

Research Article

Cytotoxic Agents Can Cure Cancer, but Can Also Kill Cancer Patients

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Abstract

The objective of this article is to rectify cytotoxic cancer therapies which are inadequate to cause escalating cancer mortality, and to promote cell differentiation agent (CDA) formulations as perfect cancer drugs to reduce cancer mortality. Cancer mortality is the ultimate judgment of the success of cancer therapy. Cancer mortality keeps on increasing, which is an indication that cancer therapies currently in practice are apparently wrong. To effectively solve cancer, we must find out how the problem of cancer evolves. Cancer evolves due to wound unhealing because of the collapse of chemo-surveillance, which is the nature's creation of allosteric regulation on abnormal methylation enzymes (MEs) to ensure perfection of wound healing. Progenitor stem cells (PSCs) are the cells involved in wound healing. The inability to heal wound allows PSCs to evolve into CSCs and then to progress to faster growing cancer cells (CCs). Solution of CSCs is essential to achieve life time remission. CSCs are protected by drug resistance, anti-apoptosis and DNA repair mechanisms. Thus, CSCs are unresponsive to cytotoxic therapies. Cytotoxic therapies must rely on the restoration of chemo-surveillance to subdue surviving CSCs to achieve cancer therapy. Only early stage cancer patients whose chemo-surveillance have not yet been fatally damaged can benefit from cytotoxic therapies. CDA formulations are the best drugs for the elimination of CSCs, which can come to the rescue of advanced cancer patients whose chemo-surveillance have been fatally damaged. The approval of CDA formulations is blocked by cancer establishments because these drugs cannot make tumor to disappear. The requirement of tumor shrinkage must be removed for the approval of CDA formulations to save advanced cancer patients.

Keywords

Cancer Mortality, CDA Formulations, Cancer Stem Cells, Cytotoxic Agents, Progenitor Stem Cells, Wound Healing

1. Introduction

Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells, which was a mistake made at a time when we did not have complete knowledge of cancer. The mistake was excusable. Perpetual proliferation of cancer cells was the most outstanding feature of cancer. Toxic chemicals and radiation were very effective to stop proliferation of cancer cells, which became the top choice of cancer establishments for cancer

therapy, and the reduction of tumor became the standard criterion for the judgment of success. Cytotoxic chemotherapy and radiotherapy were the top choice of cancer establishments to combat cancer when President Nixon declared war on cancer during 1971-1976, which was not successful to reduce cancer mortality. Despite the failure, cancer establishments kept using the failed cancer drugs, because they could not find

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drugs to reduce tumor better than the failed drugs. That was inexcusable. Naturally, cancer mortality kept on increasing. The latest cancer statistics of the world compiled by NCI were the year of 2019 showing 19 million cancer incidence and 10 million cancer mortality, which were an increment of 5.0% and 5.3%, respectively, over the previous year [1]. The US statistics were better, showing 1.96 million cancer incidence and 0.61 million cancer mortality in 2023 compiled by ACS, which were an increment of 2.0% and 0.2%, respectively, over the previous year. Cancer mortality is the ultimate judgment of the success of cancer therapy. If cancer mortality is on the way to increase, that means cancer therapy is not successful. Both the world and the US cancer mortalities are on the way to increase, therefore, cancer therapies currently in practice are inadequate to solve cancer. That also means the commanding principle of cell killing is wrong. Cytotoxic chemotherapy, radiotherapy, cytotoxic cancer therapies based on induction of apoptosis and immunology are all based on cell killing, which are definitely unable to reduce cancer mortality. We have to develop therapeutic strategies not based on cell killing to reduce cancer mortality to successfully solve cancer.

2. Commentaries and Discussion

2.1. The Fundamental Basis of Cancer Evolution

To effectively solve a problem, we have to know the fundamental basis of the problem. Cancer evolves due to wound unhealing. The concept of cancer evolves due to wound unhealing was first introduced by the great German pathologist Virchow in the 19th century [2]. It was again brought up by Dvorak in 1986 [3]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrugh and Martin [4]. We provided the most important details on this subject that included abnormal MEs to contribute to the perpetual proliferation of CCs by blocking differentiation [5-7]; chemo-surveillance as the nature's creation of allosteric regulation on abnormal MEs to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing [8-10]; hypomethylation of nucleic acids as a critical mechanism on the induction of terminal differentiation of cells with abnormal MEs [11]; mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [12-14]; and the evolution of CSCs from PSCs due to wound unhealing through a single hit to silence TET-1 enzyme [15]. These studies very convincingly establish the validity of cancer evolution due to wound unhealing. Our carcinogenesis studies also confirmed the validity of this concept. During the challenges with hepatocarcinogens, we noticed the appearance of numerous tiny hyperplastic nodules displaying abnormal MEs before the appearance of hepatocarcinomas, which must represent the active proliferation of PSCs in the process of wound healing [16]. Most of these hyperplastic nodules disappeared shortly afterward, indicating the completion of wound healing. Only a few large size carcinomas appeared

later from unhealed nodules. During the challenge with hepatocarcinogens, if the animals were given Antineoplaston A10, which was phenylacetylglutamine effective to protect the integrity of chemo-surveillance [8], the occurrence of hepatocarcinomas could be prevented [17]. These are a clear indication that chemo-surveillance is a very important mechanism created by the nature to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing. The reason of wound unhealing is because of the collapse of chemo-surveillance to achieve induction of terminal differentiation of PSCs. The nature does not have a mechanism to detect the collapse of chemo-surveillance to rectify the problem, instead, to force the proliferation of PSCs. PSCs are normal stem cells subjected to contact inhibition. They are then forced to evolve into CSCs to escape contact inhibition. It takes a single hit to silence ten-eleven translocator-1 enzyme (TET-1), an enzyme responsible for lineage transitions, for the conversion of PSCs to become CSCs [18-20], which is an easy task of PSCs since these cells are equipped with exceptionally active MEs. The proliferation of CSCs still cannot heal the wound, because the problem is the breakdown of chemo-surveillance. Chromosomal abnormalities set in to activate oncogenes or to inactivate suppressor genes eventually forcing CSCs to progress to faster growing CCs. It is the functionality of chemo-surveillance to dictate the success of wound healing to avoid cancer evolution [8-10]. The evolution of CSCs is critically linked to wound unhealing, and, therefore, the only viable solution of CSCs is the induction of terminal differentiation of CSCs [21].

2.2. Close Relationship Between Cancer and Wound Healing

Cancer and wound healing are closely related to involve PSCs as the common elements [4, 12-14]. PSCs are the most primitive stem cells to initiate the development of organs or tissues during the embryonic development of fetus. A small percentage of these cells, usually less than 2% of the organ or tissue mass, are reserved for future expansion or repair. PSCs are pluripotent stem cells capable of differentiation into all component cells of the organs or tissues. PSCs are the most tenacious stem cells protected by drug resistant, anti-apoptosis and DNA repair mechanisms [22-24]. These cells express chemokine receptors to migrate to the troubled spots.

Wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) through phospholipase A2 from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [25, 26]. AA and membrane bound phosphatidylinositol fit our descriptions of urinary differentiation inducers OA-0.79 and PP-0 [27-30]. We tend to believe that AA and PGs constitute significantly as natural differentiation inducers (DIs), which are chemicals capable of eliminating telomerase from abnormal MEs. Although PGs are active DIs [31], the induction of terminal dif-

ferentiation of PSCs at the initial stage of the wound is not the primary objective of PGs. Rather, the localized inflammatory effect of PGs [26] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound area resulting in edema response to orchestrate the healing process. Chemo-surveillance mediated through DIs and differentiation helper inducers (DHIs), which are inhibitors of MEs capable of potentiating the activity of DIs, functions as a brake to prevent the build up of cells with abnormal MEs, which must be released for PSCs to proliferate. PGs are metabolically unstable with very short half lives measured by minutes [26]. The primary objective of PGs is to promote proliferation of PSCs, whereas the induction of terminal differentiation of PSCs at the final stage of wound healing is accomplished by chemo-surveillance. The stable end products of PGs, dicycloPGs, may get involved in the promotion of terminal differentiation of PSCs at the final stage of wound healing. The biological response of wound is good for wound healing.

The immunological response of wound prompts the production of cytokines, which is not good for wound healing. Tumor necrosis factor (TNF) is notoriously bad for wound healing. TNF is also named cachectin after its effect to cause cachexia symptoms. A manifestation of cachexia symptoms is to promote excessive urinary excretion of low molecular weight metabolites because of the membrane hyperpermeability induced by TNF [32, 33]. DIs and DHIs are among low molecular weight metabolites excreted, resulting in the collapse of chemo-surveillance. It is the balance of the biological response and the immunological response to dictate the outcome in favor or in disfavor of wound healing. In the case of acute wound, usually biological response prevails to favor wound healing. In the case of chronic wound, usually immunological response prevails to disfavor wound healing. Evidently, wound healing is an extremely important health issue. So, the nature creates chemo-surveillance and immuno-surveillance as the protection mechanisms to prevent the damages, chemo-surveillance to prevent the damages from toxic chemicals and physical means, whereas immuno-surveillance to prevent the damages from infectious agents. In this sense, chemo-surveillance and immuno-surveillance act synergistically in favor of wound healing. But chemo-surveillance and immuno-surveillance can also act antagonistically, since immuno-surveillance can trigger production of TNF to damage chemo-surveillance.

2.3. Chemo-surveillance Destroyed in Cancer Patients

Chemo-surveillance was a terminology we created to describe the observation that healthy people were able to maintain a steady level of metabolites active as DIs and DHIs,

whereas cancer patients tended to show deficiency of such metabolites [8]. DIs and DHIs are wound healing metabolites produced by the body naturally. The breakdown products of erythrocytes are a major source of DIs as OA-0.79 and PP-0 and DHI as uroerythrin for CDA-2 and Antineoplastons [27-32]. Steroid metabolites are important natural DHIs which must come from organs involved in steroid metabolism. Pregnenolone is an important DHI of CDA-2 [30]. Pregnenolone is the master substrate of all metabolically active steroids. It is a single metabolite to have a profound influence on cancer. The production of pregnenolone is bell shape in relation to ages with a peak daily production of around 50 mg at 20-25 years old [35]. The youngest and the oldest people produce relatively smallest amounts, and these are the most vulnerable age groups to develop cancer. It appears that chemo-surveillance is always operating at the maximum capacity, which can be easily destroyed by pathological assaults to induce cachexia symptoms. An active infection may be enough to destroy chemo-surveillance for cancer to evolve in very young and very old people.

DIs and DHIs are hydrophobic metabolites that can be purified by reverse phase chromatography on C18 as the adsorbant. Peptides share similar physical chemical properties with DIs and DHIs, and, therefore, can be used as surrogate molecules to represent wound healing metabolites in the blood and urine. Peptides were initially purified by C18 cartridge from plasma deproteinized with sulfosalicylic acid and urine, followed by HPLC analysis on a column of sulfonated polystyrene to resolve peptide profile and quantitative Ninhydrin assay. The quantitative analyses of plasma/urinary peptide ratios of 108 cancer patients are presented in Table 1 which is reproduced from the reference [8]. It is evident that chemo-surveillance is badly damaged in cancer patients. Only 1.8% of cancer patients can manage to maintain CDA level at 5.0 of healthy people, 25% of cancer patients above CDA level 2.5 and 75% of cancer patients below CDA level 2.5. Evidently, the progression of cancer causes CDA level to decline, and the treatment with cytotoxic agents aggravates the damage to chemo-surveillance. CDA 2.5 is very likely the breaking point to determine the responsiveness to cytotoxic therapies. Above CDA 2.5, patients are responsive to cytotoxic therapies, relying on the restored chemo-surveillance to subdue surviving CSCs. Below CDA 2.5, chemo-surveillance of cancer patients are fatally damaged, so that cancer patients are either becoming unresponsive to further treatment or even still responsive to reach complete remission are eventually succumbed to recurrence. So, Cytotoxic cancer therapies can cure a minority of early stage cancer patients whose chemo-surveillance have not yet fatally damaged, but cause the deaths of a majority of cancer patients in advanced stage whose chemo-surveillance have been fatally damaged.

Table 1. Chemo-surveillance destroyed in cancer patients.

Plasma/Urine Ratios	CDA Level	Patient Numbers	% Distribution
0.83-0.80 (Normal)	5.0	2	1.8
0.80-0.60	4.3	7	6.5
0.60-0.40 (Responsive)	3.1	18	16.7
0.40-0.20	1.8	38	35.2
0.20-0.10	0.9	24	22.2
0.10-0.02 (Unresponsive)	0.37	19	17.6

Plasma Peptides: nmoles/ml; Urinary Peptides: nmoles/mg creatinine

CDA levels reflect very well the healthy status of cancer patients. If patients underwent Antineoplaston therapy and responded well, CDA levels would increase to approach 5, and if not, CDA levels continued to decline [36]. Obviously, not all patients responded positively to Antineoplaston therapy. Antineoplaston preparations are natural wound healing metabolites purified from urine by reverse phase chromatography on C18. Cancer cells are known to express a high level of degradative enzymes to salvage substrates for macromolecular syntheses to support their faster growth. Natural wound healing metabolites may be quickly degraded to lose activity. We strongly recommend to have two sets of CDA formulations for cancer therapy: one set CDA-CSC made by natural DIs and DHIs to target CSCs, and another set CDA-CC made by unnatural DIs and DHIs to target CCs [20, 21]. Natural DIs and DHIs can access CSCs, and unnatural DIs and DHIs can resist degradation by degradative enzymes. We have carried out extensive studies of natural and unnatural DIs and DHIs which have been published [21, 27-32]. Antineoplastons were effective to save cancer patients. Unfortunately, they were blocked by cancer establishments around 1990.

2.4. CDA-2 as the Drug of Choice for the Elimination of CSCs

We were convinced that wound healing metabolites were excellent cancer drugs, which were not allowed in the USA. Antineoplastons are very much like Chinese herbal medicine, which are therapeutic efficacy oriented medicine. We were confident that cancer drugs such as Antineoplastons were acceptable in China. We went to China to develop CDA-2 which was a product of wound healing metabolites using XAD-16 instead of C18 as the adsorbant. C18 was a privileged method of Burzynski [8]. Metabolites retained by XAD-16 were similar but not exactly the same as those retained by C18. The differentiation inducing activity of both preparations were

comparable. Peptides were important active components of Antineoplastons, which were not retained by XAD-16. PP-0, which was membrane fragments containing active DIs, was a major DIs of CDA-2, but was only a minor active component of Antineoplastons. Both CDA-2 and Antineoplastons had OA-0.79, uroerythrin, and steroid metabolites as active components. Basically, CDA-2 and Antineoplastons are similar preparations of wound healing metabolites from urine.

Myelodysplastic syndromes (MDSs) are diseases due to wound unhealing at the stage of CSCs [37]. These diseases are ideal for the test 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 MDSs. Vidaza and Decitabine are also approved by the US FDA for the therapy of MDSs. Professor Jun Ma, the Director of the Institute of Hematology and Oncology of Harbin, was instrumental in conducting the clinical trials of all three MDSs drugs. According to his assessments based on two cycles of treatment protocols, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy based on hematological improvement evaluation, namely becoming independent on blood transfusion to stay healthy as shown in Figure 1, which is reproduced from the reference [38]. The effectiveness of MDSs therapy is based on the inactivation of abnormal MEs to achieve terminal differentiation of pathological cells, which are CSCs. CDA-2 achieves the inactivation of abnormal MEs by the elimination of the tumor factor telomerase from abnormal MEs [7], whereas Vidaza and Decitabine achieve the inactivation of abnormal MEs by covalent bond formation between methyltransferase and 5-aza-cytosine incorporated into DNA [39]. CDA-2 is without adverse effects, whereas Vidaza and Decitabine are proven carcinogens [40, 41], and very toxic to DNA [42-44]. It is obvious that CDA-2 is the drug of choice for the therapy of MDSs, and, therefore, should be considered the standard care

of MDSs. The induction of pathological CSCs to become functional erythrocytes, platelets or neutrophils is necessary to cure MDSs. Killing of CSCs cannot cure MDSs. The obsession of cancer establishments to kill cancer cells is definitely wrong, at least with respect to CSCs.

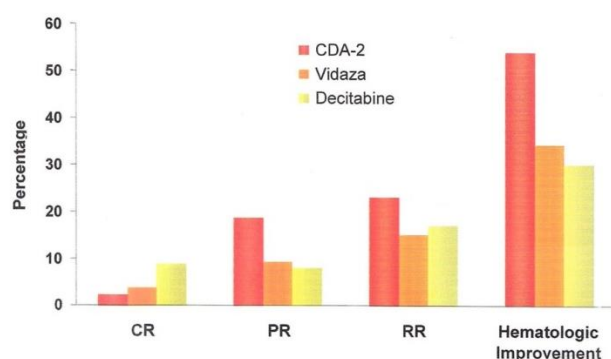


Figure 1. Relative Effectiveness of MDSs Drugs.

Induction of terminal differentiation of CSCs is the only option to cure cancer. Induction of terminal differentiation of PSCs is also a critical mechanism of wound healing [12]. Therefore, curing cancer is like healing wound. Healing wound is a simple matter. It comes naturally without having to put up any effort if the functionality of chemo-surveillance is intact at CDA level of 5. Therapy of cancer should also be a simple matter if CDA level can be restored to the level of 5 [45, 46]. Restoration of the functionality of chemo-surveillance is not a big deal. Anti-cachexia chemical phenylacetylglutamine is very effective to stop leakage of renal tubule [8], and the administration of CDA-CSC, a preparation made up by natural DIs and DHIs, can restore the collapsed chemo-surveillance. Solution of cancer is a simple matter if it is done correctly according to wound healing process [1, 47-49]. The cancer establishments make cancer very difficult to success, because they are doing the opposite to create wounds, resulting in ever-increasing cancer mortality.

2.5. CDA Formulations to Reduce Cancer Mortality

CSCs became a known issue in 1997 [50] which are evolved from PSCs as above described. CSCs share biological properties and missions very similar to PSCs. CSCs are responsible for tumor generation and treatment failure. Although CSCs constitute only a small subpopulation, usually less than 2% of the primary tumor mass, these cells contribute major fatal effects of cancer as metastasis, drug resistance, angiogenesis, unresponsiveness, and recurrence are the making of CSCs [22-24, 51, 52]. We have predicted that the winner of the contest to eradicate CSCs wins the contest of cancer therapies [53]. Of course cancer establishments knew the

importance of CSCs as the cause of treatment failure. The pharmaceutical giant GSK put up 1.4 billion, the most expensive investment on a cancer drug, about 18 years ago to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University. The attempt failed to materialize because killing was not an option. Cancer establishments knew the solution of CSCs was extremely important. They were unable to come up a good solution. But they are still unwilling to accept CDA formulations and Antineoplastons which we and Dr. Burzynski have presented very convincing data to show effectiveness to take care of CSCs [1, 15, 20, 21, 29, 36, 47, 53-55]. Evidently only cancer therapies which are able to take care of CSCs can produce life time remission. A comparison of cancer therapies on the effectiveness of patient survival is listed in Table 2, which shows CDA formulations as the best drugs to provide long term survival of cancer patients. CDA formulations are perfect cancer drugs that can take out both CSCs and CCs by inducing these cells to undergo terminal differentiation, and to restore chemo-surveillance to ensure life time remission. CDA formulations do not affect NCSs, nor immuno-surveillance. Therefore, these drugs do not produce adverse effects. The only disadvantage is that CDA formulations cannot make tumor to disappear. The tumor residue is harmless, which is made up by terminally differentiated cells unable to replicate. If it is too annoy, it can be safely removed by surgery. Vidaza and Decitabine can also take out both CSCs and CCs by induction of terminal differentiation. But these two drugs can also affect NSCs and immuno-surveillance to produce adverse effects. Nucleic acid interacting drugs are always very dangerous. CDA formulations are better choice to avoid dangerous adverse effects due to interaction with nucleic acids.

Cytotoxic agents including cytotoxic drugs, radiation and immuno-therapeutic agents are ineffective on CSCs because these cells are protected by drug resistance, anti-apoptosis and DNA repair mechanisms. So, the success of cancer therapies by cytotoxic agents relies on the restoration of chemo-surveillance. Therefore, cytotoxic therapies can only save a small minority cancer patients in the early stage whose chemo-surveillance have not yet fatally damaged. Late stage cancer patients whose chemo-surveillance have been fatally damaged have no chance of survival. Obviously cytotoxic cancer therapies kill more cancer patients in the advanced stage than the small minority of cancer patients in the early stage these therapies can manage to save. That is why cancer mortality keeps on escalating. Immunotherapy is definitely a better version of cytotoxic therapy to selectively target on the programmed death target on the cell membrane to spare adverse effects on NSCs and immune-surveillance. Actually CDA therapy and immunotherapy can make a good combination therapy, relying on CDA therapy to eliminate CSCs and to restore chemo-surveillance to save cancer patients, and relying on immunotherapy to kill CCs to achieve tumor shrinkage.

Table 2. A Comparison of Cancer Therapies on the Effectiveness of Patient Survival.

Cancer Therapies	CSCs	CCs	NSCs	Chemo-surveillance	Immuno-surveillance	Tumor Shrinkage	Patient Survival
CDAs	+	A	-	+	0	-	+
Vidaza & Decitabine	+	A	+	+	-	-	+
Chemo	-	B	+	-	-	+	+, Early -, Late
Radio	-	B	+	-	-	+	+, Early -, Late
Immuno	-	B	-	-	+	+	+, Early -, Late
Gene	-	A	-	+	0	-	+
Targeted	-	A	-	+	0	-	+
Anti-angiogenesis	-	B	-	+	0	+	-

Effects of cancer therapies on CSCs: + means ability to induce terminal differentiation of CSCs, - means inability to induce terminal differentiation of CSCs; on CCs: A means terminal differentiation, B means cell death; on normal stem cells (NSCs): - means without damaging effects, + means adverse damaging effects; on chemo-surveillance: + means improving effect, - means damaging effect; on immuno-surveillance: 0 means no effect, + means improving effect, - means damaging effect; on tumor shrinkage: - means no effect to induce tumor shrinkage, + means positive to induce tumor shrinkage; on patient survival: + means effective to save patients, - means ineffective to save cancer patients, +, Early means effective to save early stage patient, -, Late means ineffective to save late stage patient.

Gene and targeted cancer therapies were the focus of attention during 1976-1996 right after the failure of the war on cancer declared by President Nixon. These are legitimate cancer therapies to target on chromosomal abnormalities which are a critical issue of cancer. Although these therapies cannot induce terminal differentiation of CSCs, these therapies do not contribute to the damage of chemo-surveillance because the therapeutic endpoint is terminal differentiation of CCs. So, these therapies can rely on the restoration of chemo-surveillance to subdue surviving CSCs. Development of gene therapy was not successful simply because it was too difficult. Targeted cancer therapies produce several excellent cancer therapies. These therapies are not favored by the cancer establishments, because these therapies like CDA therapy cannot cause tumor to shrink. It is ironic that cancer drugs that kill CCs to result in tumor shrinkage favored by cancer establishments tend to cause the fatalities of advanced cancer patients, whereas cancer drugs that induce terminal differentiation of CSCs and CCs disfavored by cancer establishments can save cancer patients.

Anti-angiogenesis therapy was the focus of attention during 1996-2016 right after the failure to develop gene therapy, which was a total failure because patients ended up dying from internal bleeding.

It appears that cancer therapies effective to induce terminal differentiation of CSCs and CCs and to restore the functionality of chemo-surveillance have a better chance to save cancer patients. Killing of CCs and tumor shrinkage are ineffec-

tive to save a majority of cancer patients in the advanced state. Tumor shrinkage can be a promising diagnosis toward remission or can also be an ominous diagnosis toward fatality [56]. It is wrong to use tumor shrinkage as a criterion for the assessment of cancer therapy.

3. Conclusion

Elimination of CSCs is essential to achieve life time remission. Cytotoxic therapies are unable to affect CSCs. These therapies must rely on the restoration of chemo-surveillance to subdue surviving CSCs. Only early stage cancer patients whose chemo-surveillance have not yet been fatally damaged can benefit from cytotoxic therapies. CDA formulations are the best drugs to eliminate CSCs, which can come to the rescue of advanced cancer patients whose chemo-surveillance have been fatally damaged. Cancer establishments must remove the requirement of tumor shrinkage to allow the approval of CDA formulations to save advanced cancer patients.

Abbreviations

AA	Arachidonic Acid
ACS	American Cancer Society
A10	Antineoplaston 10
CCs	Cancer Cells
CDA	Cell Differentiation Agent

CSCs	Cancer Stem Cells
DIs	Differentiation Inducers
DHIs	Differentiation Helper Inducers
MDSs	Myelodysplastic Syndromes
MEs	Methylation Enzymes
NCI	National Cancer Institute
NSCs	Normal Stem Cells
AO	Organic Acid
PGs	Prostaglandins
PP	Pigment Peptide
TET-1	Tem Eleven Translocator-1
TNF	Tumor Necrosis Factor

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Consent and Ethical Approval

It is not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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