The paradox of response and survival in cancer therapeutics

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Although most patients with cancer respond to therapy, few are cured. Moreover, objective clinical responses to treatment often do not even translate into substantial improvements in overall survival. For example, patients with indolent lymphoma who achieved a complete remission with conventional-dose therapies in the pretruximab era did not experience a survival advantage over similar patients treated with a “watch and wait” approach. Several studies have also shown that neither the magnitude nor the kinetics of clinical response has an impact on survival in multiple myeloma. Recent data suggesting many malignancies arise from a rare population of cells that exclusively maintains the ability to self-renew and sustains the tumor (ie, “cancer stem cells”) may help explain this paradox that response and survival are not always linked. Therapies that successfully eliminate the differentiated cancer cells characterizing the tumor may be ineffective against rare, biologically distinct cancer stem cells. New methods for assessing treatment efficacy must also be developed, as traditional response criteria measure tumor bulk and may not reflect changes in rare cancer stem cell populations. In this article, we discuss the evidence for cancer stem cells in hematologic malignancies and possible ways to begin targeting these cells and measuring clinical effectiveness of such treatment approaches. (Blood. 2006;107:431-434)

Introduction

More than 30 new anticancer drugs have been approved over the past 2 decades. Approval required all of these drugs to show a clinical benefit, which can be documented by objective measurements of tumor response,1 improvements in quality of life as assessed by questionnaires, or a delay in the time to recurrence. However, these benefits have led to only modest increments in survival for the majority of patients with cancer.2-4 Emerging laboratory and clinical data are beginning to point out potential flaws in the current methodologies used to develop new cancer therapies.

Clinical response may not predict survival

The clinical development of new anticancer agents usually proceeds through sequential steps, or phases. Phase 1 clinical trials, the first step in testing new therapies, establish safe drug doses and look for the first hints of clinical activity. Phase 2 trials focus on the efficacy of new treatments in specific cancers, and phase 3 trials compare new treatments with the current standard therapy. Most new therapies will not be optimally effective alone, and further development in combination strategies likewise requires sequential steps. A cardinal principle of cancer therapeutics has been that objective evidence of clinical response will translate into clinical benefit, especially improved survival. The major advantage of using clinical response as a primary trial end point is that it is measurable over weeks to months, allowing the stepwise process of drug development to occur more rapidly and efficiently. In contrast, demonstrating a delay in the time to recurrence or an improvement in overall survival adds significant complexity to trial design, usually requiring accrual of large patient numbers and long follow-up to provide statistical significance. Further, looking for an overall survival benefit can be confounded by crossover between treatment groups.

Although objective responses clearly can produce clinical benefit through decreasing side-effects and improving quality of life, there is surprisingly little evidence that it is a surrogate for survival; in fact, there are numerous well-accepted examples where response and survival do not correlate. Indolent lymphoma5 patients who achieved complete remissions (ie, elimination of all detectable disease) with conventional-dose therapies in the pretruximab era did not experience a survival advantage over similar patients treated with a “watch and wait” approach.6,7 In multiple myeloma, neither the magnitude nor the kinetics of clinical response has an impact on survival.8,9 Similarly, significant clinical responses in pancreatic10 and prostate cancer11,12 have not translated into survival benefits. Further, despite many new treatments for metastatic breast cancer, survival has been minimally impacted.13 Even when responses are associated with statistically significant improvements in survival, the survival advantage is often incrementally small, frequently a few weeks to months, as in a recent large randomized phase 3 trial for advanced non–small-cell lung cancer14 and similar trials in pancreatic and prostate cancer.15,16

In actuality, the major rationale for the use of objective clinical response as a surrogate for biologic activity is the premise that a complete remission must precede cure. Since cure can currently be...
established only by long-term follow-up, a complete remission will always precede verification of cure. As we will discuss, however, a complete remission by standard criteria may be neither a prerequisite nor a requirement for the actual generation of a cure. Understanding the basis for this apparent paradox, that treatment response and survival in cancer are not necessarily linked, is essential for progress in the development of effective therapeutics.

**Cancer stem cells and cancer therapeutics**

It is becoming clear that many, if not most, malignancies arise from a rare population of cells that exclusively maintain the ability to self-renew and sustain the tumor. Moreover, these “cancer stem cells” are often biologically distinct from the bulk of differentiated cancer cells that characterize the disease. Chronic myeloid leukemia (CML) was the first malignancy suspected to arise from stem cells. CML occurs at the level of hematopoietic stem cells and, like their normal counterparts, CML stem cells undergo orderly differentiation. Thus, the bulk of the leukemic mass in CML consists of differentiated blood cells, whereas the rare cells responsible for disease maintenance resemble normal hematopoietic stem cells. Another illustrative example of the cancer stem cell concept is multiple myeloma. Although myeloma is characterized by neoplastic plasma cells, these cells appear to be terminally differentiated like their normal counterparts. The myeloma plasma cells that form the bulk of the tumor arise from a minute population of less differentiated cancer stem cells that resemble post–germinatal center B cells. Other diseases that appear to arise from cancer stem cells are acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome, breast cancer, and brain cancer.

The existence of cancer stem cells has profound implications for the development of new anticancer agents, especially those explicitly targeted at specific cellular pathways or antigens. Imatinib has largely replaced interferon-alpha (IFN) as the standard-of-care for newly diagnosed patients with CML, based on an interim analysis of a multicenter, randomized trial showing higher response rates for imatinib. Although follow-up is ongoing, to date this study has not shown a survival advantage for imatinib. Moreover, emerging data suggest that imatinib may not be able to completely eradicate CML. Patients with CML who achieve the best responses toward imatinib and IFN are quite different, and may be explained by in vitro findings suggesting that imatinib, although effective and leads to high cure rates. In these cancers, it is principal at the rare CML stem cells. IFN’s treatment effects are consistent with data suggesting that IFN’s activity is directed principally at the rare CML stem cells. IFN’s treatment effects mimic attacking just the root of the dandelion. Although this has no immediately discernible effect on the weed, over time the weed will eventually wither and die. Thus, treatments that selectively attack cancer stem cells will not immediately eliminate the differentiated tumor cells. In this situation, cure (elimination of the cancer stem cells) in effect precedes the clinical demonstration of complete remission (clearance of the differentiated cancer cells) and could occur without actual disease shrinkage.

The “dandelion phenomenon” also applies to other malignancies. The novel antmyeloma agents bortezomib and lenalidomide can inhibit myeloma plasma cells but appear to have little activity against myeloma stem cells in vitro; this differential activity may explain why these compounds yield significant clinical responses but not cures. Conversely, rituximab kills myeloma stem cells in vitro, but has no activity against myeloma plasma cells that lack the relevant target antigen (CD20). Not surprisingly, rituximab was found to have limited activity against myeloma in a short-term clinical trial. Rituximab’s activity against myeloma stem cells probably could not have manifested as immediate clinical responses in this trial because of the persistence of the long-lived, but terminally differentiated, myeloma plasma cells. Gemtuzumab (anti-CD33 monoclonal antibody linked to calicheamicin) has been approved for relapsed AML and is currently being studied in newly diagnosed patients. Although most AML cells express the myeloid antigen CD33, the leukemic stem cells in most cases of AML phenotypically resemble hematopoietic stem cells and do not express antigens specific for more differentiated blood cells, including CD33. In addition, monoclonal antibody conjugates directed against the B-cell antigen CD19 expressed by most ALL cells are being studied in ALL patients. Yet, it appears that many cases of ALL also arise from hematopoietic stem cells that do not express CD19. Hence, targeting antigens not expressed by leukemic stem cells (CD33 and CD19 in AML and ALL, respectively) is unlikely to improve the curability of these diseases. It should be noted that in some cancers, such as pediatric ALL, testicular cancer, and Hodgkin lymphoma, chemotherapy is very effective and leads to high cure rates. In these cancers, it is likely that the treatment targets both the cancer stem cells and their differentiated progeny, leading to successful eradication of the disease.

Traditional response criteria measure tumor bulk and may not reflect changes in rare cancer stem cell populations. Therapies (eg, imatinib in CML, bortezomib in myeloma, and gemtuzumab in AML) that target mature cancer cells (ie, the visible parts of the weed) may produce clinical improvement and indeed dramatic responses. However, such therapies are unlikely to effect cures if the rare cancer stem cells (ie, the roots) responsible for disease maintenance are not also targeted. Imatinib could even induce undetectable BCR-ABL expression by polymerase chain reaction without affecting CML stem cells that represent less than 0.1% of the CML cell population. Standard response parameters may not only potentially overestimate the effect of therapy on the minute population of stem cells, but may also underestimate it. As with IFN in CML and rituximab in myeloma, therapy directed against cancer stem cells might be prematurely abandoned if clinical
activity is judged solely by criteria that reflect the effects of treatment on the bulk of the cancer.

**Surmounting the clinical response barrier**

Disease-free survival may be the best reflection of activity against rare cancer stem cells, but this requires long studies and large patient numbers. Thus, using survival as the primary clinical end point is often impractical, and new clinical paradigms and methodologies are needed. Although it may not be obvious what these new methodologies should be, we believe it is time to begin discussions aimed at changing clinical paradigms. Consideration should be given to relying more heavily on preclinical modeling, to eliminating traditional measures of clinical response as trial end points, and to using novel statistical methods to evaluate activity on rare cancer stem cells.

A detailed preclinical knowledge of the effects of new treatments on cancer stem cells would greatly enhance the development of clinical trials. However, healthy skepticism exists as to how well these models reflect the actual clinical situation, and thus preclinical studies and clinical trials with new therapies often proceed somewhat in isolation. Preclinical models, such as immunodeficient mice and novel in vitro culture systems, for studying cancer stem cells are being developed, and emerging data suggest that many of these systems parallel the in vivo behavior of cancer stem cells quite closely. Using the correct models, it may be possible to develop a detailed understanding of the mechanisms of action of new treatments, as well as strategies for optimizing activity; this may allow a fully developed new approach to be taken directly from the "bench to the bedside."

**References**


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