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Cancer Stem Cells: From Bench to Bedside

Richard J. Jones, William Matsui

Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

Correspondence and reprint requests: Richard J. Jones, MD, Room 244, Bunting-Blaustein Cancer Research Building, 1650 Orleans Street, Baltimore, MD 21231 (e-mail: rjjones@jhmi.edu).

ABSTRACT

Objective clinical responses to anticancer treatments often do not translate into substantial improvements in overall survival. Recent data suggesting many cancers arise from rare self-renewing cells (cancer stem cells) that are biologically distinct from their more numerous differentiated progeny may explain this paradox. Current anticancer therapies have been developed to target the bulk of the tumor mass (ie, the differentiated cancer cells). Although treatments directed against the bulk of the cancer may produce dramatic responses, they are unlikely to result in long-term remissions if the rare cancer stem cells are also not targeted. Better understanding the biology of cancer stem cells and re-examining our preclinical and clinical drug development paradigms to include the cancer stem cell concept have the potential to revolutionize the treatment of many cancers.
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KEY WORDS

Cancer stem cells • Imatinib • Leukemia • Multiple myeloma

HISTORICAL PERSPECTIVE

It has been clear since at least the 1970s that only a minority of cells from most hematologic malignancies and solid tumors are clonogenic in vitro and in vivo [1,2]. Investigators called these rare clonogenic cells "tumor stem cells" [1,2]. However, this low clonogenic potential could represent proliferative capacity exclusively restricted to a small subset of cancer cells or alternatively all the cells within a cancer retaining the capacity to proliferate but only at a low rate. Insufficient tools available at the time precluded investigators from distinguishing which of these 2 possibilities explained the low clonogenicity of most cancers.

Fialkow and his colleagues [3] first suggested that CML arose from a transformed hematopoietic stem cell nearly 40 yr ago, when they showed that granulocytes and RBCs from patients with CML had a common cell of origin. The stem cell origin of CML was confirmed nearly 15 yr ago when several groups, using characteristics known to define normal HSC, identified and isolated CML stem cells capable of expansion ex vivo [4]. Dick and colleagues extended these observations >10 yr ago, showing that primitive hematopoietic stem cells purified from patients with AML [5] and CML [6] would generate leukemia in vivo when injected into NOD/SCID mice. More recently, cancer stem cells that are biologically distinct from the differentiated cells that make up the bulk of the tumor have also been found in myelodysplastic syndromes [7], breast cancer [8], multiple myeloma [9], brain cancer [10,11], and lung cancer [12]. However, the biologic and clinical relevance of cancer stem cells remains unclear.

PARADOX OF RESPONSE AND SURVIVAL

A cardinal principle of cancer therapeutics has been that evidence of a clinical response will translate into improved survival. The major advantage of using clinical response as the primary endpoint of therapeutic trials 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 survival benefit adds significant complexity to clinical trial design, usually requiring the accrual of large patient numbers and long follow-up to provide statistical significance.

Although clinical responses can clearly decrease side effects and improve quality of life, there is surprisingly little evidence that disease response is an appropriate surrogate for survival [13]. There are numerous examples in which response does not predict for an improved survival. Patients with indolent lymphoma who achieved a CR with conventional-dose therapies in the pre-rituximab era did not show a survival advantage over similar patients treated with a

"watch and wait" approach [14]. In multiple myeloma, neither the magnitude nor the kinetics of clinical response had an effect on survival [15]. Even the most intensive therapy for myeloma, blood transplantation or BMT [16,17], provided no overall survival advantage in a recently published national intergroup trial [18] or a recent meta-analysis [19]. Similarly, significant clinical responses in pancreatic cancer [20] and prostate cancer [21] have not translated into survival benefits. Further, despite new treatments that currently produce CRs in most women with ovarian carcinoma, cures are rare [22].

CANCER STEM CELLS AND CANCER THERAPEUTICS: THE DANDELION PHENOMENON

Emerging data with 1 of the most successful new anticancer agents has helped shed light on this paradox that response and survival are not always linked. Imatinib has replaced IFN-α as the standard of care for patients with newly diagnosed CML based on an interim analysis of a multicenter, randomized trial showing higher response rates for imatinib [23]. With up to 5 yr of follow-up, most of the cytogenetic CRs to imatinib remain durable [24]. However, it now appears that imatinib may not be able to completely eradicate CML. Patients with CML who achieve the best responses to imatinib (RT-PCR negativity for BCR-ABL transcripts) can relapse quickly when the drug is discontinued [25-27] or even progress while remaining on the drug [28].

BCR-ABL gene amplification or mutations prevent productive imatinib binding [29], and secondary genetic mutations capable of driving BCR-ABL independent leukemic growth may also be present, even at initial diagnosis [30]. However, these genetic mechanisms of resistance are probably not responsible for the persistent CML in most patients treated with imatinib. Several investigators have provided evidence that imatinib has differential effects on CML cells depending on their state of differentiation: although imatinib is toxic to differentiated CML progenitors, CML stem cells may be relatively or even completely resistant to the drug [31-33]. The basis for the differential activity of imatinib toward CML stem cells and their differentiated progeny is likely multifactorial [33]. CML stem cells share many biologic properties with their normal counterparts [4] that likely limit the effectiveness of therapeutic strategies targeting BCR-ABL signaling. Hematopoietic stem cells are largely quiescent and normally express high levels of ATP-binding cassette (ABC) transporters, such as the multidrug resistance 1 gene [34] and ABCG2 [35]. Both factors may limit the cellular uptake of imatinib, which is a substrate for the ABC transporters [36,37]. Maybe most important, BCR-ABL appears to have different effects on CML stem cells and their differentiated progeny [33]. The cellular expansion in CML occurs primarily in the differentiated progenitors, rather than the in stem cell pool [4,38]. Moreover, BCR-ABL expression appears to be required for the survival of CML progenitors, but the same does not appear to be true for CML stem cells, where the BCR-ABL gene can be silent [4,39]. These data suggest that BCR-ABL may produce only subtle effects in CML stem cells, and thus its inhibition may similarly have only minor consequences for these cells [33]. Therefore, based on the longevity (possibly >10 yr) of their normal counterparts, CML stem cells likely survive for years even if BCR-ABL activity is completely inhibited [4]; eventually, because of intrinsic genomic instability, CML stem cells and their progeny may develop genetic resistance to imatinib.

The rapid responses induced in patients with CML by imatinib [23] are likely a consequence of its impressive activity against differentiated CML progenitors that make up the bulk of the leukemia. An inability to cure CML [25-28] in the face of such potent initial activity is consistent with 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 (Figure 1) [13,33,40]. Conversely, the slow, but occasionally durable, responses seen in IFN-treated patients [41] is consistent with reports showing that the activity of IFN is directed principally at the rare CML stem cells [33,42]. This treatment effect mimics 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 if its root has been eliminated (Figure 1) [13,33,40].

The "dandelion phenomenon" also appears to apply to other cancers. Although multiple 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 actually arise from a minute population of less differentiated cancer stem cells that resemble memory B cells and have the ability to self-renew, differentiate, and maintain the disease [9]. It appears that most cancer stem cells arise from normal counterparts with stem cell features; although not stem cells in the classic sense, memory B cells could be considered "honorary" stem cells, ie, they are long-lived, self-renew, and differentiate into plasma cells to maintain long-term immune memory. We found that the novel antimyeloma agents, bortezomib and lenalidomide, have little activity against myeloma stem cells in vitro, despite being quite active against the plasma cells [43]. Conversely, rituximab and alemtuzumab eliminated myeloma stem cells in vitro, but

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