Cell Differentiation Agents Recommended for the Rescueof Metastatic, Unresponsive and Recurrent Cancer Patients

ABSTRACT

The objective of this article is to develop cell differentiation agent (CDA) formulations to the rescue of cancer patients whose cancer stem cells (CSCs) have become a dominantissue such as metastatic, unresponsive and recurrent cancer patients.Although CSCs are only a small minor subpopulation, they contributethe major fatal effects of cancer, such as metastasis, unresponsiveness, recurrence, drug resistance and angiogenesis.These cells are protected by drug resistance and anti-apoptosis mechanisms, and, therefore, are very resistant to therapies aimed to kill cancer cells (CCs).Perfect cancer drugs must be able to take out both CCs and CSCs, and to restore chemo-surveillance. Imperfect cancer drugs can only solve a fraction of cancer problems. Cytotoxic chemotherapeutic drugs, radiation, apoptosis inducing drugs and immunotherapeutic drugs put up by cancer establishments are imperfect cancer drugs which can only kill CCs but cannot affect CSCs. These imperfect cancer drugs also cause damage to chemo-surveillance.The inability to eliminate CSCs and the damage to chemo-surveillance are responsible for the failure of imperfect cancer drugs to saveadvanced cancer patientsthat include metastatic, unresponsive and recurrent cancer patients.

CDA formulations are perfect cancer drugs made up by differentiation inducers (DIs) and differentiation helper inducers (DHIs), which can induce both CSCs and CCs to undergo terminal differentiation.Evidently, induction of terminal differentiation is the only option for the solution of CSCs. And the solution of CSCs is essential to cure cancer. DIs and DHIs are the active players of chemo-surveillance to restore the functionality of chemo-surveillance often badly damaged in cancer patients. Thus, CDA formulations are the right solution to the rescue of cancer patients with CSCs as a dominant issue.

Keywords: Cancer cells, cancer stem cells, chemo-surveillance, differentiation inducers, differentiation helper inducers,methylation enzymes, wound healing.

1. INTRODUCTION

Cancer is an old and unsolved problem. Evidently, cancer therapies based on killing of CCs are ineffective to save advanced cancer patients. That is why cancer mortality continues to increase. Recent cancer diagnoses of royal family members offer a supreme authority to rectify cancer therapy to save cancer patients [1]. Immuno-surveillance and chemo-surveillance are the nature's creation of protection mechanisms to ward off cancer, immune-surveillance byeliminating the damages created by infectious agents, and chemo-surveillance by eliminating the damages created by toxic chemicals, including carcinogens. Cancer arises if such protection mechanisms fail to function. Cancer therapies based on killing of CCs can only benefit early stage cancer patients, whose chemo-surveillance have not yet fatally damaged, relying on the

recovery of chemo-surveillance to subdue surviving CSCs[2]. Advanced cancer patients require cell differentiation agent (CDA) formulations to restore the functionality of chemo-surveillance to achieve cancer therapy [3]. The success of cancer therapy depends on the success of the elimination of CSCs. CDA formulations are very effective on CSCs [4].Metastasis is the making of CSCs.Therefore, CSCs area dominant issue ofmetastatic cancer patients. CSCs are also a dominant issue of unresponsive and recurrent cancer patients. Elimination of CSCs is very critical to the success of cancer therapy[5-7]. Somehow, cancer establishments are trapped in belief that killing of CCs is the most importantmatter and ignore CSCs. That strategy does not seem to work as cancer mortality keeps on increasing.

Cancer evolves as a consequence of wound unhealing [8-10]. The nature creates chemo-surveillance to ensure perfection of wound healing [11]. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs) [12]. Wound unhealing is due to the collapse of chemo-surveillance [13, 14], but the nature does not have a mechanism to detect the collapse of chemo-surveillance to make correction. So, the nature responds by forcing progenitor stem cells (PSCs) to proliferate. The build up of PSCs is limited by contact inhibition. PSCs are then forced to evolve into CSCs to escape contact inhibition. By a single hit to silence ten-eleven translocator-1 (TET-1) enzyme, the enzyme responsible for lineage transitions, PSCs can be converted to CSCs, which is within the reach of PSCs since these cells are equipped with abnormally active methylation enzymes, which play a pivotal role on the regulation of cell replication and differentiation. The evolved CSCs are still unable to undergo terminal differentiation to heal the woundbecause the collapsed chemo-surveillance remains unsolved. CSCs are then forced to progress to faster growing CCs by chromosomal translocations to activate oncogenes or deletions to inactivate suppressor genes. Thus, carcinogenesis is a process of wound unhealing that forces PSCs to evolve into CSCs, and then to progress to faster growing CCs. Reversal of this process is the right approach of cancer therapy [15, 16]. Evidently, CDA formulationsmade up by differentiation inducers (DIs) and differentiation helper inducers (DHIs)involved in wound healing are the best drugs to take out CSCs to the rescue of cancer patients with CSCs as a dominant issue. DIs and DHIs are wound healing metabolites effective to destabilize abnormal MEs of PSCs to achieve terminal differentiation. DIs are chemicals capable of eliminating telomerase of abnormal MEs, and DHIs are inhibitors of MEs capable of potentiating the activity of DIs. Abnormal MEs pass on from PSCs to CSCs, and thenfrom CSCs to CCs.Cells with abnormal MEs gain great advantage on cell growth. Cancer is basically a problem of growth regulation going awry. MEs play a pivotal role on the regulation of cell growth, and, therefore, are critically related to cancer. Destabilization of abnormal MEs provides the best approach for cancer therapy [2-7]

2. COMMENTARIES AND DISCUSSION

2-1. CSCs as A Very Critical Issue of Cancer

Although CSCs constitute only a small minor subpopulation, these cells contribute the major fatal effects of cancer, fatal effects such as metastasis, unresponsiveness, recurrence, drug resistance and angiogenesis.The solution of CSCs is very critical to the success of cancer therapy

[5-7]. But cancer establishments ignore the important issue of CSCs[17, 18].They tend to pay attention to the very visible but not so critical issue of cancer.CCs make up the absolute majority of tumor mass.They put up imperfect cancer drugs to eliminate CCs,such as cytotoxic chemotherapeutic agents, radiation, apoptosis inducing drugs and immunotherapeutic drugswhich cannot affect CSCs [19-23]. Imperfect cancer drugs can only benefit a small % of cancer patients in the early stage whose chemo-surveillance have not yet been fatally damaged, allowing the recovery of chemo-surveillance to subdue surviving CSCs, whereas these drugs cause fatality of majority ofcancer patients in advanced stage whose chemo-surveillance have been fatally damaged [11, 13, 14]. The inability to eliminate CSCs and the contribution to the damage of chemo-surveillance are responsible for the failure of imperfect cancer drugs to put cancer away. Cancer mortality remains at historical high, and keeps on increasing. According to NCI experts, cancer incidence and mortality worldwide in 2019 were 19 million and 10 million, respectively, which were exactly 5% above the statistics of 2018 [24]. They predicted an annual increment of 5% likewise in the following years. President Joe Biden brought up cancer moonshot initiative in 2022, requesting a reduction of cancer mortality by 50% in 25 years [25].A drastic change of cancer leaderships away from those focused onkilling of CCs is necessary to fulfill the goal of cancer moonshot initiative [1, 26]. Development of drugs effective against CSCs is very critical to save cancer patients to reduce cancer mortality, since CSCs are responsible for the most fatal effects of cancer [5-7].CDA formulations are the drugs very effective to eliminate CSCs.The development of CDA formulations is, therefore, very important for the success of cancer therapy. But the development of CDA formulations has been blocked by cancer establishments, since these agents cannot cause the disappearance of tumor they set up as a criterion to evaluate the effectiveness of cancer therapy.That is a grave mistake committed by the cancer establishments to result in the failure of cancer therapy. Health profession is an authoritarian profession, when the mistake is made by the very top of the profession. There is no mechanism to rectify the mistake. The mistake carries on to hurt cancer patients. This is the reason of the horrendous cancer mortality of more than 10 million annually worldwide.Cancer establishmentsin the USA arealso not successful to reduce cancer mortality. But they are doing better than the world data shown. The increment of cancer mortality is only 0.2% in 2023 [24], which is still far from the request of reducing annual mortality of 2% by President Biden. Obviously, the commanding principle of killing CCs is unable to reduce cancer mortality.

2-2. Wound Healing as A Very Important Health Issue

Wound healing is a very important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing,that can be tissue fibrosis, dementia, organ failure and cancer [8-11, 19, 27]. Chemo-surveillance was a term we created to describe the nature's creation of protection mechanism to benefit humans [11]. Chemo-surveillance was based on the quantitative analyses of plasma and urinary peptides. Peptides sharephysical chemical properties ofwound healing metabolites DIs and DHIs, therefore can be used as surrogate molecules to represent DIs and DHIs. Acidic peptides are actually very active DIs [7, 28]. Quantitative analyses of plasma and urinary

peptides through initial purification by C18 cartridge, followed by HPLC resolution of peptides on a column of sulfonated polystyrene and Ninhydrin reaction allowed us to show that healthy people were able to maintain a steady level of CDA at level 5, whereas only 2% of cancer patients could maintain this high level, 25% at CDA level above 3, and 75% at CDA level below 3. CDA levels reflect very well the severity of cancer patients. It appears that the damage to chemo-surveillance allows cancer to occur, the progression of cancer causes CDA levels to decline further, and the treatment with cytotoxic agents accelerate the decline of CDA levels. Antineoplastons are preparations of urinary DIs and DHIs by reverse phase chromatography on C18 [29]. If patients responded well to Antineoplaston therapy, CDA levels would increase to approach CDA level at thehealthy level of 5. If not, CDA levels continued to decline [30]. This is a clear indication that the collapse of chemo-surveillance is responsible for cancer to occur, and the restoration of chemo-surveillance can lead to the cure of cancer. Evidently, not all patients responded positively to Antineoplaston therapy. Antineoplastons are preparations of natural wound healing metabolites. Cancer cells, particularly those replicating very fast, are known to express a high level of degradative enzymes to salvage substrates for the syntheses of macromolecules to support faster growth. Natural metabolites may be quickly degraded to lose activities. For cancer therapy, it is advisable to provide two sets of CDA formulations: one set CDA-CSC with natural DIs and DHIs which can easily access CSCs but may not resist destruction of degradative enzymes of CCs, and another set CDA-CC with non-natural DIs and DHIs which may not access CSCs but can resist destruction of degradative enzymes of CCs.Natural DIs are arachidonic acid (AA) and its metabolitesprostaglandin derivatives (PGs) [31, 32], and natural DHIs are inhibitors of MEs such as steroid metabolites, uroerythrin, fatty acid and amino acid derivatives [33-37]. Unnatural DIs and DHIs are synthetic chemicals functioning as inhibitors of telomerase or MEs [31, 36]

Wound healing and cancer are closely related to involve progenitor stem cells (PSCs) as the common elements [12, 38, 39]. Wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs) [40], which are good for wound healing. PGs are excellent DIs [31, 32] and very active inflammatory agents (41). PGs are metabolically unstable with very short half lives. They are produced at the initial phase of wound. Their effect on wound healing is believed to trigger inflammatory response to result in edema for the extravasation of inhibitors such as DIs and DHIs in order for PSCs to proliferate. The promotion of terminal differentiation of PSCs at the final phase of wound is carried out by chemo-surveillance. Thus, the functionality of chemo-surveillance dictates the success of wound healing [13, 14]. The stable end products of PGs are also active as DIs, although not as good as PGs [32]. These stable end products of PGs may play a significant role as DIs on wound healing. The immunological response of wound prompts the production of cytokines which are bad for wound healing. Tumor necrosis factor (TNF) among cytokines produced is particularly bad on wound healing. TNF is also named cachectin after its effect to cause cachexia symptoms. A manifestation of cachexia symptoms is excessive excretion of low molecular weight metabolites due to the membrane hyperpermeability caused by TNF [42, 43]. DIs and DHIs are among low molecular weight metabolites excreted, resulting in the collapse of chemo-surveillance to cause wound unhealing and the disastrous consequences of wound unhealing.

In the case of acute wound, biological response prevails to favor wound healing. In the case of chronic wound, immunological response prevails to result in wound unhealing. The functionality of chemo-surveillance dictates the success or the failure of wound healing [13, 14]. Wound healing is a simple matter if chemo-surveillance is at a healthy CDA level of 5. Therapy of cancer should also be a simple matter if chemo-surveillance can be restored to the healthy CDA level of 5 [2, 15, 16].

2-3. CDA-2 as An Effective Drug for the Solution of CSCs

A perfect cancer drug is a drug capable of destabilizing abnormal MEs to take out both CSCs and CCs by inducing these cells to undergo terminal differentiation, and to restore chemo-surveillance [44].Myelodysplastic syndromes (MDS) are a unique case to show the evolution of cancer due to wound unhealing. MDS have been attributed to immunological disorders [45], that prompts the production of inflammatory cytokines. Among such cytokines, TNF is a critical factor related to the development of MDS, because the antibody of TNF can stop the progression of MDS [46]. It causes excessive apoptosis of bone marrow stem cells, thus severely affects the ability of the patient to produce hematopoietic cellssuch as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance as above described. As a consequence, chemo-surveillance normally operating in healthy people to keep PSCs in check becomes dysfunctional, allowing PSCs to build up toevolve into CSCs.The high level of telomerase expression in the peripheral and bone marrow leukocytes in MDS patients is an indication of the widespread multiplication of CSCs [47,48]. The propagating pathological cells have been identified as human CSCs [49]. So, MDS are ideal for the study of drugs effective against CSCs. So far, Vidaza, Decitabine and CDA-2 are the three drugs approved by the Chinese FDA for the therapy of MDS. Vidaza and Decitabine are also approved by the US FDA for the therapy of MDS. CDA-2 is our creation, which was a preparation of wound healing metabolites purified from freshly collected urine by reverse phase chromatography on XAD-16 [50]. Wound healing metabolites are hydrophobic chemicals that can be retained by C18 and XAD-16.Both peptides and organic acid metabolites are active DIs and DHIs. C18 retains peptides better, but not membrane fragments designated as PP-0, XAD-16 retains acidic metabolites including PP-0 better, but not peptides. So, the very active PP-0 of CDA-2 is only a minor active component of Antineoplastons, and very active acidic peptides of Antineoplastons are not present in CDA-2.Otherwise, CDA-2 and Antineoplastons are similar preparations effective to induce terminal differentiation of both CSCs and CCs. Antineoplastons were blocked by the cancer establishments. CDA-2 was approved by the Chinese FDA, but unlikely it will be accepted by the US FDA. US FDA approvedonly imperfect cancer drugs that killed CCs.

Inactivation of MEs is the mechanism of action by these three drugs for MDS, CDA-2 by the elimination of telomerase associated with abnormal MEs [50], whereas Vidaza and Decitabine eliminate methyltransferase by covalent bond formation between the enzyme and 5-azacytosine incorporated into DNA [51].CDA-2 is selective to eliminate the tumor factor of abnormal ME, whereas the covalent bond formation between methyltransferase and 5-azacytosine is non-selective. CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [52, 53] and display considerable toxicity to DNA [54-56]. Professor Jun

Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental to direct clinical trials of all three MDS drugs. According to his assessments based on two cycles of treatment protocols, each cycle 14 days, he has found that CDA-2 had a noticeably better therapeutic efficacy based on cytological evaluation, and a markedly better therapeutic efficacy based on hematological improvement evaluation, which was an evaluation based on the dependency of blood transfusion to stay healthy[57]. Obviously, CDA-2 is a better drug for the therapy of MDS, showing superior therapeutic efficacy and devoid of adverse effects. Abnormal MEs are an excellent cancer target, because these enzymes play a pivotal role on the regulation of cell replication and differentiation [58-60]. These enzymes are subjected to exceptional double allosteric regulations: one on the individual enzymes and one on the enzyme complex [61]. Perpetual proliferation is the most outstanding feature of cancer. The blockade of differentiation is a critical factor for cell to keep on replication. Chemo-surveillance is a mechanism created by the nature to prevent the cells with abnormal MEs to build up unnecessarily to become clinical problems. When this mechanism fails, cancer evolves. Chemo-surveillance is the creator's prescription of cancer therapy. The restoration of chemo-surveillance is therefore the top priority of cancer therapy [2]. Chromosomal abnormalities affecting oncogene and suppressor gene expressions are also an important factor on perpetual proliferation of cancer cells. We considered abnormal MEs as the most important factor, namelythe bullseye of cancer target [62], because once abnormal MEs are solved, cancer cells will exit cell cycle to undergo terminal differentiation. The abnormal chromosomal problems can also be put to rest. After all, oncogenes and suppressor genes are cell cycle regulatory genes. They have important roles to play when cells are in cell cycle replicating. But if replicating cells exit cell cycle to undergo terminal differentiation, they have no roles to play. Solution of chromosomal abnormalities cannot put away abnormal MEs. Cancer establishments devoted 20 years, 1976-1996, right after the failure to win the war on cancer declared by President Nixon [17], to develop gene therapy [19]. They gave up because it was simply too difficult and too expensive to develop gene therapy. They wasted 20 years to learn the difficulty of gene therapy. They wasted another 20 years, 1996-2016, on the development of anti-angiogenesis [19]. Can they succeed in the development of immunotherapy during 2016-2036? Very unlikely, because the commanding principle of killing CCs is basically wrong! Cancer establishments have killed too many advancedcancer patients [18]. They have to be removed to save advanced cancer patients. [1, 26].

CDA-2 is the best drug for the therapy of MDS. Induction of terminal differentiation of CSCs is the only option to cureMDS to generate depleted erythrocytes, platelets or neutrophils. Killing of CSCs cannot cure MDS. Induction of terminal differentiation is definitely the only option to solve CSCs, which are critically linked to wound unhealing.CDA-2 stands out as the best drug on the solution of CSCs. CDA-2 can serve as a good model for the development of effective drugs against CSCs [63].

2-4. Development of CDA Formulations to Target Abnormal MEs for the Elimination of CSCs and CCs.

Cancer is basically a problem of growth regulation going awry. MEs are at the center of growth regulation. Therefore, these enzymes are closely related to cancer. We have presentedevidenceto indicate that cancer is evolved due to wound unhealing, because of the collapse ofchemo-surveillance,thus allowing PSCs to evolve into CSCs, and then to progress to CCs. The solution of CSCs is closely linked to wound unhealing. Therefore, the induction of terminal differentiation of CSCs is the only option to solve the problem of CSCs, just like the completion of wound healing depends on the terminal differentiation of PSCs. The solution of CCs is not as critically linked to wound unhealing as CSCs. CCs can be eliminated by induction of terminal differentiation we prefer or by killing preferred by cancer establishments. The progression of CCs is caused by wound unhealing, wound healing process is the right approach. Therefore, direction of the terminal differentiation of CCs, like the direction of terminal differentiation of CSCs is the right approach.Cancer establishments insist on opposite approach, allowing only killing of CCs by setting up the rule of tumor disappearance as the acceptable cancer drugs.The problem is CSCs refused to be killed, because these cells are protected by drug resistance and anti-apoptosis mechanisms [20-23]. The biological mission of CSCs, like their precursors PSCs, is to repair the wound. Cytotoxic drugs create wounds to trigger the proliferation of CSCs to work on the repair [64].Eventually, the proportion of CSCs will increase from less than 2% in the primary tumor to reach more than 10% like the primary brain cancers [65, 66], which are unresponsive to cytotoxic therapies. Thus, controlling the building up of CSCs is very critical to the success of cancer therapy. Evidently, pro-wound healing strategy we prefer has the advantage over anti-wound healing strategy preferred by cancer establishments on this issue.

We have carried out extensive studies on natural and unnatural DIs and DHIs for the manufacture of CDA formulations for cancer therapy [5-7, 28, 31-37,50].DIs and DHIs can bevery effective cancer drugs. ATRA is an effective DI which is the standard care for the therapy of acute promyelocytic leukemia [67]. It requires the expression of the receptor of ATRA, namely RAR, to activate oligoisoadenylate synthetase to achieve the therapeutic effect [68]. The product of this enzyme, oligoisoadenylate, is the actual DI. Gleevec is an effective DHI which is the standard care for the therapy of chronic myeloid leukemia [69]. Thus, effective cancer drugs are not necessary the drugs that must cause the tumor to disappear. ATRA and gleevec cannot cause solid tumor to disappear. So, they are primarily used in the therapy of hematological cancers.The criterion of the therapeutic efficacy of hematological cancers is the disappearance of cancer cells which are morphologically distinguishable from terminallydifferentiated cells.

SAHH and MT inhibitors are much better DHIs than MAT inhibitors. MAT is the most stable enzyme of the three MEs [58]. The association with telomerase further increases its stability. Therefore, it is not easy to shake loose of this enzyme. Pregnenolone is a major DHI of CDA-2 [5]. Apparently, pregnenolone is an important player of chemo-surveillance. It is the master substrate of biologically active steroids to exercise a great influence on growth regulation. The production of pregnenolone is bell shape in relation to ages with a peak production of around 50 mg daily at 20-25 years old [70]. The oldest and youngest people produce relatively little amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer.

It appears that pregnenolone is a single metabolite to greatly influence the evolution of cancer. It is our top choice of natural DHI to make CDA formulations.

Effective CDA formulations can be ED_{25} of a DI + 3x$RI_{0.5}$ of a DHI, or ED_{50} of a DI + 2x$RI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [5]. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI. Reductiveindex$_{0.5}$ ($RI_{0.5}$)can be determined by the procedure provided [64]. These data have been provided in the previous publications above listed. In the design of CDA formulations, we must take into consideration the non-cancer issues such as blood brain barrier of brain cancer, collagen envelop of pancreatic cancer and hypoxia factor of melanoma to select DIs and DHIs to overcome non-cancer issues, in addition to drug resistance issue of CSCs and degradative enzymes of fast growing CCs we bring up in the previous section 2-2.

3. CONCLUSION

A perfect cancer drug must be able to take out both CCs and CSCs, and to restore chemo-surveillance. Induction of terminal differentiation is the only option to solve CSCs. CCs can be taken out by killing or induction of terminal differentiation. CSCs are a dominant issue of metastatic, unresponsive and recurrent cancers, which can be best solved by CDA formulations, or CDA formulations in combination with drugs aimed to kill CCs.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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