Abstract. The concept of individualized cancer chemotherapy emerged three decades ago from the observation that a small fraction of cells in primary tumors can form colonies in soft agar similar to stem cells of the hematopoietic system. In a series of retrospective and prospective clinical studies, clonogenic tumor growth and effects of anticancer agents on the putative cancer stem cells were assessed as predictive factors. The results of these trials showed that clonogenic growth is associated with poor outcome and drug resistance. Recent breakthroughs enabling isolation and the molecular classification of cancer stem cells have renewed interest in cancer stem cells as a therapeutic target. Here, we provide a current overview of cancer stem cell biology and highlight possibilities for targeted intervention with existing and novel experimental anticancer agents.

Despite drastic improvements in the use of existing therapeutic modalities and the advent of “molecularly targeted agents”, the outlook for most cancer patients, particularly those with advanced solid tumors, is still poor. Even though many of the new anticancer drugs can result in tumor shrinkage, their impact on survival has been modest (1). Resistance to cancer chemotherapeutic agents, both new and old, remains a major problem (2).

There is emerging evidence that a rare and biologically distinct subpopulation of cancer cells has the ability to self-renew, self-protect, and proliferate indefinitely. The characteristics of this population are analogous to normal stem cells and therefore these cells have been described as “cancer stem cells”. Most conventional chemotherapies affect differentiated cancer cells that make up the bulk of a tumor, but are often ineffective against cancer stem cells (3, 4). As a consequence, an initial reduction in tumor bulk is frequently followed by rapid relapse of the tumor. One of the characteristics of cancer stem cells is a high expression of drug efflux pumps. Thus, tumors repopulating after relapse are frequently composed of chemotherapy resistant cells. The current challenge in anti-cancer drug development is therefore to find means to selectively target and eradicate cancer stem cells. In this article, we will review the historical background of stem cells and cancer stem cells, as well as the role of targeting cancer stem cells for individualized cancer therapy (5).

The Stem Cell Concept

The stem cell concept was proposed in the early 1900s. However, not until the early 1960's stem cells were actually identified. Two Canadian scientists, Ernest A. McCulloch and James E. Till, pioneered the field by injecting bone marrow cells into irradiated mice. Visible nodules were observed in the spleens of the mice and were described as “spleen colonies”. They initially speculated that each nodule arose from a single marrow cell and perhaps a stem cell. Later on, they were able to demonstrate that each nodule did indeed arise from a single cell (6, 7). Hence, stem cells are cells with the exclusive ability to self-renew, and develop into multiple lineages through differentiation (8). During embryonic development and adult life, stem cells divide in a particular pattern. Polarity is the unequal spatial distribution of cellular constituents. For instance, there are two types of polarity in simple epithelia: planar cell polarity and apicobasal polarity. Stem cells are capable of dividing asymmetrically and possess an axis of polarity. After asymmetric division, one daughter cell will retain stem cell properties and remain undifferentiated (Figure 1). The other daughter cell will become a committed progenitor. There is evidence that disruption of the process of...
asymmetric cell division and loss of polarity can induce a cancer-like state in neuronal stem cells (9, 10). In addition to their capacity for self-renewal, recent work has demonstrated that stem cells can “self-protect” through high expression of drug efflux pumps including BCRP (ABCG2), p-glycoprotein, and MRP (11).

Cancer Stem Cells

Stem cells and cancer cells are similar in many aspects including their self-renewal ability, the ability to differentiate, their limitless proliferate capacity by expression of telomerase, the ability to activate anti-apoptotic pathways, increased membrane transporter activity, resistance to cytotoxic agents, and their ability to migrate. It was formerly believed that cancer is a homogenous disease and that each cancer cell can give rise to the entire tumor. However, recent studies have demonstrated that only a rare and biologically distinct subset of cancer cells is capable of extensive proliferation. In the 1960s, Bruce and Van Der Gaag (12) found that only 1 in 130 (0.77%) murine lymphoma cells were capable of forming a colony in the spleen. Subsequently, McCulloch (13) illustrated that 1 in 10,000 to 1 in 100 mouse myeloma cells was able to form colonies in clonal in vitro colony-forming assays. This subset of cells was described as leukemic stem cells (LSC). McCulloch also proposed that in order to be successful in controlling the tumor growth, these tumor stem cells must be eradicated. Nevertheless, based on these early observations it remained still possible that all leukemic cells are clonogenic, but may have been unable to proliferate under the assay conditions used. In order to demonstrate that cancer cells are in fact heterogeneous and only a distinct subset of cells has clonogenic capacity, it was essential to separate different populations and define one subset of cancer cells that has extensive proliferating capacity. This has been recently accomplished by John E. Dick et al. (14). The latter evaluated cell surface markers that are used to identify hematopoietic stem cells in acute myeloid leukemia (AML) and demonstrated that only cells with a CD34+/CD38− phenotype were able to initiate human AML in non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice. These cells were capable of self-renewal, proliferation and differentiation in vivo into the original leukemic blast, indicating leukemic stem cells. More recently, it was demonstrated that leukemic stem cells are not functionally homogeneous but consist of a distinct hierarchically arranged class similar to normal hematopoietic stem cells (15).

Importantly, the pathways that regulate the self-renewal of normal stem cells (16-18), including Wnt, Notch, and Hedgehog, have been found to play an important role in human carcinogenesis (18). Dysregulation of these pathways has been reported in colon, pancreatic, gastric, prostate (19), cervical, leukemic, skin (20) and breast cancers (18, 21, 22).

Cancer Stem Cells in Solid Tumors

Similar to hematological malignancies, solid tumors have been demonstrated to possess a phenotypically distinct and rare population of clonogenic cancer cells (23, 24). Merely 1 in 1,000 to 1 in 5,000 lung cancer, ovarian cancer or neuroblastoma cells were able to form colonies in soft agar (8, 25). Recently, Al-Hajj et al. (26) described a distinct cell population with a CD44+/CD24−/low lineage− phenotype in breast cancer. As few as 100 cells of this particular population were capable of generating a phenotypically diverse breast tumor similar to the original patient tumor in NOD/SCID mice, whereas as many as 20,000 cells with CD44+/CD24− phenotype were unable to generate a tumor (18, 26). Singh et al. (27, 28) demonstrated that a CD133+/Nestin+/Lineage− population from human brain tumors was capable of generating clonal tumor spheres in suspension culture. Again, only 100 cells of this explicit subpopulation could produce the phenotypically diverse tumor resembling that from the patient in the NOD/SCID mouse repopulation assay, while 10^5 of CD133− cells engrafted but were unable to form a tumor. Matsui et al. (29) demonstrated that a distinct CD138− population in multiple myeloma cells was clonogenic in vitro and in NOD/SCID mice. Furthermore, Collins et al. (30) illustrated that only the population with CD44+/α5β1hi/CD133+ phenotype in prostate cancer was capable of self-renewal and recapitulation of the original tumor. In contrast to the report by Singh in brain tumors, the fraction of this population in prostate cancer was relatively small and constant regardless of tumor grade. In addition, cancer stem cells were also recently described in lung cancer (31), head and neck (32), pancreas (33) and colon (34) carcinomas. Interestingly, several stem cell surface markers are shared by cancer stem cells in different tumor types. These markers include CD44, α5 integrin, β6 integrin, and CD133. Owing to the exponentially increasing reports on the identification and definition of cancer stem cells in the scientific literature, it is possible that cancer stem cells will be identified for every known tumor type.

Changes in the Cancer Treatment Paradigms

The vast majority of the over 100 registered and clinically utilized anticancer drugs are “classical” cytotoxic agents. Their common mechanism of action is the preferential killing of rapidly dividing cells by either interruption of the mitotic spindle apparatus or by targeting DNA. Many cancers have a relatively higher proportion of proliferating cells than most normal tissues, and consequently are more sensitive to cytotoxic agents, creating a therapeutic window. Even though some tumors may initially show measurable response to these treatments, the reduction in bulk tumor mass is often short lived and associated with severe side
Figure 1. Cancer stem cell (CSC) hierarchy and possibilities for therapeutic intervention. Attractive CSC targets include the self-renewal pathway, asymmetrical division, the cancer stem cell niche and differentiation. Transient amplifying cancer cells (TA) and differentiated cancer cells (DC) can be treated by conventional debulking methods such as chemotherapy, surgery and radiation.

Figure 2. Cancer treatment paradigms. The two curves demonstrate the typical courses of disease for more than 95% of tumors (red) if treated with currently available cytotoxic chemotherapy alone, and the potential impact of cancer stem cell-directed therapies (black) on the curability of cancer.
effects (Figure 2). Due to the associated toxicities, cytotoxic agents are often given intermittently to allow recovery of normal tissues. However, this also can lead to tumor regrowth, and repopulation of tumor mass with drug resistant cancer cells. To date, only about 4% of advanced cancers requiring systemic treatment are curable (35).

“Molecularly targeted agents”, i.e. drugs designed to inhibit specific pathways critical for the maintenance and proliferation of cancer cells, have raised much hope that advanced cancer could become a chronically treatable condition, instead of an acutely fatal disease. In fact, several new approved therapies inhibiting a disease-specific target have shown substantial clinical benefit. The best-known illustration is chronic myeloid leukemia (CML), a disease defined by constitutive activation of a tyrosine kinase as a result of a chromosomal translocation. The BCR-ABL kinase can be inhibited by the tyrosine kinase inhibitor, imatinib (1, 36). Imatinib has become the standard-of-care for CML progenitors/stem cells, relapse is inevitable after discontinuation of the drug. This highlights the imperative of devising new approaches designed to both eradicate cancer stem cells as well as reduce tumor bulk in order to achieve cure (Figure 2).

The Human Tumor Stem Cell Assay (HTCA) and Individualized Patient Chemosensitivity Testing

There are multiple and potentially complementary strategies in development to target cancer stem cells (Figure 1). In an approach analogous to the culture and sensitivity assays used for the management of microbial infections, Salmon and Hamburger pioneered the concept of targeting cancer stem cells and concomitantly individualizing cancer therapy in the late 1970s (41). Single cell suspensions prepared from cancer patients’ tumor tissues or effusions were cultured in multilayered soft agar and treated with anticancer drugs. This technique was termed “clonogenic assay” or “human tumor stem cell assay” (HTCA). Salmon and Hamburger based their hypothesis that tumor stem cells grow in soft agar on the fact that tumor cells in this semi solid matrix had a low plating efficiency (0.001 to 0.1%), similar to the extent of colony formation by bone marrow. Additionally, the homogenous appearance of tumor colonies as well as the staining of these colonies with cell type specific dyes was consistent with a stem cell hypothesis (41, 42). Moreover, the secondary colonies that arose when primary HTCA colonies were disaggregated and replated, were observed to be similar to the primary colonies in size, morphology, and culture requirements demonstrating stem cell-like self-renewal properties (43). The HTCA was subsequently used in a first approach to personalize cancer medicine by assessing a patient’s prognosis and response to chemotherapy. E.g. Dittrich et al. (44) demonstrated that clonogenic growth in the HTCA is an independent prognostic factor for worse outcome in patients with ovarian cancer and most likely reflects the aggressiveness of tumors with a higher cancer stem cell fraction. Unlike the culture and sensitivity assays for antimicrobial drugs, the HTCA was found to be a better predictor for clinical resistance rather than sensitivity (41, 45) (Table I). Hamburger et al. performed the first HTCA chemosensitivity studies comparing in vitro drug activity to clinical response and found a correct prediction for drug resistance in ovarian carcinoma and myeloma of 100%, whereas the predictive value for drug sensitivity was only 89% (Table I). Similarly, when Fiebig et al. compared the response of a cohort of 66 assorted patient tumors in the HTCA in vitro to the clinical response, 62% of the comparisons for drug sensitivity, and 92% of the comparisons for drug resistance were accurate (Table I).

The first randomized clinical trial using the HTCA as a guidance for treatment decisions was published by Von Hoff et al. in 1983 (46). There were a total of 470 patients with 27 types of advanced metastatic cancers. The overall response rate in the assay-guided therapy was 25%, compared to 14% in the empiric treatment group (p=0.0005) (Table I) (46, 47). Subsequently, a second randomized clinical trial with 211 ovarian cancer patients showed that the response rate (22 %) was significantly higher in assay-guided therapy (p=0.03) compared to the empiric therapy group (3%) (47, 48). However, selecting chemotherapy for individual patients based on the in vitro drug sensitivity testing is not currently recommended outside of the clinical trial setting (41). Indirectly, these data demonstrate that a fraction of extremely therapy-resistant cancer cells exists, which appears to be at least partially composed of cancer stem cells.

Cancer Stem Cell-Directed Therapies

There are several mechanisms of drug resistance in cancer stem cells. Cancer stem cells primarily exist in G0 phase and thus are resistant to cell cycle specific drugs such as 5-Flouracil (5-FU) (49). Cancer stem cells also have a
remarkable capacity for repair of DNA damage such as that caused by alkylating agents (50). Most importantly, cancer stem cells exhibit a high expression of the ATP-binding cassette (ABC) transporters especially BCRP (breast cancer resistance protein or ABCG-2) and MDR1 (multi-drug resistance-1, ABCB1, or P-glycoprotein) as part of their self-protection capabilities. Amongst the substrates of these transporters are anthracyclines, vinca alkaloids and other natural product derivatives (51). This mechanism of drug resistance has significant potential for development of stem cell-directed treatment regimens. Several ABC transporter inhibitors are currently under clinical investigation (Table II). Phase I/II clinical trials include e.g. combining of the novel potent P-glycoprotein inhibitor, Zosuquidar, with chemotherapy. It will be interesting to evaluate whether the combination of conventional cytotoxic debulking therapy and the novel strategy of resistance reversal can lead to a better outcome (52).

In addition, cancer stem cells also express higher levels of antiapoptotic proteins, especially the Bcl-2 family members. Oblimersen, a Bcl-2 antisense oligonucleotide, is also currently been studied in multiple cancers (53, 54) (Table II).

Targeting self-renewal pathways of cancer stem cells such as Notch, Wnt, and Hedgehog signaling is a third avenue under investigation. While these essential pathways are shared by normal stem cells, multiple studies in animal models have shown that interdicting these self-renewal pathways may selectively target cancer stem cells (18). Inhibitors of the Hedgehog pathway, such as cyclopamine (Table II), were identified and have a therapeutic window with remarkable activity against a wide range of human cancer cell lines and tumor xenografts including ovarian cancer (55), medulloblastoma (56), gastrointestinal neuroendocrine carcinomas (57), and prostate cancer (19). Similarly, gamma secretase inhibitors such as LY-411,575, which block Notch activation, were found to have activity in Kaposi’s sarcoma (58), breast cancers (59) and melanoma (60).

Another possibility to target the self-renewal capacity of cancer stem cells is to force them into differentiation (61). Retinoic acid can induce differentiation in embryonic stem cells (62). All-trans retinoic acid (ATRA) has been used with great success in combination chemotherapy in acute promyelocytic leukemia (APL), a disease with a cure rate of more than 70%. This suggests that cancer stem cells are being successfully eliminated in this particular disease (63-65). Arsenic trioxide, an agent that may function through telomere targeting (described below), has recently been demonstrated to further improve the rate of cure in patients with APL (66, 67). Histone deacetylases (HDACs) regulate gene transcriptional activity. HDAC inhibitors can be used for epigenetic reprogramming of silenced genes and thus induce cell differentiation (Table II). The HDAC inhibitor, vorinostat (SAHA), has been found to have activity in multiple malignancies including leukemia (68), lymphoma (69), thyroid cancer (70), myeloma (71), and hepatocellular carcinoma (72). Thus, SAHA might have the potential for targeting CSCs and prove a good combination partner for debulking agents.

The stem cell niche (Figure 1), although not well defined at present, must also be considered as a CSC target. The niche is a specialized cellular environment that provides stem cells with the support needed for self-renewal (73). Vascular endothelial growth factor (VEGF) has recently been validated as a target for anti-cancer therapeutics with demonstrated improvement in outcomes in colon (74), lung (75) and breast cancer (76, 77) when bevacizumab (anti-VEGF antibody) has been combined with cytotoxic chemotherapy (Table II). The driving hypothesis for this approach was that tumors could not grow beyond a certain size without generating a new blood supply and therefore, inhibition of the blood supply would obliterate the malignancy, resulting in “normalization” of blood supply (78). More recently, a stem cell-related hypothesis has been proposed that would better explain the efficacy of bevacizumab. It has become
apparent that cancer stem cells live in vascularized lacunae and that anti-VEGF therapy may destroy these niches and consequently improve outcome (79).

Finally, limitless proliferation is a key feature that defined stem cells and is accomplished by activation of the enzyme telomerase. Telomerase prevents telomere-associated replicative senescence and DNA-damage by adding telomeric repeat sequences at chromosomal ends. Over-expression of the catalytic subunit of telomerase, hTERT, has been found to promote stem cell mobilization, whereas short telomeres have been reported to cause stem cell failure (80, 81). Although telomerase is present in embryonic tissues, germ cells, adult stem cells, and tumor cells, a therapeutic window for targeting cancer might exist. CSCs may have shorter telomeres than normal stem cells and be more susceptible to loss of telomerase/telomere uncapping, thereby providing a promising therapeutic target which is discussed in more detail below (35).

### Table II. Drugs with cancer stem cell targets.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Specific Targets</th>
<th>References</th>
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<tbody>
<tr>
<td>Zosuquidar</td>
<td>P-glycoprotein</td>
<td>Sandler et al., 2004 (52)</td>
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<td>Oblimersen</td>
<td>Bel-2 antisense oligonucleotide</td>
<td>Bedikian AY et al., 2006 (53)</td>
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<td></td>
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<td>Badros AZ et al., 2005 (54)</td>
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<td>Cycloamine</td>
<td>Hedgehog pathway</td>
<td>Chen X et al., 2006 (55)</td>
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<td>Romer JT et al., 2004 (56)</td>
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<td>Shida T et al., 2006 (57)</td>
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<td>Karhadkar SS et al., 2004 (19)</td>
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<td>LY-411,575 Gamma</td>
<td>Notch pathway</td>
<td>Pece S et al., 2004 (59)</td>
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<td>secretase inhibitor</td>
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<td>Nickoloff BJ et al., 2005 (60)</td>
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<tr>
<td>Retinoic acid (ATRA)</td>
<td>Differentiation</td>
<td>Sanz MA et al., 2000 (63)</td>
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<td>HDAC inhibitors e.g.</td>
<td>Differentiation</td>
<td>Jones IJ et al., 2005 (68)</td>
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<td>SAHA</td>
<td>Epigenetic reprogramming</td>
<td>O’Connor OA et al., 2005 (69)</td>
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<td>Luong QT et al., 2006 (70)</td>
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<td>Yaccoby S et al., 2006 (71)</td>
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<td>Ocker M et al., 2005 (72)</td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>Stem cell niche</td>
<td>Yang ZJ et al., 2007 (79)</td>
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<td>RHP54</td>
<td>Telomerase (hTERT)</td>
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<tr>
<td>Cisplatin</td>
<td>Telomerase</td>
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<tr>
<td>GRN163L</td>
<td>Telomerase (hTERC)</td>
<td>Dikmen et al., 2005 (91)</td>
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ATRA (All-trans retinoic acid); HDAC (histone deacetylase); hTERT (human telomerase reverse transcriptase); hTERC (human telomerase RNA component).

### Telomerase Inhibition and Cancer Stem Cell Targeting

When telomerase emerged as a cancer inhibitory target, our laboratory was the first to note that the standard agent cisplatin (CDDP) has telomerase inhibitory properties and that these effects might contribute to the curability of testicular germ cell tumors (TGCT) by CDDP (82-84). The fact that telomerase modulation is associated with the eradication of TGCTs, which contain undifferentiated pluripotent stem cells, supports telomerases and telomerase as cancer stem cell targets (Table II). We have recently created a unique pair of stable isogenic breast cancer cell lines, MCF-7 cells and mutant MCF-7 hTERT-expressing clones (85). In mutant hTERT MCF-7 cells, telomerase activity was drastically reduced and telomere length shortened to a critical size of 1.9Kb after 120 population doublings. In the HTCA, these MCF-7 clones were less clonogenic and formed much smaller colonies compared to control cells, demonstrating a function for telomerase in...
clonogenic growth. Similar to genetic telomerase inhibition by mutation, the telomere targeting agent RHPS4, which specifically inhibits telomerase by displacing hTERT from the telomeres (85) was significantly more active in cell populations that grow in the HTCA than bulk MCF-7 cells assayed by using the methyltetrazolium (MTT) proliferation test. This observation was made in many other tumor cell lines including the epithelial ovarian cancer lines A2780 and ADDP for which data are depicted in Figure 3. ADDP is a cisplatin resistant subclone of A2780 (resistance factor 10x) (86) with up-regulated telomerase activity levels and elongated telomeres (87). This translates into a 25-times higher plating efficiency in the HTCA compared to parental A2780 cells, suggesting an expansion in cancer stem cells in the ADDP line. We further analyzed these cell lines with the side population (SP) method. The SP is enriched with stem/primitive progenitor cells and has the distinct capacity to efflux Hoechst 33342 dye due to the presence of ABC transporters (88-90). This leads to a unique appearance of SP cells by fluorescence-activated cell sorting (FACS). While the original epithelial ovarian cancer cell line A2780 exhibits no measurable SP phenotype, SP was detected in ADDP, a cisplatin resistant subclone, at a mean percentage of 0.03% (data not shown). Notably, while the telomere targeting agent RHPS4 is largely cross-resistant with cisplatin in effecting bulk tumor cell growth (resistance factor ~8, Figure 3), both A2780 and ADDP cells were equally sensitive to RHPS4 when grown in the HTCA (Figure 3). These data indicate that RHPS4 might be able to target cancer stem cells and overcome their resistance to standard cytotoxic agents (Table II). RHPS4 is currently undergoing preclinical toxicology evaluation and is scheduled for entry into phase I clinical trials. The first telomerase inhibitor in clinical development is GRN163L, a 13-mer antisense oligonucleotide N3'→P5' thio-phosphoramidate targeting the telomerase RNA component, which has also shown activity against clonogenic tumor cell growth (35, 91). Both, RHPS4 and GRN163L have potential as combination partners with cytotoxic debulking agents (Figures 1, 2). Moreover, novel strategies utilizing cisplatin-based regimens should be considered with the new insight that they target telomerase and thus inhibit cancer stem cell growth.

**Future Perspectives and Importance of Cancer Stem Cell Therapies**

More than three decades ago, the culturing of cancer stem cells from patient tumors and evaluating their response to anticancer drugs was a first attempt toward individualized cancer therapy (25, 41). The approach was unsuccessful because of the intrinsic resistance of cancer stem cells to...
cytotoxic agents, the only available drugs at that time. Now, with a better understanding of the underlying molecular mechanisms and biology, we are able to rationally attack cancer stem cells (Figure 1). Most interestingly, combination chemotherapy regimens, that can cure tumors such as testicular cancers and APL, contain agents that in retrospect target crucial stem cell pathways, namely self-renewal and limitless proliferation. As summarized in Table II, multiple new compounds that target key cancer stem cell pathways have evolved from anticancer drug development efforts. However, clinical trials must be designed to examine cancer stem cell markers and effects of new agents on this rare cell population. For this purpose the HTCA should be revisited as a prognostic factor (44). We must further understand that an ultimate cure for cancer may require a multi-step approach. Initially, differentiated cancer cells that make up the bulk of the tumor could be treated with conventional chemotherapy, radiation, or surgery (Figures 1, 2). These strategies will not only alleviate patients’ symptoms caused by the bulk tumor mass, but they may also mobilize cancer stem cells from their niches and render them more susceptible to therapy. Subsequently, when tumor burden is low, cancer stem cell-directed treatments should be initiated. It is possible that these treatments may require long-term administration in order to prevent relapses and recurrences (Figure 2). However, it is conceivable that short term administration of these agents may be beneficial as has been demonstrated with cisplatin based therapy in germ cell tumors.

Finally, individualized cancer therapies that are highly specific and effective will require the recognition of tumor cell heterogeneity and follow a multifaceted approach. Preclinical testing will be needed to optimize strategies and novel clinical trial designs must be implemented that will test the efficacy of this approach.

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