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 prerituximab 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)

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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, 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-germinai 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 to imatinib (reverse-transcriptase–polymerase chain reaction negativity for BCR-ABL transcripts) invariably relapse quickly when the drug is discontinued, and many have evidence of progression despite remaining on the drug. These observations may be explained by in vitro findings suggesting that imatinib, although highly active against differentiated CML progenitors, may have limited activity against CML stem cells.

The dandelion phenomenon

The pattern of the clinical responses that patients with CML display toward imatinib and IFN are quite different, and may be explained by these agents’ divergent effects on CML stem cells and differentiated progenitors. The rapid responses induced by imatinib are likely a consequence of its impressive activity against differentiated CML progenitors that make up the bulk of the leukemia. Data suggesting that these early responses may not be durable could be explained by CML stem cell resistance to imatinib. This pattern of activity is analogous to cutting a dandelion off at ground level. Although this will eliminate the visible portion of the weed, the unseen root also needs to be eliminated to prevent regrowth of the weed. Conversely, responses to IFN are slow and gradual, often taking years to develop, but can be durable; this is 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 leukemia 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.46

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,22,23,27,28 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.”

Effective preclinical models for cancer stem cells may ease the task of clinical trial development, but will not eliminate the need for new clinical paradigms. For example, evaluating the efficacy of treatments against cancer stem cells should be possible by using them after debulking the differentiated cells that constitute the majority of the tumor. Such an approach could be considered in many cancers where clinical debulking is successful, but transient. For example, IFN could be used in patients with CML after they have achieved remissions to imatinib, thus optimizing the activity of both drugs against their respective targets: imatinib for the committed CML progenitors and IFN for the CML stem cells. The primary end point of such a trial would be progression-free survival off imatinib with a secondary end point of serially measuring the CML stem cells in vitro. A similar trial design could be used with rituximab in myeloma, using bortezomib for debulking. The fate of the cancer stem cells could also be assessed serially as a secondary end point using preclinical models. Using Bayesian models, the statistical validity could be analyzed. A positive correlation between survival and cancer stem cell assays would validate the use of these assays for future clinical trials. At the same time, there is a need for novel statistical methods to describe changes in cancer stem cell populations over time and in response to treatment. Rethinking both our preclinical and clinical methodologies for new drug development to include the cancer stem cell concept has the potential to open new avenues of treatment for many cancers.

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