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Molecular Cancer Therapeutics

Review

It's About Time: Lessons for Solid Tumors from Chronic Myelogenous Leukemia Therapy

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Abstract

The use of imatinib in chronic myelogenous leukemia (CML) transformed the disease, rapidly changing the median survival from 4 years to at least 20 years. In this review, we outline the causes of this revolution, including the identification of a critical driving molecular aberration, *BCR-ABL*, and the development of a potent and specific inhibitor, imatinib. Equally important was the timing of the targeted therapy, specifically its administration to patients with newly diagnosed disease. In solid tumors, targeted therapies are often both developed and used in metastatic malignancies after conventional approaches have failed. We postulate that this strategy is similar to using imatinib in blast-crisis CML, in which response rates are less than 15%, all patients relapse, and median survival remains only about 1 year. We hypothesize that the imatinib-led revolution in CML, including the critically important factor of timing, may be applicable to other cancers as well. Therefore, it will be important to use promising targeted therapies in the earliest phases of biomarker-defined solid tumors, before metastatic progression, to determine if outcomes can be significantly improved and, thus, establish if the success of imatinib in CML is an anomaly or a paradigm. *Mol Cancer Ther; 11(12); 2549–55. ©2012 AACR.*

Introduction

The use of imatinib in chronic myelogenous leukemia (CML) transformed the disease, rapidly changing the median overall survival from 4 years to an estimated 19 to 25 years and counting. This revolution occurred because of several factors, including the identification of a critical driving molecular aberration, *BCR-ABL*, and the development of an effective and specific inhibitor, imatinib. However, these two factors alone were not transformative. Equally important was the timing of the use of the targeted therapy, specifically its administration to patients with newly diagnosed disease. Indeed, if therapy for CML with imatinib had been restricted to advanced disease, imatinib may have been regarded as having moderate efficacy, as response rates in blast crisis are <15%, all patients relapse, and median survival remains approximately 1 year.

Like blast-crisis CML, metastatic solid malignancies are significantly more complex genetically and challenging to effectively treat with targeted therapies than newly diagnosed early-stage disease. Responses can be achieved, but they are generally transient. We hypothesize that the imatinib-led revolution in CML, including the critically important factor of timing, may be applicable to other cancers as well. Therefore, it will be important to use promising targeted therapies in the earliest phases of biomarker-defined solid tumors, before metastatic progression, to determine if outcomes can be significantly improved and, thus, establish if the success of imatinib in CML is an anomaly or a paradigm.

The Era of Targeted Therapy

The era of molecularly targeted cancer therapy ushered in by imatinib began with incredible expectations. Magazine covers proclaimed "A New Hope For Cancer" and news reports questioned if the "magic bullet" could represent a long-awaited turning point in the war on cancer (1). Imatinib specifically and effectively targets cells harboring the 9;22 translocation, the *sine qua non* of CML, and is considered a modern-day version of Erhlich's "magic bullet" (Fig. 1; refs. 2–4). If left untreated, CML inevitably progresses from chronic to accelerated phase, and finally to end-stage blast crisis, exemplifying the malignant evolution believed to occur in most cancers (2). Before

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When torrential water tosses boulders, it is because of its momentum. When the strike of a hawk breaks the body of its prey, it is because of timing.
Sun Tzu, *The Art of War*
Life is really simple, but we insist on making it complicated.
Confucius
This thing all things devours:
Birds, beasts, trees, flowers;
Gnaws iron, bites steel;
Grinds hard stones to meal;
Slays king, ruins town,
And beats high mountain down
J.R.R Tolkien, *The Hobbit*, Gollum's riddle about time

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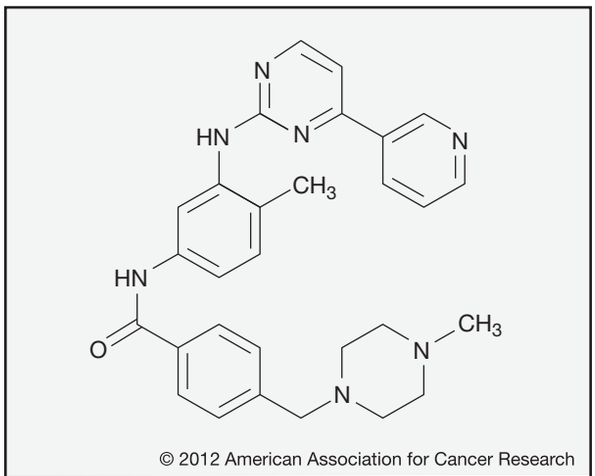

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Figure 1. Chemical structure of imatinib.

imatinib, therapies for CML were mainly "cosmetic". Hydroxyurea normalized blood counts but had no impact on survival. Interferon-based treatments yielded complete cytogenetic responses (absence of the 9;22 translocation in the bone marrow) in less than 15% of newly diagnosed patients and a median survival of approximately 4 years (5, 6). In contrast, in newly diagnosed CML, imatinib achieves complete cytogenetic responses in approximately 70% of individuals, and the median survival has increased to an estimated 19 to 25 years (Table 1; refs. 7–20). Imatinib has unequivocally revolutionized the treatment of CML, transforming a uniformly fatal disease into one easily managed with nontoxic agents.

In the 11 years since the U.S. Food and Drug Administration (FDA) approval of imatinib, dozens of targeted agents have been approved, and many more are currently under investigation, confirming the dawn of a new era in oncology. However, few if any have lived up to the initial high expectations that a dramatic shift in patient with solid tumor survival would occur, as it did for CML.

Impact of targeted therapy in solid tumors

The development of imatinib in CML has been described as a paradigm for targeted therapy (21). First, a target critical to the survival of the cancer was identified. Second, a potent, specific, and relatively nontoxic inhibitor was developed. Yet, despite heroic efforts to emulate the imatinib in CML story in solid tumors, most targeted therapies have modest effects (22). Targets critical to the

Table 1. Efficacy of BCR-ABL tyrosine kinase inhibitors by disease stage

	Phase	CHR	MCyR	CCyR	MMR	Median OS (mo)	OS at 12 months	Ref.
Blast crisis								
Imatinib	I	11%	5%	0%	—	—	—	7
Imatinib	I/II	23%	3%	8%	—	6.5	22%	8
Imatinib	II	15%	16%	7%	—	6.9	32%	9
Dasatinib[a]	II	27%	36%	26%	—	11.8	50%	10
Nilotinib[a]	I	6%	18%	6%	—	—	—	11
Accelerated-phase relapse								
Imatinib	II	53%	24%	17%	—	NR	74%	12
Dasatinib[a]	II	39%	33%	24%	—	NR	74%[b]	13
Previously treated chronic phase								
Imatinib	I	77%	31%	13%	—	—	—	14
Imatinib	III	82%	55%	39.6%[c]	—	NR	>97%	15, 16
Dasatinib[a]	II	91%	59%	49%	—	NR	>96%	17
Newly diagnosed chronic phase								
Imatinib	III	95%	85%	73.8%[c]	—	NR	>97%	15, 16
Imatinib	III	—	—	66%[d]	28%[d]	NR	99%	18
Imatinib	III			65%[d]	22%[d]	NR	—	19
Dasatinib	III	—	—	77%[d]	46%[d]	NR	97%	18
Nilotinib	III	—	—	79%[d]	44%[d]	—	—	19

Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematologic response; MCyR, major cytogenetic response; MMR, major molecular response; OS, overall survival; NR, not reached; —, not reported.

[a]Imatinib-resistant or intolerant.

[b]Progression-free survival at 12 months.

[c]Best observed response.

[d]Response at 12 months.

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Table 2. Activity of targeted agents in molecularly defined populations

Cancer	Common genetic driver	Targeted therapy	Primary	Relapse	Clinical benefit rate	Ref.
CML	BCR-ABL	Imatinib/dasatinib/nilotinib	X		>95%	15, 16
GIST	c-KIT	Imatinib	X		84%	23
Melanoma	V600E BRAF	PLX4032		X	>90%	24
Lung cancer	EGFR	Erlotinib/gefitinib		X	92%	25
Lung cancer	EML4-ALK	Crizotinib		X	>90%	26
Basal cell carcinoma	PTCH1/SMO	GDC-0449		X	87%	27
Breast cancer	ERBB2	Lapatinib		X	31%	28

NOTE: Clinical benefit: complete response, partial response, and stable disease.

survival of other cancers, such as *EGFR*, *KIT*, *BRAF*, and *ALK*, have been identified and targeted by relatively specific inhibitors (Table 2; refs. 15, 16, 23–30). Gastrointestinal stromal tumor (GIST), the most common mesenchymal tumor of the gastrointestinal track, is notoriously chemotherapy-refractory, but responds to imatinib. GIST has driving mutations in KIT or PDGFR-α in the vast majority of cases, which predict for response to imatinib (31). In newly diagnosed and resected high-risk GIST, adjuvant imatinib results in a significant recurrence-free interval, but the disease often returns when imatinib is stopped (32). The implication of this finding, similar to disease recurrence after cessation of imatinib in CML, is that a subclinically detectible clone has a therapeutically dependent dormancy and, thus, may require continuous exposure to an inhibitor or novel strategies to eliminate the dormant clone (33). Notably, CML that recurred after imatinib cessation was responsive to resumption of therapy in all patients treated on the STIM (Stop Imatinib) trail (33).

Many solid tumors, like small cell lung and bladder cancers, do not yet have a known driving aberration(s) amenable to current targeted therapies despite significant genetic derangements found in tumor samples. As our understanding of the complex signaling networks that drive these cancers improves, it is possible that even cancers currently considered a "black box" will be amenable to therapies targeting the yet undefined aberration-associated critical survival pathways.

Unlike CML and resected GIST, targeted therapies for advanced solid tumors may occasionally show evidence of dramatic disease regression, even in extensively pretreated patients, but often prove fleeting (24, 34–36). For example, nearly 90% of patients achieved tumor regression in the phase I trials of vemurafenib in BRAF-mutant melanoma and crizotinib in ALK-rearranged lung cancer (24, 26). These responses are generally achieved with minimal side effects, especially compared with cytotoxic chemotherapy. However, they are rarely durable. The "Lazarus" restaging images featured in publications are often from patients who still die of their disease (Fig. 2). These remarkable but transient responses confirm the continued relevance of the target to the survival of cancer cells in at least a portion of patients with advanced disease.

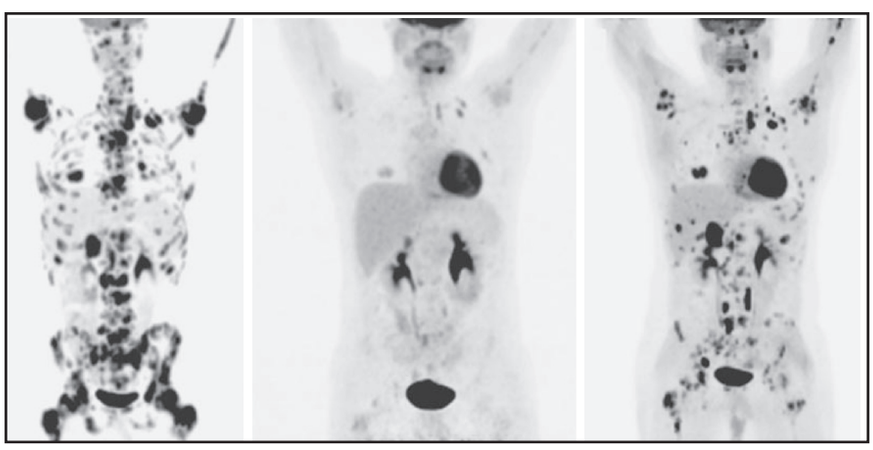

Figure 2. Transient response to targeted therapy in a heavily pretreated patient. 2[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) images of a patient with metastatic medulloblastoma pretherapy after 2 months and after 3 months of vismodegib. Adapted with permission from the Massachusetts Medical Society (35).

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If the target is present and the drug active, why are these dramatic responses infrequent and impermanent? Numerous models of targeted therapy resistance show the activation of alternate survival pathways, mutations in the target of the inhibitor, or both (37–40). These mechanisms of resistance are also found in blast-crisis CML, and are thought to explain its persistently poor outcomes (41). In hindsight, it is now clear that the timing of targeted therapy in CML, specifically its use before the development of complex resistance mechanisms, was critical in the transformation of disease outcomes.

The Significance of Timing

The imatinib in CML paradigm speaks to the critical nature of timing of targeted therapy: patients with accelerated phase and blast-crisis CML do not receive the same benefit from Bcr-Abl inhibition as do newly diagnosed patients with chronic phase CML. Furthermore, there is a precipitous decrease in the benefit that patients with previously treated chronic-phase CML receive as compared with those who had newly diagnosed disease (Table 1). In 2001, simultaneous landmark publications of imatinib in chronic phase and blast-crisis CML (along with relapsed t(9;22)+ acute lymphoblastic leukemia) showed striking differences in outcome (7, 14). In newly diagnosed chronic phase CML, imatinib has shown an astounding 65% to 74% rate of complete cytogenetic remission. In previously treated chronic phase, this rate drops to from 13% to 40%. With transformation to blast-crisis CML, only 0% to 8% of patients achieve complete cytogenetic responses, and these responses are transient (Table 1). Although the efficacy of imatinib in blast-crisis CML is disappointing, the fact that late-stage disease could respond provided proof-of-principle for the use of imatinib, and showed the continued importance of Bcr-Abl activity in at least a portion of blast-crisis CML (7). However, even today, median survival of patients with blast crisis remains at less than 1 year. Transforming outcomes in CML required moving imatinib therapy to newly diagnosed patients.

As CML progresses, much of the initial resistance to imatinib is due to mutations in the kinase domain of *BCR-ABL*. The resulting resistance to imatinib led to the development of a second generation of tyrosine kinase inhibitors (TKI), dasatinib, and nilotinib. Both agents, now FDA-approved for newly diagnosed and relapsed CML, have shown superior efficacy, at least molecularly, to imatinib in first-line phase III trials (Table 1; refs. 18, 19). However, in accelerated phase and blast-crisis CML, the efficacy of second-generation TKIs is essentially equivalent to imatinib (7–11). This may be due to other genetic changes supplanting the role of Bcr-Abl in late-stage disease. Despite superior efficacy in newly diagnosed chronic phase CML, dasatinib and nilotinib are no match for CML after transformation has occurred.

Moving Forward

Is advanced cancer analogous to advanced CML?

In 1957, Foulds defined neoplastic progression as "the acquisition of permanent, irreversible changes" in a neoplasm (42). Three years later, Nowell and Hungerford observed a minute chromosome in CML, the first genetic example of a "permanent, irreversible change" in cancer (43).

Advanced cancers have multiple genetic derangments that accumulate as subsequent generations of tumor cells develop, selected for the advantages they confer on subpopulations (44). Metastatic lesions are often significantly heterogeneous compared with their parent lesions, including in clinically used biomarkers (45). Compared with CML, even newly diagnosed localized solid tumors are considered genetically complex, with multiple subpopulations possessing unique biologic characteristics (46, 47). Indeed, a rapid autopsy study in pancreatic cancer found that mutations present in metastatic disease were present in subclones of the original primary tumor (48). However, even the "genetically simple" chronic phase CML, if left untreated, will eventually develop therapeutic resistance and increasing genetic complexity, remarkably similar to metastatic solid tumors (49, 50). Newly diagnosed localized solid tumors may not be as genetically simple as chronic phase CML, but are certainly less complex than refractory metastatic solid tumors.

On the basis of both biologic and clinical observations, by the time a solid tumor metastasizes, it is likely analogous to accelerated-phase or blast-crisis CML. Therefore, based on the CML paradigm, even newly diagnosed metastatic disease is too late for targeted agents to achieve their maximal effect.

Is this paradigm applicable in other cancers?

The CML paradigm supports three conclusions that warrant exploration in the context of solid tumors.

The evaluation of a targeted therapy in advanced disease is valuable for proof-of-principle, but may dramatically underestimate the efficacy in early-stage disease. Patients with either advanced CML or metastatic solid tumors respond to matched targeted therapy, albeit usually without achieving complete or durable remissions (Table 2). Similar to the situation in CML, response rates decline with progression in solid tumors. For instance, lapatinib, a dual EGFR-erbB2 TKI, is FDA approved to treat advanced or metastatic HER2+ breast cancer. The response rates decline from 24% to 6.9% when lapatinib is used to treat patients with previously untreated versus previously treated metastatic HER2+ breast cancer (28, 51). Although both previously untreated and treated metastatic breast cancer are likely analogous to advanced CML, they serve as an example of the further degradation of outcomes with increasingly advanced disease. It is unclear how much the efficacy of targeted agents would improve if they were used

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in newly diagnosed, localized disease. The innovative I-SPY2 breast cancer trial aims to evaluate neoadjuvant targeted agents together with standard chemotherapy in newly diagnosed localized disease, and develop predictive biomarkers to optimally match patients and therapy.

Compared with current standard therapies, drugs with superior efficacy in early-stage disease may be equivalent in late-stage disease. Dasatinib and nilotinib display superior molecular outcomes in chronic phase CML, but achieve similar dismal results as imatinib in blast-crisis CML (Table 1). The lack of efficacy of the more potent TKIs in late-stage CML speaks to the complexity of the disease after transformation occurs. The *BCR-ABL* translocation remains present, but inhibitors have little effect on survival. It is plausible that this phenomenon may also apply in solid tumors. Because of the significant financial cost of drug development, it is unfortunately possible that drugs that are superior preclinically but essentially equivalent in relapsed/refractory patients may have their development halted despite the possibility they would prove superior in newly diagnosed patients.

The optimal time to use the most potent targeted therapies is early in the course of the disease, before transformation. In CML, the increases in survival would be much less significant had investigators stayed focused on advanced disease, or even later chronic phase disease (Table 1). The lesson learned in CML is that, for optimal results, matched targeted therapy must be given to newly diagnosed patients to prevent progression, rather than to disease that has already progressed. Although there is evidence that remarkable disease regression may occasionally occur with targeted therapy in metastatic solid tumors, durable responses are the exception (22, 24, 26). Metastatic solid tumors are generally considered incurable with cytotoxic chemotherapies: it is not unreasonable to extrapolate the same expectation to targeted therapies. It is therefore worth investigating whether or not both response rates and duration would improve if targeted agents were used in the earliest phases of solid tumors, before development of advanced disease.

Challenges in treating newly diagnosed cancer

The predominant approach to early-stage solid tumors is surgical resection, perhaps with adjuvant cytotoxic chemotherapy or radiotherapy. If the disease recurs, targeted agents previously evaluated in relapsed disease may be used, but often patients are treated with cytotoxic chemotherapy alone [e.g., erlotinib, an EGF receptor (EGFR) inhibitor, is approved to treat non–small cell lung cancer that has failed 1 or more prior chemotherapy regimen].

A concern of potential harm emerges when considering changing this treatment paradigm to include targeted agents earlier in the disease course, especially if cure is possible with surgery, cytotoxic chemotherapy, and/or radiotherapy. These standard therapies have known efficacy, but also result in serious sequelae that impact quality of life (52) Moving forward, oncologists should aim to eliminate cancer without permanently disrupting the lives of their patients. Early-stage solid tumors are more genetically complex than early-stage CML and may contain significant heterogeneity; thus, using targeted therapies in lieu of surgery may pose a significant risk of harm to patients with potentially curable cancers. If a portion of a small primary tumor harbors *de novo* resistance to a targeted therapy, metastatic disease may result and prove difficult to control. However, it is conceivable that with improved knowledge of disease-critical aberrations and greater technology to account for tumor heterogeneity, it may eventually be possible to give targeted therapy to biomarker-selected patients with newly diagnosed, early-stage solid tumors in lieu of current "curative" therapies. Initially, this approach would be most appropriate for patients who are unfit for standard therapies (e.g., high risk of perioperative mortality). If these patients receive benefit greater than expected on the basis of initial trials in relapsed or refractory patients, it would support the further investigation of targeted therapy in first-line cancer therapeutics. Other investigators have treated borderline resectible renal cell carcinomas with neoadjuvant-targeted agents typically reserved for advanced disease, and shown efficacy in a retrospective series (53).

Less controversially, newly diagnosed patients with localized disease could receive standard treatments together with neoadjuvant targeted agents previously found efficacious and tolerable in relapsed patients. Examples of this approach include the innovative I-SPY2 breast cancer trial. Another approach would be to add tumor-specific targeted therapy as an adjuvant to patients rendered free of disease who remain at high risk for early relapse, similar to imatinib in GIST or trastuzumab in HER2+ breast cancer (32, 54).

An additional essential step to long-term disease control or cure with targeted therapy is identification of biomarkers predictive of response to targeted therapy. The neoadjuvant breast cancer I-SPY 1 and 2 clinical trials aim to develop biomarkers correlating with pathologic response and adaptively randomize patients to targeted therapies with a higher likelihood of success (55, 56). These innovative and informative clinical trial designs can facilitate the rapid translation of new targeted agents and disease knowledge from the bench to the therapy for early-stage cancers.

Conclusion

It is estimated that 12.7 million cancer diagnoses and 7.6 million cancer-related deaths occurred worldwide in 2008 alone (57) In 2030, these numbers are projected to increase to 21.3 million new cases and 13.1 million deaths (58). Clearly, new innovative strategies are needed to deal with this problem.

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A critical question is whether the lessons learned from the dramatic shift in CML outcomes attained with imatinib when used in the earliest phases of the disease are applicable to any solid cancers. Administering potent, specific inhibitors to patients with advanced disease has yielded occasional impressive responses and served as a proof-of-principle in both CML and solid tumors (Tables 1 and 2). However, the full therapeutic potential of these inhibitors in CML that transformed median overall survival from 4 years to 19 to 25 years was not realized until they were used in newly diagnosed patients. Leukemia investigators found the key to improved survival was preventing, rather than treating, progression. Late-stage CML has significant similarities, both in genetic complexity and therapeutic responses, to metastatic disease in solid tumors.

It is possible that after a localized solid tumor is established, an agent targeting a driver molecular aberration may not be sufficient to control the cancer, even if used immediately. However, even if dramatic and durable effects are not achieved with targeted therapy in newly diagnosed solid tumors, their efficacy should exceed what is currently observed in the relapsed or refractory setting. Furthermore, unraveling resistance is likely to be a far less herculean task early in the disease than when multiple events of molecular evolution have occurred in its later stages.

In conclusion, although scientific knowledge about cancer biology, genomics, and complex networks is advancing rapidly, successful translation to the clinic lags behind (59). To lessen this gap, a third factor may need to be added to the original description of CML as a paradigm for targeted therapy: (i) identification of the crucial driving molecular aberration, (ii) development of potent, specific inhibitors, and importantly (iii) use of the inhibitors early enough in the disease course to allow for maximum efficacy. To date, it has been assumed that the biologic properties of CML are unique, and thus amenable to therapy in a way unheard of for solid tumors. Yet, fundamentally, the response of patients with advanced CML and those with metastatic solid tumors to matched target therapy are similar: only a minority of patients achieves remission; all relapse, and survival increases are measured in months, not years. The treatment of CML was revolutionized, not by a targeted therapy alone, but by giving it to patients with newly diagnosed disease to prevent progression to blast crisis. This strategy has not been fully explored in solid tumors. To determine if CML is indeed a biologic exception or whether the lessons learned from CML are a paradigm for success, it will be necessary to administer matched targeted therapy to patients with newly diagnosed, localized solid tumors.

Disclosure of Potential Conflicts of Interest

R. Kurzrock has a commercial research grant from Novartis. No potential conflicts of interest were disclosed by J.R. Westin.

Authors' Contributions

Conception and design: J.R. Westin, R. Kurzrock
Development of methodology: J.R. Westin
Analysis and interpretation of data: J.R. Westin
Writing, review, and/or revision of the manuscript: J.R. Westin, R. Kurzrock.

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