response to therapy for patients with chronic myeloid leukemia (CML) because it is associated with a survival benefit. However, patients who have failed initial therapy with a tyrosine kinase inhibitor (TKI) frequently achieve only partial or minor cytogenetic responses. The clinical benefit of such responses is unclear.

Patients and Methods—We analyzed the records of all 165 consecutive patients treated in clinical trials with TKI as second line therapy or beyond after failure to prior imatinib therapy.

Results—A CCyR was achieved with second-line TKI therapy or beyond in 52% of patients, while 7% achieved a partial cytogenetic response (PCyR), 14% a minor cytogenetic response (mCyR), 14% complete hematologic response (CHR) only, and 17% no response. The 3-year survival probability was 98% for those with CCyR, compared to 83% with PCyR, 83% for mCyR, 76% for CHR and 71% for no response. Survival free from transformation rates at 3 years were 93%, 73%, 84%, 88%, and 0%, respectively.

Conclusions—CCyR is associated with the greatest survival benefit among patients treated with 2nd line therapy or beyond and remains the optimal cytogenetic goal of therapy. However, patients with partial and minor cytogenetic response derive a benefit compared to patients who have no response. This benefit should be recognized and evaluated against any alternative option available to a given patient before a change in therapy is recommended.

Introduction

The landscape of the treatment of patients with chronic phase chronic myeloid leukemia has changed dramatically over the last two decades. First, the introduction of interferon alfa

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(IFNa) resulted in a major shift in the treatment paradigm that resulted in a significant Improvement in patient outcomes, albeit with considerable toxicity.[1] By the end of last century, a new shift came with the introduction of tyrosine kinase inhibitors, first imatinib and later second generation tyrosine kinase inhibitors (TKIs) such as dasatinib and niloitnib. Imatinib proved to be considerably more effective and better tolerated than IFNa in the landmark IRIS study[2], establishing as frontline therapy for CML, with dasatinib and niloitnib soon becoming establish salvage options for those in whom imatinib had failed.[3,4] More recently these agents have proven to be superior to imatinib in terms of response when used as initial therapy.[5,6] This sequence has changed the natural history of the disease, with an expected survival at 8 years of nearly 90%, significantly better than the historical expectation of 4 to 5 years.

The improvement in long-term outcome has been a result of the ability of these therapies to suppress the malignant clone, as represented by the cell bearing the Philadelphia-chromosome (Ph). IFNa was the first agent that consistently was able to induce complete cytogenetic response in a significant number of patients.[7] The realization that achievement of a complete cytogenetic response (CCyR) was associated with a survival advantage,[1] made this outcome an important goal as a surrogate marker for improved survival. With improved therapies, CCyR rates improved from 5%-25% with IFNa, to 50-85% with imatinib,[8] and up to 95% with the newer agents.[9-11] Thus, achieving CCyR has become the minimum acceptable response for patients receiving any initial therapy for chronic phase (CP) CML.

The clinical value of achieving a CCyR is undisputed, and with newer therapies, there is even interest in further improving this response to major and possibly complete molecular responses. However, once patients develop resistance to imatinib, therapy is considerably less effective. Second generation TKIs can induce a CCyR in only approximately 50% of patients when used after imatinib failure,[3,4] and the probability of CyR is even lower for patients who have failed 2 or more prior lines of therapy.[12] Although achieving CCyR is the undisputed minimal optimal outcome to be obtained with therapy, many patients fall short of achieving this response but still demonstrate some lesser cytogenetic responses, such as partial (PCyR) or minor cytogenetic responses (mCyR). At the present time the clinical long-term clinical value of achieving such responses in second line therapy or beyond has not been investigated. This is important for several reasons. One is that patients may be offered a change in therapy because a response that is less than a CCyR has been achieved with their 2nd or greater TKI, frequently in favor of an investigational and/or less proven treatment option. Also, new agents in development are frequently judged for their ability to achieve complete or at least major cytogenetic responses, discarding lesser responses as clinically irrelevant.

We conducted the present study to determine the clinical value of achieving different levels of cytogenetic response for patients treated with 2nd TKI or beyond, as determined by their impact on survival and survival free from transformation to accelerated (AP) and blast phase (BP).

Patients and Methods

For the purpose of this analysis, all patients with CML in CP treated at MD Anderson Cancer Center with a TKI after having failed prior therapy with at least one other TKI were included. Failure was defined as resistance of intolerance to the prior agent(s) as previously described,[13] with some variability according to the particular clinical trial in which patients were enrolled. All but 4 of the patients with intolerance to imatinib also met criteria for failure according to current definitions. All patients included in this analysis were included in multi-center or institutional trials for this indication, all of whom were approved by the

Institutional Review Board and all patients signed an informed consent document according to the Declaration of Helsinki.

All patients were in CP as previously defined,[14] including a blast count of <15%, basophils <20%, blasts + promyelocytes <30%, platelets ≥100 (unless related to therapy), and with no cytogenetic clonal evolution. Cytogenetic response was established by G-banding in 20 metaphases, and the criteria were standard, including complete (0% Ph+ metaphases), partial (5-35% Ph+ metaphases), minor (40-95%% Ph+) and none (100% Ph+). Complete hematologic response (CHR) included normalization of peripheral blood counts, with normal differential, including <2% basophils, and absence of splenomegaly.

Patients were followed routinely with complete blood counts at least once monthly for the first 6 months, and at least every 3 months thereafter. A cytogenetic analysis was performed at least every 3 months for the first 12 months and at least every 6 months thereafter. Patients are followed for survival at least every month.

Survival endpoints were calculated by the Kaplan-Meier method, and compared using the log-rank test.[15] Survival was measured from the time treatment with the TKI in question was started until the time of death (event) from any cause or last follow-up (censored). Survival free from transformation to AP or BP was calculated from the time treatment with the TKI in question was initiated to the time of transformation to AP or BP, or death from any cause, whichever occurred first (event) or last follow-up (censored). Patients who received an allogeneic stem cell transplant were not censored at the time of transplant as events that happen after transplant, whether favorable or unfavorable, cannot be considered fully unrelated to the events that led to the transplant.

Results

From November, 2003 to December, 2008 a total of 170 patients were treated with TKI as second line (n=140) or beyond (n=30). Five patients (4 in the second line and 1 in the third line groups) were considered inevaluable as they received therapy for less than three months and were thus never assessed for cytogenetic response (2 died of CML-unrelated causes, 2 stopped therapy for personal reasons, 1 due to pregnancy). Thus, 165 patients were included in the analysis. The patient characteristics of the total population are described in Table 1. The median age was 57 years (range, 21 to 91 years) and the median time form the time of diagnosis to start of latest TKI was 70 months (range, 4 to 268 months). All patients included for response with 2nd TKI had received prior imatinib therapy. The reason for imatinib treatment discontinuation was intolerance in 33 (19%) and resistance in 137 (81%). For those 26 considered for 3rd TKI, all had received imatinib, while 15 (58%) had received prior dasatinib, 7 (27%) prior nilotinib, 2 (8%) had received prior bosutinib, 2 (8%) had received prior INNO-406. Four patients had received prior 3 TKI, in all instances including imatinib. Reasons for discontinuation from 2nd TKI was intolerance in 11 (42%) and resistance in 15 (58%).

Response to therapy

The response to therapy is presented in Table 2. Within the small number of patients for each individual TKI, there were no significant differences between the responses achieved with different inhibitors, which is consistent with published data. Thus, all patients are considered together for the purpose of the analysis. The median time to complete hematologic response was 8.7 weeks (range, 1.7 to 27.1 weeks) and to any cytogenetic response was 6 months (range, 1 to 35 months). For 2nd line TKI, 78 of 136 evaluable patients (i.e. had at least 3 months follow-up) (57%) of patients achieved a CCyR as their best response, with corresponding rates for PCyR 6% (n=8), mCyR 16% (n=22), CHR 14%

(n=13/102 evaluable for CHR), and no response 11% (n=15). Eighty-three patients have been taken off therapy after a median of 16.4 months (range, 0.4 to 52.6 months) from the start of therapy. This included 29 (35%, 21 of total 2nd line) patients who were taken off therapy for lack or loss of response while still in chronic phase; an additional 10 (12%, 7% of the total 2nd line) patients were taken off therapy for progression to AP or BP, 5 (6%) because of death on study, and 39 (47%) for other reasons (17 for toxicity, 12 lost to follow-up, 4 patient's choice, 3 other illnesses, 1 financial, 1 non-compliance, and 1 received a SCT). Fifty-seven (41%) patients remain on study, of whom 52 (91%) have CCyR. The median duration of CCyR was 38.5+ months compared to 5.2 months for PCyR and 5.9 months for mCyR.

Best response to TKI as 3rd line or beyond among 29 evaluable patients included CCyR in 7 (24%), PCyR in 4 (14%), CHR in 4 of 23 evaluable for CHR (17%) and no response in 13 (45%). Treatment was discontinued in 21 (70%) patients after a median of 8.6 months (range, 0.7 to 53.8 months) from the start of therapy. Reasons for treatment discontinuation were lack or loss of response while still in chronic phase in 10 (48%) patients, progression to AP or BP in 2 (10%), death on study in 1 (5%), and other reasons in 8 (38%) (5 toxicity, 2 lost to follow-up outside, 1 financial). Five of the 9 (24%) patients that remain on study have a sustained CCyR.

A total of 9 patients received an allogeneic stem cell transplant after 2nd (n=7) or 3rd (n=2) TKI, only one of them while in CCyR. Five of these patients are in CCyR at their last follow-up, 3 died of GVHD, and 1 relapsed.

Long term outcome

After a median of 48.5 months (range, 13.1 to 79.3 months) from the start of therapy, a total of 21 (12%) patients have progressed to AP or BP or died (including 6 who died on treatment from non-CML-related reasons), for a survival free from transformation to AP and BP of 86% at 36 months. The 3-year rate of survival free from transformation was 89% for those with low-risk Sokal score at the time of start of therapy with 2nd generation TKI, 91% for those with intermediate risk score, and 70% for those with high risk. The rate of transformation was lowest for patients who achieved a CCyR (6%), with no significant difference among all other groups (Table 2). Considering only patients treated with 2nd line TKI, the rate of transformation was 6% for those who achieved a CCyR and 40% for those who did not achieve any response and intermediate rates (8% to 25%) for those with other levels of response. The rate of survival free from transformation at 36 months according to best response to 2nd TKI was 94% for those whose best response was CCyR, and lowest for those with no response (0%). Those with intermediate responses had similar probabilities, all superior to those with no response (PCyR 63%, mCyR 88%, CHR 86%).

Thirty-six (21%) of the 170 patients have died at the time of the last follow-up. The 3-year survival probability for patients according to their Sokal risk score at the time of start of 2nd line therapy was 90%, 88%, and 70% for patients with low, intermediate, and high risk, respectively. The rate was lowest for patients who achieved CCyR (7%), with no differences between those with any other responses (29% to 39%). Considering only patients treated with 2nd line TKI, 8% of those who achieved CCyR have died, compared to 47% for those with no response. Those with PCyR (38%), mCyR (27%) or CHR (38%) had similar, intermediate rates of death. The 36-month survival probability was 97% for those who achieved CCyR, somewhat inferior for those with PCyR (88%) or mCyR (90%), and lower for those with CHR (67%) or no response (67%).

Considering that there is a minimum time necessary to be able to assess the achievement of response, we then performed a landmark analysis considering only patients who were still

alive and free from transformation to AP and BP at 6 months from the start of therapy. As expected, patients treated with 2nd TKI and beyond that achieved CCyR had the best probability of survival (98%) and survival free from transformation to AP and BP (95%) at 36 months. Patients with PCyR and mCyR had similar probabilities of survival (89% and 85%, respectively) and survival free from transformation (73% and 84%, respectively). Patients with CHR had a better transformation-free survival probability (88%) than those with no response (0%), but similar overall survival (72% and 67%, respectively). Similar trends were observed when considering only patients treated with 2nd line TKI.

Discussion

The natural history of CML has been changed dramatically with the introduction, first of interferon, and more recently and more prominently, with tyrosine kinase inhibitors. The expected overall survival has shifted form a median of 4 to 5 years to greater than 90% at 5 years.[16,17] Patients are routinely followed with cytogenetic analyses, fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR) to assess for the achievement of cytogenetic and molecular responses. These responses are valuable as surrogate markers of long term outcome. In the era of tyrosine kinase inhibitors, the minimum acceptable response for patients is a CCyR. To date, this is the only level of response that has been demonstrated to confer a survival advantage. This observation has been constant regardless of therapy, from its origins with interferon therapy, to the use of tyrosine kinase inhibitors. However, most of this information relates to the initial therapy of patients with CML in chronic phase. In this report, we confirm that the survival advantage for patients who achieve a CCyR is maintained also among patients who are receiving 2nd line therapy and beyond with TKI after having failed prior imatinib therapy.

The value of achieving CCyR is thus undisputed and remains a goal of therapy regardless of the line of treatment the patient is receiving. However, as patients advance form first line of therapy to 2nd line and beyond, the probability of achieving CCyR decreases. For example, in the IRIS trial, the rate of CCyR among patients receiving imatinib as initial therapy for CML in chronic phase was 83%.[8] For patients receiving dasatinib or nilotinib after imatinib failure, the reported rate of CCyR has been 45% to 50%,[4,18] but only 24% when these agents are used as third line of therapy.[12] Achievement of PCyR has been considered an acceptable second best, clustered with CCyR into what has been termed a major cytogenetic response (MCyR). MCyR have been accepted in regulatory settings as acceptable outcomes, particularly for second line therapy, assuming a survival benefit for these patients. Such survival benefit has been demonstrated in frontline therapy with interferon. Patients who achieved a CCyR after interferon therapy had a projected 10 year survival of 78% compared to 39% for those with PCyR, and only 25% for those with mCyR or lesser responses.[1] The survival benefit conferred by the achievement of PCyR with 2nd line TKI has not been previously demonstrated. In our report, we confirm that patients achieving this level of response with 2nd line TKI therapy indeed have a survival benefit. This is evidently not as great as when a CCyR is achieved (36-month survival probability 89% for PCyR versus 98% for CCyR) but clearly superior than when no response is achieved (57%). This validates the use of PCyR as an acceptable endpoint for regulatory and clinical purposes.

A question that has less often been addressed is whether obtaining a minor cytogenetic response is of any clinical benefit to patients. In fact, this is frequently discarded as a failure to therapy, and is not considered as a measure of success when evaluating new therapies. However, our analysis suggests that such responses have similar clinical benefit to patients as a PCyR. On a landmark analysis at 6 months, the 3-year probability of survival for patients achieving a minor cytogenetic response is 85%, similar to the 89% for those achieving a PCyR. Similarly, the probability of survival free from transformation to AP or

BP is 84% for those achieving a mCyR and 73% for those achieving PCyR. This finding has important implications. When considering frontline therapy, this is clearly not an acceptable endpoint because there are effective salvage therapies that offer a high (approximately 50%) probability of CCyR. However, in 2nd line therapy the value seems to be greater. Not only, as shown in our results, does the long-term survival benefit of a minor response mirror that of a partial response, but the options available for patients are much more limited. A patient that has the option for stem cell transplant should be considered for this option. But for all others, the use of the alternative 2nd generation TKI has limited value, with a rate of complete cytogenetic response rate of 25% at best, and a failure-free survival of only 20 months.[12] In addition, when evaluating new agents that are used for patients who have failed multiple prior lines of therapy, some patients may not achieve more than a minor cytogenetic response. Our results suggest that these responses should not be discarded as having little benefit and should be included as part of the overall rate of acceptable responses.

One common argument is that the value of these responses is not as great as that of CCyR thus the diminished interest in these as valid endpoints. It is indeed true that the long-term outcome for these patients is not as favorable as that of patients who achieve CCyR. However, one should consider that when a patient is facing failure to prior therapy, the background expectation is not that conferred by a CCyR, but that conferred by the untreated disease (ie, equivalent to no response). The patient has an active CML that, without therapy, will inevitably lead to death. This is the benchmark that has to be improved. CCyR improves it the most, but both PCyR and mCyR also improve it in a way that is of real value to patients.

In conclusion, patients receiving TKI therapy as second line or beyond frequently achieve responses lesser than CCyR. Patients who achieve CCyR have the greatest clinic long-term benefit, but achievement of PCyR and mCyR also confer a clear albeit more modest survival advantage. The value of such responses should be considered in the context of the expectations if the patient had no response at all and the alternative treatment options available to the patient.

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Table 1

Patient characteristics (n=170)

Characteristics	Median [range]	No. (%)
Age, y	57 [21-91]	
Months from diagnosis	70 [4-268]	
Months on imatinib	40 [1-108]	
Imatinib failure		
Resistance		137 (81)
Intolerance		33 (19)
Prior interferon therapy		91 (54%)
Best response to imatinib		
CCyR		44 (26)
PCyR		34 (20)
mCyR		23 (14)
CHR		53 (31)
No response		16 (9)
Mutations at start of latest TKI		57/128 (45)
Mutations among resistant patients		55/137 (40)
% Ph at start of TKI	100 [0-100]*	
2nd line TKI		
Nilotinib		28 (16)
Dasatinib		67 (39)
Bosutinib		41 (24)
INNO-406		4 (2)
3rd line TKI		
Nilotinib		3 (2)
Dasatinib		6 (4)
Bosutinib		12 (7)
INNO-406		5 (3)
4th line TKI		
Nilotinib		3 (2)
INNO-406		1 (1)

* 4 patients with intolerance to imatinib started 2nd TKI with a CCyR. All 4 of these patients maintained a CCyR.

Table 2

Outcome with second line TKI and beyond (n=165)

Treatment group	Best Response	No. with Response	(%)	No. Dead	(%)	No. Transformed	(%)
Overall	CCyR	85	52	6	7	5	6
N=165	PCyR	12	7	4	33	2	17
	Min CyR	23	14	7	30	4	17
	CHR only	17/125	14	5	29	1	6
	No response	28	17	11	39	7	25
2nd TKI	CCyR	78	57	6	8	5	6
N=136	PCyR	8	6	3	38	2	25
	Min CyR	22	16	6	27	3	14
	CHR only	13/102	14	5	38	1	8
	No response	15	11	7	47	6	40
3rd and beyond	CCyR	7	24	0	0	0	0
n = 29	PCyR	4	14	1	25	0	0
	Min CyR	1	3	1	100	1	100
	CHR only	4/23	17	0	0	0	0
	No response	13	45	4	31	0	8

Table 3

Probability of survival and survival free from transformation to accelerated and blast phase at 36 months by best response. All patients (A) Overall and (B) By landmark analysis at 6 months, and only patients treated with 2nd TKI (C) Overall and (D) By landmark analysis at 6 months.

(A)				
Best response responses to TKI	**Survival**		**Survival free from transformation**	
	%	**95% C.I.**	**%**	**95% C.I.**
CCyR	98	95-100	95	90-100
PCyR	83	65-100	73	47-100
MinCyR	86	72-100	84	69-100
CHR only	76	57-100	88	67-100
No response	71	56-90	0	NA

(B)				
Overall responses	**Survival**		**Survival free from transformation**	
	%	**95% C.I.**	**%**	**95% C.I.**
CCyR	98	94-100	95	90-100
PCyR	89	71-100	73	47-100
MinCyR	85	71-100	84	69-100
CHR only	72	52-100	88	67-100
No response	67	45-100	0	NA

(C)				
Best response responses to TKI	**Survival**		**Survival free from transformation**	
	%	**95% C.I.**	**%**	**95% C.I.**
CCyR	97	94-100	94	89-100
PCyR	88	67-100	63	32-100
MinCyR	90	78-100	88	75-100
CHR only	67	45-100	86	63-100
No response	67	47-95	0	NA

(D)				
Overall responses	**Survival**		**Survival free from transformation**	
	%	**95% C.I.**	**%**	**95% C.I.**
CCyR	97	94-100	94	89-100
PCyR	86	63-100	63	32-100
MinCyR	89	77-100	88	75-100
CHR only	64	41-100	86	63-100
No response	71	45-100	0	NA