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Commentary

At the right time: Moving precision therapy to newly diagnosed cancer

Adam Wahida,[1,*] Ben George,[2] and Razelle Kurzrock[2,3,*]
[1]Institute of Metabolism and Cell Death, Helmholtz Zentrum München, Neuherberg, Germany
[2]MCW Cancer Center, Medical College of Wisconsin, Milwaukee, WI, USA
[3]WIN Consortium, Paris, France
*Correspondence: adam.wahida@helmholtz-munich.de (A.W.), rkurzrock@mcw.edu (R.K.)
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Precision oncology aims to match the right drug(s) to the right patient. Equally important is ensuring that precision therapies are offered at the right time. Transformative, rather than incremental, outcome improvement may require treatment at diagnosis rather than in the advanced/metastatic setting after genomic evolution.

The application of novel agents and diagnostic tools to improve patient care is constrained by ethical considerations aimed at preventing potential errors, aligning with the principle of "first, do not harm." But while the principle that physicians should first do no harm is an appealing one, it really does not prohibit harming because, if it did, no patient with cancer would have surgery or potentially lethal chemotherapy before a bone marrow transplant. The "do not harm" principle means that the benefits should outweigh the risks for tests and treatment. Therefore, we need to recalibrate our clinical research enterprise within this framework, the breathtaking advances in our understanding of malignancies' fundamental molecular biologic underpinnings, and the development of highly targeted medications. In particular, human genome sequencing ~20 years ago marked a pivotal moment,[1] enabling an understanding of the molecular changes underlying the growth and development of individual cancers. This understanding opened the door for personalized/precision gene- and immune-directed therapeutic choices. While these therapies can have side effects, they are potentially less debilitating than some of the side effects associated with conventional therapies, such as cytotoxic agents, surgery, and radiation.

The increasing availability of omics data and corresponding pharmacological strategies underscores a pressing issue that demands immediate attention—the timing of therapy.[2–4] We maintain that introducing new therapies to patients with solid cancers earlier in their disease trajectory (i.e., at diagnosis), once their efficacy is established in late-stage disease, is crucial. One of the most significant barriers to bringing therapies earlier in the disease course is the ethical concern that lives will be lost because of the failure to apply conventional treatments such as surgery, radiation, and neoadjuvant/adjuvant cytotoxic regimens.

A salient model for interrogating and prosecuting pathogenic genomic anomalies to transform outcomes is the conversion of chronic myelogenous leukemia (CML) from a fatal leukemia to one with a near-normal life expectancy.[2,3,5] This critical accomplishment was enabled by exploiting specific tyrosine kinase enzyme inhibitors (such as imatinib) that targeted the CML driver, i.e., the Bcr-Abl fusion protein, a product of *BCR-ABL* genomic t(9:22) translocation.[6] However, understanding and suppressing the Bcr-Abl driver were insufficient to revolutionize this fatal disease. A third factor, often not acknowledged, was equally vital—the timing of using the Bcr-Abl targeted therapy. In particular, imatinib must be administered to patients with newly diagnosed disease; its impact on the course of the disease is almost negligible in late stages, known as accelerated phase and, later, blast transformation (Figure 1). The importance of this observation cannot be overstated. Indeed, if therapy of CML with imatinib had been relegated to advanced disease, imatinib could, at best, be regarded as having moderate activity, since response rates in advanced CML are <15%, all patients relapse, and median survival remains approximately 1–2 years.[7] Directing treatment at a tumor driver with a cognate targeted therapy has also been implemented in solid cancers, with multiple successes, including a Lazarus-type effect and the dramatic response of end-stage disease.[8] However, almost ineluctably, the tumors relapse, often within months. Therefore, the remarkable impact of matched targeted treatment in CML has not been recapitulated in solid cancers, wherein matched medications increase life expectancy by months to, at best, a few years, but not anywhere close to the near-normal life expectancy of CML.

The limitations of applying gene-targeted therapy in solid tumors have been attributed to solid malignancies being more complex than diseases such as CML. However, this might not reflect the full story. The challenge in applying these treatments to late-stage metastatic solid malignancies is that by the time molecular evolution occurs, targeting single genetic alterations often fails to produce complete or lasting responses.[9] Moreover, conventional treatment often induces DNA damage, increasing genomic complexity, and selection of resistance clones leading to clonal evolution. Investigation of precision oncological paradigms in advanced/metastatic disease with combinations of matched drugs customized to the

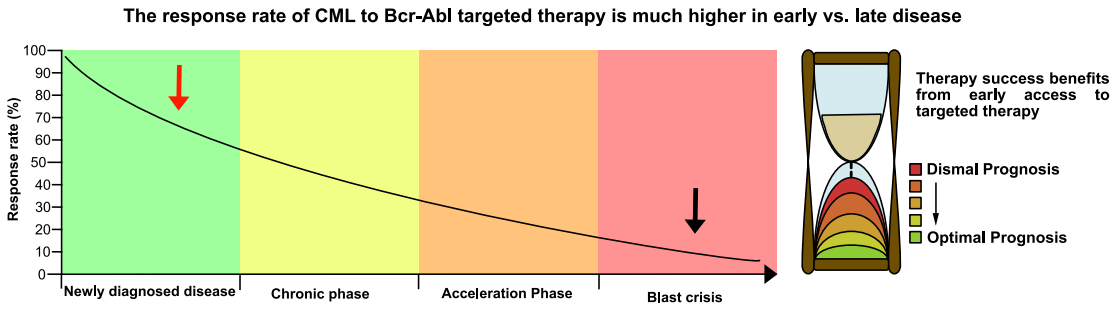

Figure 1. Time is a critical determinant of treatment efficacy

Bcr-Abl translocated CML treatment efficacy dramatically decreases in late-stage versus early disease. As such, therapy success benefits from early access to targeted therapy, which may serve as a treatment paradigm in other entities beyond CML.

molecular portfolio of each patient's malignancy addresses this conundrum.[10] While these improve outcomes, they often still fail to reproduce the astonishing effectiveness of targeting *BCR-ABL* in CML. Even so, in solid cancers, the hypothesis that early therapy—that is, treatment at the time of diagnosis—yields more satisfactory responses has been successfully applied to anti-PD1 immunotherapy, at least in newly diagnosed rectal cancer with microsatellite instability,[11] and is being tested with gene-targeted therapy in biomarker-driven subsets of lung cancer. However, the CML paradigm supports a conclusion that merits broad exploration in the context of solid tumors—that is, the evaluation of a matched gene- or immune-targeted therapy in advanced disease is valuable for proof of principle but may dramatically underestimate the efficacy of that treatment in early-stage disease.

Assuming that the conjecture that early treatment with cognate targeted drugs would yield better and more durable response rates is a reasonable one, so what has prevented its application in solid cancers? The invisible line these approaches need to cross is the fact that there exist therapies that have often (but not always) been tested in randomized trials and show a survival advantage. Conventional treatment strategies for solid cancers usually include surgery, chemotherapy, and radiation therapy. The problem is the ethical conundrum, i.e., that some patients will lose their chance for a cure if these standard-of-care therapies are delayed or substituted. It is the "first do not harm" (*primum non nocere*) of Hippocrates. As a result, newly diagnosed patients afflicted with localized solid cancers have not been well addressed in trials of gene- or immune-targeted therapies, even though the dramatically improved results in freshly diagnosed versus late-stage CML have been known for two decades[12] and even though, when imatinib was moved to the frontline in CML, curative therapies in the form of allogeneic bone marrow transplantation existed, even for those patients treated with imatinib at diagnosis.

The obligation to improve without causing harm prompts the inquiry of how evidence can be created and effectively assessed for the clinical decision-making process in this emerging era of gene- and immune-directed precision therapies. There is a need to re-engineer our strategies for producing next-generation evidence, and, precisely, to move forward, we must surmount self-imposed restrictions shackling the early targeting of genomic drivers. To illustrate, one might examine the unquestionably evidence-/randomized-control-trial-backed use of therapy in pancreatic cancer; pancreatic cancer is almost always diagnosed at an advanced stage, and the 5-year survival for patients with metastatic disease is less than 3%,[13] with about half of the patients dead at 1 year. In the classic randomized trial that established combination chemotherapy with the FOLFIRINOX regimen as the standard of care for metastatic disease, the median survival was only 11 months for the FOLFIRINOX arm in first-line patients, who were selected for their excellent performance status, and only about 10% of patients were alive at 2 years. The median survival after FOLFIRINOX for patients treated in the second line was only 4.2 months. This standard of care has not changed since 2011, when this trial was published.[14] Moreover, FOLFIRINOX therapy also has substantial toxicity for many of these patients. While the data supporting these treatments may seem indisputable from an evidence-based perspective because a survival advantage was established through randomized trials, the outcomes might not be deemed acceptable when compared to the current standard of care for other diseases, such as metastatic testicular seminoma, wherein standard chemotherapy cures the vast majority of patients.[15] Further, the concern regarding error or medical reversal in subsequent studies for cancers with poor outcomes should be less important than the imperative to move the field forward. Indeed, there could be a benefit threshold below which trying a different approach is acceptable or desirable. As an example, new approaches for diseases with 90% cure rates need to be advanced with more caution than diseases in which the majority of patients can be expected to have died in 2 years. While the exact threshold for informed innovations may not be clear, the outer edges of the boundary conditions, as above, can be defined.

Other factors may also be critical when considering new therapies at the time of diagnosis. For instance, circumstances in which conventional treatment leaves the patient with considerable loss of function due to the morbid effects of, for example, surgery (pelvic exenterations, mutilating head and neck surgeries, and so forth) might weigh in favor of trying innovative approaches, even if the risk is losing the chance for a cure. The patient's perspective represents an often insufficiently considered dimension of this

ethical dilemma. In the face of ambiguous or uncertain evidence, a poor prognosis, or life-altering/-disfiguring standard therapies, the patient deserves the opportunity to choose. A valid critique arises from the lack of clarity regarding how a physician's personal biases might influence the authentic decision-making process for an affected patient. Yet, giving a patient with a poor prognosis facing life-changing surgery, radiation, or chemotherapy no choice but to undergo standard-of-care therapy also ignores the moral imperative of hearing the patient's opinion regarding the value of quality of life and respecting patient autonomy. Finally, a biomarker-matched immune- or gene-targeted therapy could also be considered as maintenance therapy for a period of time in newly diagnosed disease, for patients at high risk of relapse despite remission after standard of care, or for those with suboptimal response to conventional therapy. Notably, to apply biomarker-matched therapy early in the disease course, next-generation sequencing would need to become part of the initial diagnostic workup, in addition to light microscopy. Moreover, multidisciplinary teams, such as those in expert molecular tumor boards, must be available for patients.

In conclusion, patients should be allowed to decide on a different pathway of care in the context of clinical trials, especially if the usual pathway is likely to lead to morbid loss of function or a high chance of death at 2 years. The worry about postponing conventional, albeit life-altering treatments and/or those with limited clinical impact despite having proven statistical superiority in randomized trials for recently diagnosed patients with lethal cancers complicates the design of clinical trials. Unfortunately, this situation negatively impacts patients, exposing them to substantial morbidity and mortality. Therefore, the standard that evidence-based medicine needs to recalibrate is enabling a balance between potential lives lost by undertaking novel therapies in patients with newly diagnosed cancers, reflecting the possibility of making errors, and the lives and time saved both for the population as a whole and for individual persons, by progressing more rapidly, in the context of unambiguous, informed consent regarding the risks and benefits for patients with aggressive cancers given access to new treatments at the time of diagnosis.

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