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Development of Good Cancer Drugs Effective against Cancer Stem Cells

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

A right approach is essential to solve any illness. Cancer mortality remains at historic high and is still on the way to increase. The objective of this study is to find a right approach of cancer therapy to bring cancer mortality down. Myelodysplastic syndromes are diseases attributable entirely to cancer stem cells that can be used to screen good cancer drugs to bring down cancer mortality. Cancer is caused due to wound unhealing. Wound triggers biological and immunological responses. Biological response leads to the production of prostaglandins (PGs) which are good for wound healing. Immunological response prompts the production of tumor necrosis factor (TNF) which is bad for wound healing. TNF causes apoptosis of stem cells, thus triggering the proliferation of progenitor stem cells (PSCs) to repair wound damages. TNF is also named cachectin after its effect to cause cachexia symptom. A manifestation of cachexia symptom is the excessive urinary excretion of low molecular weight metabolites, resulting in the collapse of chemo-surveillance which is the nature's creation of allosteric regulation to keep a check on abnormal methylation enzymes (MEs). PSCs are cells with abnormal MEs. On wound healing, efficient terminal differentiation of PSCs is a critical mechanism to heal wound. If wound is not healed properly, PSCs may be forced to evolve into cancer stem cells (CSCs) through a single hit to silence TET-1 enzyme, and then to progress to faster growing cancer cells (CCs) through chromosomal abnormalities such as

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translocations or deletions to activate oncogenes or to inactivate suppressor genes. Myelodysplastic syndromes (MDS) are a classic case of cancer development at the stage of PSCs evolving to become CSCs. Therapy of MDS requires the differentiation of pathological CSCs to become functional erythrocytes, platelets or neutrophils. So far, Vidaza, Decitabine and cell differentiation agent-2 (CDA-2) are the three drugs approved for the therapy of MDS. Vidaza and Decitabine inactivate abnormal MEs through covalent bone formation between DNA methyltransferase and 5-azacytosine base incorporated into DNA, whereas CDA-2 destabilizes abnormal MEs through elimination of telomerase. Obviously, inactivation of abnormal MEs is the only way to achieve therapy of MDS. Elimination of CSCs is very critical to the success of cancer therapy. Thus, MDS can be used to screen good cancer drugs to fulfill the wish of President Biden to reduce cancer mortality.

Keywords: Cancer drugs; CDA-2; CSCs; MDS; abnormal MEs; PSCs; wound healing.

1. INTRODUCTION

Cancer mortality remains at historic high, and is still on the way to increase. According to NCI experts, the cancer incidence was 19 million and the cancer mortality was 10 million worldwide in 2019, which were on the way to increase with an annual increment of 5% [1]. The high mortality is an indication that cancer therapy has not been handled well in the past. Cancer therapy got to a bad start. Cytotoxic chemotherapy was a tragic byproduct of World War II. During the war, toxic sulfur mustard bombs were used. Victims of toxic gas all displayed depletion of lymphocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Cytotoxic chemotherapy thus became established as a standard therapy of cancer, and the disappearance of cancer cells or tumor became accepted criteria for the evaluation of therapeutic efficacy on hematological cancer or solid tumor. Cytotoxic chemotherapy and radiotherapy were the major drugs used to combat cancer during the War on Cancer declared by President Nixon in 1971-1976, which was not successful [2]. If a treatment modality has been drilled through as a presidential project and failed to achieve its goal, it was fair to conclude that this treatment modality was not good for the solution of cancer. Cancer establishments were, however, trapped in this failed modality, although they did actively search alternatives such as gene and target therapies, agents to induce apoptosis, anti-angiogenesis and immunotherapy [3]. None could cause reduction of tumor mass as effective as cytotoxic drugs or radiation. They kept using these failed drugs to solve cancer to contribute to horrendous cancer mortality.

Perpetual proliferation of CCs is the most outstanding feature of cancer. Naturally, killing of CCs is the top choice of cancer establishments. Cancer is made up by CSCs and CCs, although CSCs are merely a small minority, usually less then 2% in most popular cancers. This small minority, however, contributes the most fatal effects of cancer that include metastasis, recurrence, drug resistance and angiogenesis. Therefore, elimination of CSCs is far more important than the elimination of CCs to prevent cancer fatality. CSCs are protected by drug resistance and anti-apoptosis mechanisms making these cells unresponsive to cytotoxic agents [4]. Inability to take out CSCs is a major factor to contribute to the failure of cytotoxic agents to put cancer away [5]. The contribution to the damage of chemo-surveillance by cytotoxic agents is another important factor to account for the failure of cytotoxic cancer therapies [6,7]. Cancer therapies based on the killing of CCs can only benefit a minority of early stage cancer patients whose chemo-surveillance has not yet been fatally damaged, allowing the recovery of chemo-surveillance to subdue surviving CSCs, whereas a majority of advanced cancer patients whose chemo-surveillance has been fatally damaged cannot benefit from cytotoxic therapies. They are either wiped out as unresponsive patients, or fortunate enough to reach complete remission and then succumbed to recurrence [6,7]. We characterize cytotoxic agents as bad cancer drugs which are able to kill CCs, but are unable to affect CSCs. In addition, these drugs contribute to the destruction of chemo-surveillance. Inability to affect CSCs and the destruction of chemo-surveillance contribute to the failure of cytotoxic agents to win the war on cancer.

President Biden lost his very accomplished son, congressman Beau, to malignant brain tumor. He was genuinely concerned with high cancer mortality. On Sept. 12, 2022, the 60 anniversary of the moonshot speech of President Kennedy, he delivered cancer moonshot speech to urge health profession to come up solutions to reduce cancer mortality by 50% in the following 25 years [8]. This is a more modest project than the presidential project of war on cancer to achieve total elimination of cancer. We cannot rely on bad cancer drugs to achieve this modest goal, which are causing cancer mortality to increase 5% a year. The modest goal of President Biden requires reduction of 2% a year. Now, health profession must get serious to remove bad cancer drugs that are responsible for the horrendous cancer mortality, particularly those reacting with DNA such as nucleoside analogs, platinum derivatives, intercalating agents and radiation, and to abandon tumor shrinkage as an exclusive criterion for the evaluation of cancer drugs, which was a darn mistake of cancer establishments to block development of good cancer drugs not based on the killing of CCs. The attention must also be shifted from the elimination of CCs to CSCs which contribute most fatal effects of cancer. MDS are an ideal case to guide searching of good cancer drugs capable of eliminating both CSCs and CCs through induction of terminal differentiation.

"MDS often start with a display of immunological disorder which prompts the production of inflammatory cytokines" [9]. "Among such cytokines, TNF is the critical element related to the development of MDS" [10]. "It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets and neutrophils. TNF also cause excessive urinary excretion of low molecular weight metabolites because of its effect to induce vascular hyperpermeability" [11,12]. Wound healing metabolites are among low molecular weight metabolites lost. Wound healing metabolites are metabolites active as differentiation inducers (DIs) capable of eliminating telomerase associated with abnormal MEs [13], and differentiation helper inducers (DHIs) which are inhibitors of MEs. DIs and DHIs can effectively induce PSCs to undergo terminal differentiation to heal wound. Failure to heal wound may force PSCs to evolve into CSCs to escape contact inhibition that limits the capacity of PSCs to proliferate. It takes a single hit to silence TET-1 enzyme for PSCs to become CSCs, which is within the reach of PSCs equipped with abnormally active MEs. The propagating pathological cells of MDS have been identified as CSCs [13]. MDS are diseases attributable entirely to the propagation of CSCs suitable for the search of good cancer drugs that can eliminate CSCs. Elimination of CSCs is a top priority of cancer therapy since most fatal effects of cancer are the making of CSCs. The elimination of CSCs is far more important than the elimination of CCs to save cancer patients. We have a lot to catch up to reduce cancer mortality.

2. COMMENTARIES AND DISCUSSION

2.1 Abnormal MEs as the Most Critical Issue of Cancer

Perpetual proliferation of CCs is the most outstanding feature of cancer. Abnormal MEs blocking differentiation is an important factor, and the activation of oncogene or the inactivation of suppressor gene is another important factor to contribute to perpetual proliferation of cancer cells. We considered abnormal MEs as the most critical issue of cancer because this abnormality happened on PSCs, the precursors of CSCs, and passed on to CSCs and then to CCs [13]. Abnormal MEs are universal to all cancers [14], whereas oncogenes and suppressor genes are variable among different cancers, which happen late during the evolution of cancer. The elimination of abnormal MEs can also put to rest chromosomal abnormalities, but the correction of chromosomal abnormalities cannot affect abnormal MEs [15].

"MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH), which plays a pivotal role on the regulation of cell replication and differentiation. Because of this pivotal role, these enzymes are exceptionally subject to double allosteric regulations: one on the individual enzymes and one on the enzyme complex" [16]. "On the individual enzymes, SAHH is under the allosteric regulation of steroid hormone or related allosteric regulators" [17]. On the enzyme complex, MEs are under the allosteric regulation of telomerase and wound healing metabolites [18,19]. Enzymes playing important regulatory roles are often subject to delicate regulations. Allosteric regulation is the most pervasive mode of regulation. It is the regulation to maintain biological optimum to avoid hazardous extreme often to result in display of clinical symptoms. MEs enzymes are critical for the maintenance of optimal growth by virtue of the fact that DNA methylation controls the expression of tissue specific genes [20], and pre-rRNA methylation controls the production of ribosome [21,22], which in turn dictates the commitment of cell to initiate cell replication [23]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [24]. “In most normal stem cells, MEs are under the allogenic regulation of steroid hormone or related allosteric regulatory factors to dictate optimal growth. In telomerase expressing stem cells, MEs are associated with telomerase to change kinetic properties of MEs to tilt the regulation in favor of growth. K_m values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the normal isozyme pair” [17,24]. The increased K_m values suggest that telomerase expressing cells have much larger pool sizes of S-adenosyl methionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are important for the build up of cells with abnormal MEs. It has been shown by Prudova et al [25] that AdoMet could protect protein against protease digestion. Chiva et al. [26] found that the pool sizes of AdoMet and AdoHcy shrunk greatly when HL-60 cells were induced to undergo terminal differentiation, indicating larger pool sizes of AdoMet and AdoHcy were necessary for the build up of cells with abnormal MEs. Embryonic stem cells and PSCs express abnormal MEs. Abnormal MEs do not seem to cause problems for these cells, because there are safety mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to destabilize abnormal MEs to keep a check on abnormal MEs from flaring into clinical problems. On the contrary, pre-mature interruption of the build up of cells with abnormal MEs may be detrimental for the normal function of abnormal MEs. Interruption of abnormal MEs during fetal development by thalidomide can cause malformation, notably limbs. Therefore, regulatory mechanisms created by the nature should be followed closely to avoid disastrous consequences. Dysfunction of safety mechanisms to keep a check on abnormal MEs can lead to various clinical problems.

Cancer therapies based on the killing of CCs is the choice of cancer establishments, which do not have to take into consideration factors that cause cancer evolution. That was a big mistake of cancer establishments. They could only choose bad cancer drugs most effective to kill CCs, which unfortunately were also responsible for causing the death of advanced cancer patients. Targeted cancer therapies are better choice to offer selectivity that can avoid adverse effects. Abnormal MEs are obviously the best cancer target, because abnormal MEs are the most critical issue of cancer [13], and the elimination of this critical issue can also put to rest other important cancer contribution factors such as chromosomal abnormalities which are otherwise very difficult to solve [15]. One may argue that since abnormal MEs are also expressed in normal embryonic cells and PSCs, they cannot be considered as a cancer target, the silence of TET-1 enzyme and the collapse of chemo-surveillance qualify abnormal MEs as a specific cancer target, which is obviously the best target for cancer therapy [15].

2.2 Chemo-Surveillance as the Creation of the Nature of Allosteric Regulation to Keep A Check on Abnormal MEs

Whatever happens naturally is the nature’s creation to benefit humans. Photosynthesis is a prime example. Immuno-surveillance is another example, which is well accepted. Chemo-surveillance can also be an example, but which is not accepted, because it runs against the wish of cancer establishments. The cancer establishments want the tumor to disappear, but chemo-surveillance can not make the tumor to go away. The bad cancer drugs they developed cause the destruction of chemo-surveillance. Naturally, they cannot accept chemo-surveillance. If there is no such thing as chemo-surveillance, how can they explain wound healing that comes naturally.

Chemo-surveillance was our creation to describe a novel concept of natural mechanism against cancer [19]. The proposal of chemo-surveillance was based on the observation that healthy people were able to maintain a steady level of metabolites active as (DIs) and DHIs. DIs and DHIs are hydrophobic metabolites that can be retained by C18 and eluted with 80% methanol. Peptides share similar physical-chemical properties of DIs and DHIs, and, therefore, can be used as surrogate molecules to represent DIs and DHIs. On quantitative analysis of plasma and urinary peptide content, plasma as nmole peptides/ml and urine as nmole peptides/mg creatinine, of normal people and cancer patients, we found that normal people were able to maintain a steady plasma/urine ratio around 0.8, whereas cancer patients tended to show such levels below 0.8 as shown in Fig. 1. Data presented in Table 1 clearly show that the maintenance of cell differentiation agent (CDA), which is a term to indicate the content of DIs plus

DHIs, at the level of 5 as the healthy people is important to avoid cancer and cancer evolves as a consequence of the decline of CDA levels, namely the collapse of chemo-surveillance. The decline of CDA levels of cancer patients is obviously due to excessive urinary excretion caused by TNF. Plasma and urinary peptide profiles are similar to the peptide profile of spleen extract, but dissimilar to the peptide profiles of other organ extracts. These findings suggest that plasma and urinary peptides are the degradative products of hemoglobins since spleen is known as an organ to process dead erythrocytes. Degradation of erythrocytes is very likely a major source of plasma DIs as acidic peptides, arachidonic acid (AA) and membrane fragments with phosphatidylinositol, and DHI as uroerythrin [25-28]. Steroid metabolites are important DHIs which may be derived from organs involved in steroid metabolism [25,29,30]. Pregnenolone is an important DHI. According to Morley [30], the production of pregnenolone is bell shape with a peak of 50 mg a day produced by 20-25 year old. The very young and the very old people produce relatively smaller amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer. Evidently, chemo-surveillance is an important mechanism to protect healthy people from becoming cancer patients. Our carcinogenesis studies strongly support the importance of chemo-surveillance to ward off cancer evolution. During challenging with hepatocarcinogen, numerous tiny hyperplastic nodules appeared before the appearance of large size carcinomas [31], which displayed abnormal MEs. These tiny preneoplastic hyperplastic nodules must represent active repair by PSCs. Most of these tiny hyperplastic nodules disappeared, indicating completion of wound healing, and only a few large size carcinomas appeared later, indicating only unhealed wounds caused by carcinogen later developed to become carcinomas. If Antineoplaston A10 was provided during the challenge with hepatocarcinogen, development of carcinomas could be prevented [32]. Antineoplaston A10 is phenylacetylglutamine which is inactive as DI or DHI, neither as cytotoxic agent. It is an effective anti-cachexia agent to prevent the loss of DIs and DHIs [19]. An effective anti-cachexia agent can also be effective for the therapy of early stage cancer patients [19]. Cachexia is a symptom commonly shared by inflammatory patients and cancer patients. The progression of cancer can cause CDA levels to decline. Cytotoxic agents create wound. Therefore, the administration of cytotoxic agents can accelerate the decline of CDA levels. The destruction of chemo-surveillance is definitely a factor to contribute to the failure of cytotoxic agents to put cancer away [33]. we strongly recommended restoration of chemo-surveillance through CDA formulations as a top priority to save cancer patients [7].

2.3 Wound Unhealing to Lead to the Evolution of Cancer

"The concept of cancer due to wound unhealing was first introduced by the great German scientist Virchow in the 19th century" [34]. It was again brought up by Dvorak in 1986 [35]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [36]. We provided the most important details on this subject that included abnormal methylation enzymes to block differentiation [13-16,18,24]; chemo-surveillance as the nature's creation of allosteric regulation to keep a check on abnormal MEs [7,19,37,38]; DIs and DHIs as wound healing metabolites and also as active players of chemo-surveillance [7,19,25-28,37,38]; hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal differentiation of cells with abnormal MEs [39]; the mechanism of wound healing to involve the proliferation and the terminal differentiation

Table 1. Plasma/urine peptide ratios of cancer patients

Plasma/Urine Peptide Ratios	CDA Level	No. of Patients	% Distribution
0.8-0.83 (Normal)	5.0	2	1.8
0.6-0.8	4.3	7	6.5
0.4-0.6	3.1	18	16.7
0.2-0.4	1.8	38	35.2
0.1-0.2	0.9	24	22.2
0.05-0.1	0.46	19	17.6

Plasma peptide: nmoles/ml; Urine peptide: nmole/mg creatinine

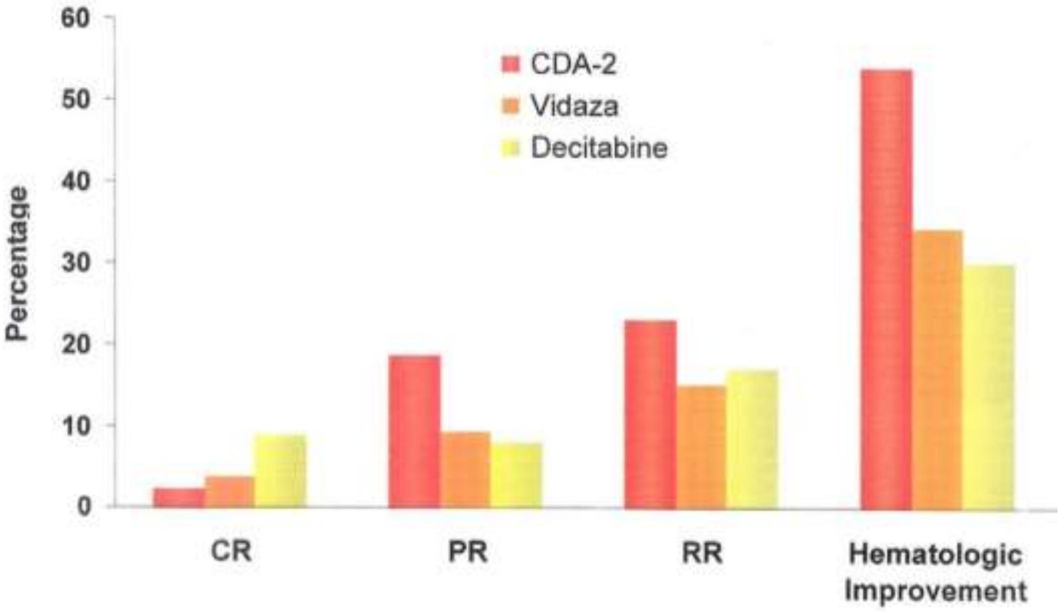

Fig. 1. A Comparison of therapeutic efficacy of CDA-2, vidaza and decitabine on MDS

of PSCs [40-42]; and the evolution of CSCs from PSCs due to wound unhealing [4,43, 44]. Our studies are very convincing to show that cancer is the consequence of wound unhealing. Therefore, the most appropriate solution of cancer is to pursue perfection of wound healing [45]. Wound healing is a simple matter that comes naturally without having to put up any effort. Cancer therapy should also be a simple matter if the therapy follows the process of wound healing. But cancer establishments prefer cancer therapies opposite to wound healing to result in horrendous cancer mortality of more than 10 million a year worldwide. These cancer establishments have to be replaced to save cancer patients [46].

"Wound healing and cancer are closely related to involve PSCs as the common elements. Wound healing requires the proliferation and the terminal differentiation of PSCs" [40]. PSCs are the most primitive stem cells to initiate the development of particular organs or tissues during the embryonic development of fetus. They are pluripotent stem cells capable of differentiation into various component cells of the organ or tissue, such as parenchyma cells, epithelial cells, connective tissue and blood vessels to repair the wound. A small percentage of these cells, usually less than 2%, are reserved for the need to expand or repair. Wound triggers biological and immunological responses [47]. Biological response involves the release of AA from membrane bound phosphatidylinositol for the synthesis of PGs, which are unstable metabolites. The function of PGs is believed to cause edema for the extravasation of inhibitors such as DIs and DHIs for PSCs to proliferate. The promotion of terminal differentiation of PSCs at the final stage of wound healing is accomplished by CDA above described. Wound healing comes naturally without having to put up any effort since healthy people can maintain CDA at healthy level of 5. Take treatment of surgical wound for example, suture and antibiotic treatment are subsidiary to speed up and to prevent infection. The integrity of chemo-surveillance dictates the success of wound healing [37,38]. If chemo-surveillance has been damaged by wounds due to accidents, surgeries, toxic chemicals or infections, wound healing will be affected to result in disastrous consequences to display clinical symptoms such as tissue fibrosis, dementia, organ failures, and cancer. Management of wound healing is an important matter. That is why the nature creates chemo-surveillance to ensure perfection of wound healing. Cancer can be solved as easy as wound healing, if the therapy fallows pro-wound healing process [45].

2.4. Screening of Good Cancer Drugs via MDS

MDS are intermediate diseases of cancer at the stage of CSCs as above described. These diseases are ideal for the evaluation of drugs effective against CSCs, which is the most important issue of cancer, because CSCs contribute the most fatal effects of cancer. Therapy of MDS requires the conversion of pathological CSCs to become functional erythrocytes, platelets or neutrophils, which requires terminal differentiation of CSCs, precisely the critical mechanism of wound healing. Killing of CSCs cannot cure MDS. Besides, CSCs cannot be easily killed. So far, Vidaza, Decitabine and CDA-2 are the three drugs approved for the therapy of MDS by China, and Vidaza and Decitabine are the two drugs approved by the USA. CDA-2 is a drug of wound healing metabolites purified from freshly collected urine of our creation [48]. Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental to conduct clinical trials for the approval of these three MDS drugs in China [49,50]. Based on two cycles of treatment protocols, each 14 days, Professor Ma found CDA-2 had a slightly better therapeutic efficacy based on cytological evaluation and a markedly better therapeutic efficacy based on hematological improvement evaluation as shown in Fig. 1. Hematological improvement was an indication of dependency on blood transfusion to stay healthy.

Obviously, CDA-2 is a better drug for the therapy of MDS based on therapeutic efficacy. Better yet, it is a drug without serious adverse effects, whereas Vidaza and Decitabine are known carcinogens [50, 51] and very toxic to DNA [52-54]. Apparently, abnormal MEs are the target of MDS drugs, which supports the validity of our claim of abnormal MEs as the most critical issue of cancer [13]. CDA-2 destabilize abnormal MEs by the elimination of telomerase from abnormal MEs, which is a specific cancer target, and Vidaza and Decitabine inactivate abnormal MEs through covalent bond formation between methyltransferase and 5-azacytosine base incorporated into DNA, which is not s specific event limited to cancer cells [54]. Although Vidaza and Decitabine can be classified as good cancer drugs because of its effectiveness to induce terminal differentiation of CSCs, they also belong to bad cancer drugs as nucleoside analogs. Therefore, CDA-2 is the only good cancer drug. CDA-2 is only available in China. The rest of the world do not have good cancer drugs to combat cancer. That is why the cancer mortality remains so horrendously high. Development of CDA formulations made up by DIs and DHIs is urgent to reduce cancer mortality [3-8,45,56].

3. CONCLUSION

Cancer arises due to the collapse of chemo-surveillance, thus allowing PSCs to evolve into CSCs and then to progress to CCs. A good cancer drug must be able to take out both CSCs and CCs, and to restore chemo-surveillance. Elimination of CSCs is far more important than the elimination of CCs, since CSCs contribute most of fatal effects of cancer. MDS are disease attributable entirely to CSCs, which are ideal for the screening of good cancer drugs that can reduce cancer mortality to fulfill the wish of President Biden who has called for the reduction of cancer mortality by 50% in the following 25 years. CDA formulations are the best good cancer drugs to save cancer patients.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests Or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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