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CDA Formulations as Persuasive Good Cancer Drugs to Save Cancer Patients

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Abstract: The objective of this study is to develop good cancer drugs to save cancer patients. Good cancer drugs are the drugs capable of inactivating abnormal methylation enzymes (MEs) to take out both cancer stem cells (CSCs) and cancer cells (CCs) by inducing these cells to undergo terminal differentiation, and to restore chemo-surveillance to save cancer patients. Bad cancer drugs are cytotoxic agents that can kill CCs but cannot affect CSCs, which can also destroy chemo-surveillance to contribute to the fatality of advanced cancer patients. Cell differentiation agent-2 (CDA-2) is a persuasive good cancer drug approved by the Chinese FDA. CDA-2 is a preparation of wound healing metabolites purified from urine, which can serve as a model for the development of CDA formulations as good cancer drugs. Wound healing metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) are the active players of chemo-surveillance created by the nature as allosteric regulators of abnormal methylation enzymes (MEs). The elimination of abnormal MEs is very critical to the success of cancer therapy. Wound healing is a simple matter that comes naturally, because the nature creates chemo-surveillance to ensure perfection of wound healing. Cancer is the consequence of wound unhealing due to the collapse of chemo-surveillance. Cancer therapy can also be a simple matter, if the therapy follows wound healing process. PSCs and CSCs are cells with abnormal MEs, which are protected by drug resistance and anti-apoptosis mechanisms. PSCs are the cells involved in wound healing. Efficient induction of terminal differentiation of PSCs is very critical to the success of wound healing. Natural DIs and DHIs are the partners of PSCs and CSCs in wound healing, which can easily access to PSCs and CSCs. If wound is not healed, PSCs are forced to evolve into CSCs and then to progress to faster growing CCs. CCs display a high level of degradative enzymes to generate substrates for the syntheses of macro-molecules to support their faster growth. Natural DIs and DHIs may be rapidly degraded in CCs. A different set of unnatural DIs and DHIs may be necessary to achieve the induction of terminal differentiation of CCs. Thus, two sets of CDA formulations, one CDA-CSC with natural DIs and DHIs, and another CDA-CC with non-natural DIs and DHIs to accomplish induction of terminal differentiation of both CSCs and CCs to achieve effective therapy of cancer.

Keywords: Cancer Drugs, CDA, CSCs, DIs, DHIs, Differentiation Therapy

1. Introduction

Cancer mortality keeps on increasing. According to NCI experts, the incidence of cancer was 19 million and the cancer mortality was 10 million worldwide in 2019, which were exactly 5% above the statistics of 2018 [1]. They predicted a 5% increment in the following years likewise. The ever increasing cancer mortalities are an indication of ineffective handling of cancer by the health profession. Cancer therapy got to a bad start to rely on toxic chemicals to kill cancer cells. Cytotoxic chemotherapy was a tragic by product of World War II. During the world, toxic sulfur mustard gas bombs were used. Victims of toxic gas all displayed depletion of white blood cells in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Cytotoxic chemotherapy became the standard therapy of cancer, and the disappearance of cancer cells or tumor became the standard criteria to evaluate the effectiveness of cancer therapy. These were tragic mistakes made by cancer establishments at a time we did not have complete information of cancer. Perpetual proliferation of CCs was the most outstanding feature of cancer known at the early

time. Toxic chemicals were apparently very effective to stop proliferation of cancer cells. When President Nixon declared War on Cancer during 1971 to 1976, cytotoxic agents were the major drugs employed to combat cancer, which were not successful to reduce cancer mortality [2]. When a treatment modality was drilled through as a presidential project with unlimited support of national resources and failed, it was fair to conclude that the treatment modality was not good for cancer therapy. Evidently, cancer establishments agreed on this conclusion, and shifted the attention immediately away from toxic cytotoxic agents to gene and targeted therapies during l976 to 1996, and then to anti-angiogenesis therapy during 1996 to 2016, and now to immunotherapy from 2016 [3]. They did not develop new cancer drugs good enough to replace those failed to win the war on cancer. Those failed cancer drugs continue to cause horrendous cancer mortality. Cancer establishments are hopelessly trapped in belief that killing of CCs is the right approach of cancer therapy despite the failures encountered in the pursuit of this objective. Actually, killing of CCs is a wrong approach of cancer therapy, because cancer is caused by wound unhealing. Killing of CCs creates more wounds to aggravate the already bad situation caused by wound unhealing, thus making the bad situation worse [4]. The right approach of cancer therapy is to follow wound healing process [5, 6].

2. Commentaries and Discussion

2.1. Good Cancer Drugs vs Bad Cancer Drugs

Good cancer drugs are the drugs capable of inactivating abnormal MEs to take out both CSCs and CCs by inducing these cells to undergo terminal differentiation, and to restore chemo-surveillance to save cancer patients [7-9]. Chemo-surveillance was a novel concept we brought up as a natural defense mechanism against cancer, which was based on 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 as shown in Table 1 [7].

Table 1. *Collapse of chemo-surveillance among cancer patients.*

Plasma/Urine Peptide Ratio	**CDA Levels**	**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
0.02- 0.1	0.37	19	17.6

Plasma and urine peptides were initially purified by C18 cartridge, and peptide profiles were quantitatively analyzed by HPLC on a column of sulfonated polystyrene through Ninhydrin reaction. Plasma peptides were nmoles/ml and urine peptides were nmoles/mg creatinine.

CDA levels reflect very well the severity of the patients. Patients if responding well to Antineoplaston therapy, CDA levels would increase; if not, CDA levels continued to decline [10]. Antineoplastons were wound healing metabolites purified by reverse phase chromatography of urine on C18.

Bad cancer drugs are cytotoxic agents that can kill CCs but cannot affect CSCs, which can only benefit a minority of cancer patients in the early stage whose chemo-surveillance has not yet been fatally damaged, allowing full recovery to subdue surviving CSCs. These drugs contribute to the deaths of a majority of advanced cancer patients whose chemo-surveillance has been fatally damaged [4, 8, 9]. CDA3 may be the critical level to determine the responsiveness of patients to cytotoxic agents. Drugs approved for the therapy of cancer are predominantly bad cancer drugs, which are responsible for the horrendous cancer mortality of more than 10 million a year worldwide and still on the way to increase by an annual increment of 5% [1]. Good cancer drugs can bring down cancer mortality not only to fulfill President Biden's cancer moonshot initiative of reducing 50% cancer mortality in 25 years [11], but also to win the war on cancer declared by President Nixon in 1971, which bad cancer drugs failed to accomplish [2, 12, 13]. Somehow cancer establishments are trapped in belief that bad cancer drugs are the right choice for cancer therapy.

Cancer evolves as a consequence of wounds unhealing due to the collapse of chemo-surveillance [7, 10, 14-17]. Chemo-surveillance is the nature's creation of allosteric regulation to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing [18-21]. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs) [18]. PSCs are the most primitive stem cells to give rise to the organ or tissue during embryonic development of the fetus. Small amounts of these cells, usually less than 2% of the mass, are reserved in the organ or tissue for the need of expansion or repair. MEs of primitive stem cells such as embryonic stem cells (ESCs) and PSCs are abnormal for the quick expansion of these cells for the development of the fetus or for wound healing. MEs becoming abnormal do not seem to cause problems for normal stem cells, because there are safety mechanisms such as contact inhibition, TET-1 enzyme to initiate lineage transitions, and chemo-surveillance to prevent unnecessary build up of cells with abnormal MEs. Problems may arise if such safety mechanisms become dysfunctional. The breakdown of safety mechanisms may result in the display of clinical symptoms such as tissue fibrosis, dementia, organ failure or cancer [17, 22]. The build up of cells with abnormal MEs is important for normal development of the fetus as premature induction of terminal differentiation by thalidomide can lead to malformation of body parts, notably limbs. It appears that biological regulations are very delicately interweaved. Abnormal MEs are important for normal functions of primitive stem cells. But if abnormal MEs are not tightly regulated, cells with abnormal MEs may flare up to become big clinical problems. Apparently, chemo-surveillance is an effective guard of abnormal MEs. Cancer is the result of the breakdown of chemo-surveillance. Naturally, the right solution of cancer is to restore chemo-surveillance [21]. Good

cancer drugs do the right thing to restore chemo-surveillance, whereas bad cancer drugs do the opposite to destroy chemo-surveillance. Good cancer drugs display the feature of cancer therapy as pro-wound healing, whereas bad cancer drugs display the feature of cancer therapy as anti-wound healing. Good cancer drugs are the right-indication of cancer therapy, whereas bad cancer drugs are the contra-indication of cancer therapy. A right approach is essential to the success of solving any problem. A wrong approach always leads to the failure. In final analysis, the ability to induce terminal differentiation of CSCs and to restore chemo-surveillance marks the difference between good and bad cancer drugs. It makes no difference either to take out CCs by killing or by induction of terminal differentiation. Both accomplish the objective to stop proliferation of CCs. However, good cancer drugs have an issue of ugly residual tumor mass to deal with, albeit a harmless issue, and bad cancer drugs have an issue of adverse effects to deal with, which may be a grave issue often fatal. If harmless tumor residue is annoying, it can be safely removed by surgery without having to worry metastasis, since the functionality of chemo-surveillance has been fully restored.

A drawing to summarize the effect of good cancer drugs to save cancer patients and bad cancer drugs to cause cancer fatality is shown in Figure 1. CDA5-1 depict CDA at different levels, 5 being the highest level of healthy people. CDA3 may be the critical level to dictate the responsiveness to cytotoxic agents. Cancer patients in the categories CDA5 to 3 constitute 25% as shown in Table 1. CDA-CSCs are CDA formulations made up by natural DIs and DHIs, whereas CDA-CCs are CDA formulations made up by non-natural DIs and DHIs. Cytotoxic agents include cytotoxic drugs, radiation, apoptosis-inducing drugs, and immuno-therapeutic drugs.

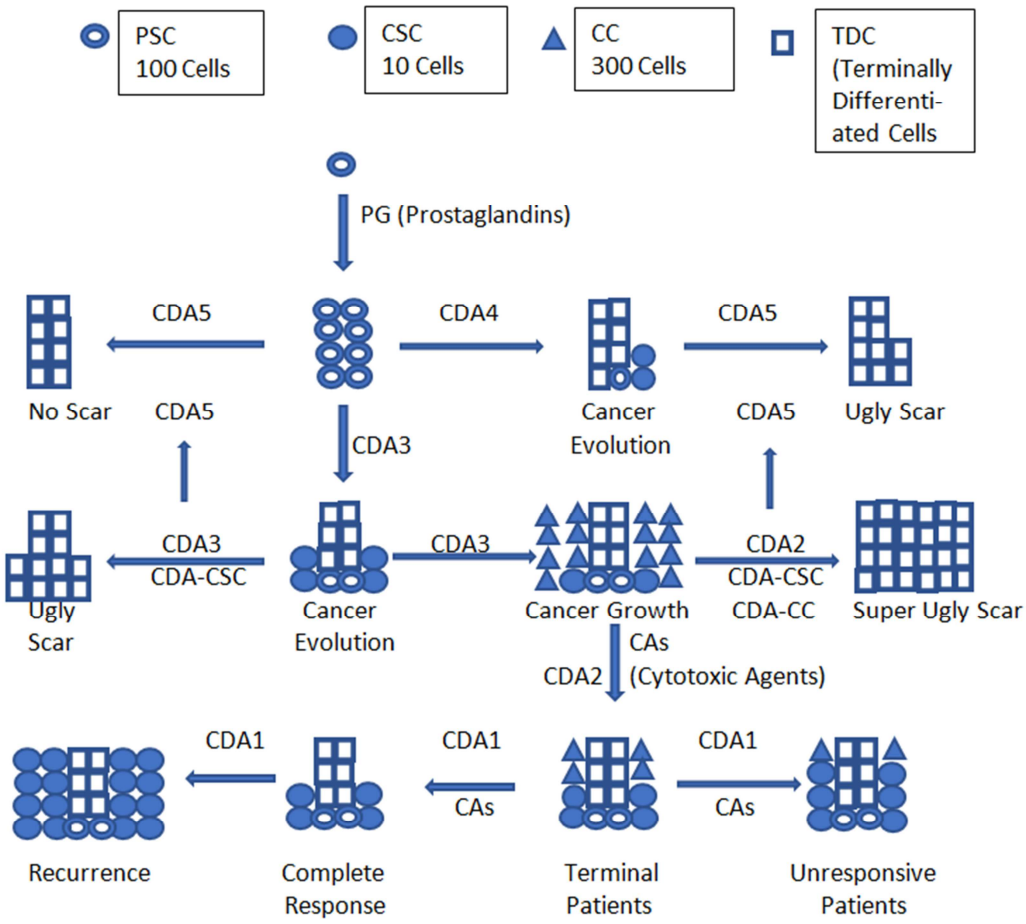

Figure 1. *Good cancer drugs to save cancer patients vs bad cancer drugs to cause cancer Fatality.*

2.2. Abnormal MEs as the Most Critical Issue of Cancer

Perpetual proliferation of CCs is the most outstanding feature of cancer. Abnormal MEs responsible for the blockade of differentiation is an important factor to contribute to the perpetual proliferation of CCs, and the activation of oncogenes or the inactivation of suppressor genes is another important factor on this issue. We considered that abnormal MEs were the most important issue of cancer on the basis that abnormal MEs were universal to all cancer that happened to PSCs, the precursors of CSCs, and passed on to CSCs and then to CCs [23, 24], whereas the occurrence of gene abnormalities was a late event of carcinogenesis process, and was variable among different cancers. When the problem of abnormal MEs was solved to direct CCs to undergo terminal differentiation, gene abnormalities could 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. On the other hand, the solution of gene abnormalities cannot affect abnormal MEs. It appears the easy way to solve gene abnormalities is to direct terminal differentiation, which are otherwise very difficult to solve. Killing of CCs is another easy way to solve gene abnormalities. It fails so far to put cancer away. Cancer establishments invested heavily on gene therapy during 1976-1996. The sequence of human genome was completed during this period in a preparation to develop gene therapy. They gave up, because it was simply too difficult and too expensive to develop gene therapy. Besides, it is not feasible. One difficult gene problem is solved, there may soon pop up another gene problem. Thus, the easy solution of difficult gene problems is to solve abnormal MEs [24].

Abnormal MEs are indeed the most critical issue of cancer, because these enzymes play a pivotal role on the regulation of cell replication and differentiation. This role is so important, so that MEs are subject to exceptional double allosteric regulations: one on the individual enzymes and another on the enzyme complex [25]. Enzymes playing important regulatory roles are often subject to delicate regulation. Allosteric regulation is the most pervasive regulation to maintain biological optimum to avoid extreme often to result in display of clinical symptoms. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltrans-ferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [26]. The functionality of MEs depends on the formation and the dissociation of enzyme complex under allosteric regulation. SAHH is a very unstable enzyme. It requires steroid hormone to assume a stable configuration to form dimeric enzyme complex with MT, which has a molecular size similar to MAT. A ternary enzyme complex is formed between MAT and MT-SAHH. The ternary enzyme complex is the stable and functional unit. On individual enzymes, MEs are under the regulation of steroid hormone or related allosteric factors. In the absence of steroid hormone or related allosteric factors, the ternary enzyme complex dissociates to become inactive. MTs in the individual enzyme state have the tendency to be modified to become nucleases which can trigger apoptosis to cause organ involution.

MEs play a pivotal role on the regulation of cell replication and differentiation by virtue of the fact that DNA methylation controls the expression of tissue specific genes [27], and pre-rRNA methylation controls the production of ribosome [28], which in turn dictate the commitment of cell to initiate cell replication [29]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [30]. Because of such important biological role, MEs subject to exceptional double allosteric regulations [25]. In telomerase expressing cells, MEs are associated with telomerase [31]. The association of MEs with telomerase changes kinetic properties of MEs and the regulation in favor of cell replication. K_m values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the normal isozyme pair. The increased K_m values suggest that telomerase expressing cells have much larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). Larger pool sizes of AdoMet and AdoHcy are needed for quick expansion of cells with abnormal MEs. It has been shown by Prudova et al. [32] that AdoMet could protect protein from protease digestion. Chiva et al. [33] found that pool sizes of AdoMeet and AdoHcy shrunk greatly when HL-60 cells were induced to undergo terminal differentiation. Obviously, abnormal MEs are essential for the build up of cells with abnormal MEs needed for the development of the fetus or for the healing of the wound. Abnormal MEs do not cause problems for normal stem cells, because there are safety mechanisms to prevent these cells from getting out of control. As discussed in the previous section, when safety mechanisms become dysfunctional, abnormal MEs become the most critical issue of tissue fibrosis, dementia, organ failure or cancer [3, 5, 6, 17-22, 24]. Henceforth, the best approach of therapies against illnesses due to wound unhealing is to pursue agents that can selectively destabilize abnormal MEs [9, 11-13, 21, 34].

2.3. Cancer Arises as a Consequence of Wound Unhealing

The concept of cancer arises as a consequence of wound unhealing was first introduced by the great German scientist Virchow in the 19th century [35]. It was again brought up by Dvorak in 1986 [14]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [15]. We provided the most important details on this subject that included abnormal MEs to block differentiation [23, 31, 36]; 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 [7, 19–21]; DIs and DHIs as wound healing metabolites and as the active players of chemo-surveillance [7, 19-21]; hypomethylation of nucleic acids as a critical mechanism on the induction of terminal differentiation [37]; mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [16-18]; and the evolution of CSCs from PSCs through a single hit to silence TET-1 enzyme [34, 38, 39]. These studies strongly support the notion that CSCs are evolved from PSCs due to the collapse of chemo-surveillance to heal wound. Wound unhealing forces chromosomal abnormalities to progress to faster growing CCs. Our carcinogenesis studies strongly support such arguments. During chemical hepatocarcinogenesis studies, we noticed generation of numerous tiny hyperplastic nodules which displayed abnormal MEs prior to the appearance of large size carcinomas [40]. These preneoplastic hyperplastic nodules must represent the proliferation of PSCs in the process active repair of wounds triggered by hepatocarcinogens. Most of these tiny hyperplastic nodules disappeared, indicating the completion of wound healing. Only a few large size carcinomas appeared later, which must result from unhealed nodules. If Antineoplaston A10 was provided during the challenge with hepatocarcinogen, It could effectively prevent the appearance of carcinomas [41]. Antineoplaston A10 is a

very effective anti-cachexia chemical to protect chemo-surveillance [7]. By protecting chemo-surveillance to ensure wound healing, Antineoplaston A10 could effective prevent hepatocarcinogenesis. Our studies convincingly establish that cancer arises as a consequence of wound unhealing.

Wound triggers biological and immunological responses [42]. Biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs), which are essential for efficacious wound healing. AA, PGs and their metabolites are effective DIs [43, 44], which are good for wound healing. PGs are also very active inflammatory agents [45]. PGs are produced at the initial stage of wound which are metabolically unstable molecules with short half lives measured by minutes. The function of PGs on wound healing is believed to promote local inflammatory response 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 chemo-surveillance. DicycloPGs are stable end products of PGs, which are less active as DIs [44]. DicycloPGs may be important components of active DIs of chemo-surveillance. Biological response usually prevail in favor of healing wound in the case of acute wound not lasting very long.

The immunological response of wound prompts the patient to produce cytokines, which are bad for wound healing. Cytokines are inflammatory agents to cause cachexia symptom. Tumor necrosis factor (TNF) among cytokines is a typical cytokine to cause cachexia symptom which is also named cachectin after this notorious effect. A manifestation of cachexia is the excessive urinary excretion of low molecular weight metabolites due to vascular hyperpermeability created by TNF [46, 47]. DIs and DHIs are among low molecular weight metabolites lost, contributing to the decline of CDA of cancer patients as shown in Table 1. It is not unreasonable to label cytotoxic agents as bad cancer drugs, because these drugs contribute to the collapse of chemo-surveillance, which is the nature's creation of allosteric regulation of abnormal MEs to ensure perfection of wound healing to prevent cancer from happening. Immunological response usually prevail to prevent healing wound in the case of chronic wound difficult to heal, leading to the evolution of cancer.

2.4. CDA-2 as a Persuasive Good Cancer Drug

Myelodysplastic syndromes (MDS) are unique diseases to illustrate the evolution of cancer due to wound unhealing, and CDA-2 is a preparation of wound healing metabolites to show excellent therapeutic effect on MDS. MDS often start with a display of an immunological disorder [48], which prompts the production of inflammatory cytokines. Among such cytokines, TNF is a critical factor related to the development of MDS [49]. It causes excessive apoptosis of bone marrow stem cells, thus severely affect the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF 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 in order to replenish unipotent stem cells wiped out by TNF. 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 evolving from PSCs [50, 51]. The propagating CSCs have been identified as human CSCs [52]. So, MDS are diseases attributable entirely to the propagation of CSCs. The build up of PSCs is limited by contact inhibition. After all, PSCs are normal stem cells, which obey the rule of contact inhibition. Since wound is not healed, these normal stem cells will be forced to evolve into CSCs in order to escape the limitation of contact inhibition. It is an easy task by a single hit to silence TET-1 enzyme to concert PSCs to CSCs, which is within the reach of PSCs equipped with abnormally active MEs. The problem of wound unhealing is the collapse of chemo-surveillance, not the insufficiency of PSCs. The propagation of CSCs still cannot heal the wound. To heal the wound, it requires inactivation of abnormal MEs to induce terminal differentiation of PSCs and CSCs to produce erythrocytes, platelets or neutrophils. Killing of CSCs cannot cure MDS. Besides, CSCs cannot be easily killed, because these cells are protected by drug resistant and anti-apoptosis mechanisms. So far, Vidaza, Decitabine and CDA-2 are the three drugs approved for the therapy of MDS in China. CDA-2 is our creation, which was a preparation of wound healing metabolites purified from freshly collected urine [53]. Vidaza and Decitabine are also the two drugs approved for the therapy of MDS in the USA. Professor Jun Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental to conduct clinical trials of all three MDS drugs. According to his assessment based on two cycles of treatment protocols each cycle 14 days, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to achieve 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 2 [54]. All three drugs achieve MDS therapy by the inactivation of abnormal MEs, Vidaza and Decitabine by the covalent bond formation between DNA methyltransferase and 5-azacytosine base incorporated into DNA to eliminate MEs [55], whereas CDA-2 destabilizes abnormal MEs by the elimination of telomerase [53]. CDA-2 achieves MDS therapy by targeting telomerase of abnormal MEs which is a selective cancer target and the most important issue of cancer [9, 13, 24, 34, 56], thus devoid of adverse effects, whereas Vidaza and Decitabine eliminate methyltransferase without specificity to affect all stem cells, which are known carcinogens [57, 58] and very toxic to DNA [59-61]. Obviously CDA-2 is a drug of choice for the therapy of MDS with better therapeutic efficacy and devoid of adverse effects. Vidaza and Decitabine can also be commended for being rare drugs able to eliminate CSCs, although not as perfect as CDA-2. Nucleoside analogs belong to bad cancer drugs. CDA-2 definitely is a persuasive model for the development of good cancer drugs. CDA-2 is the only

approved good cancer drug available in China. The rest of the world do not have a good cancer drug.

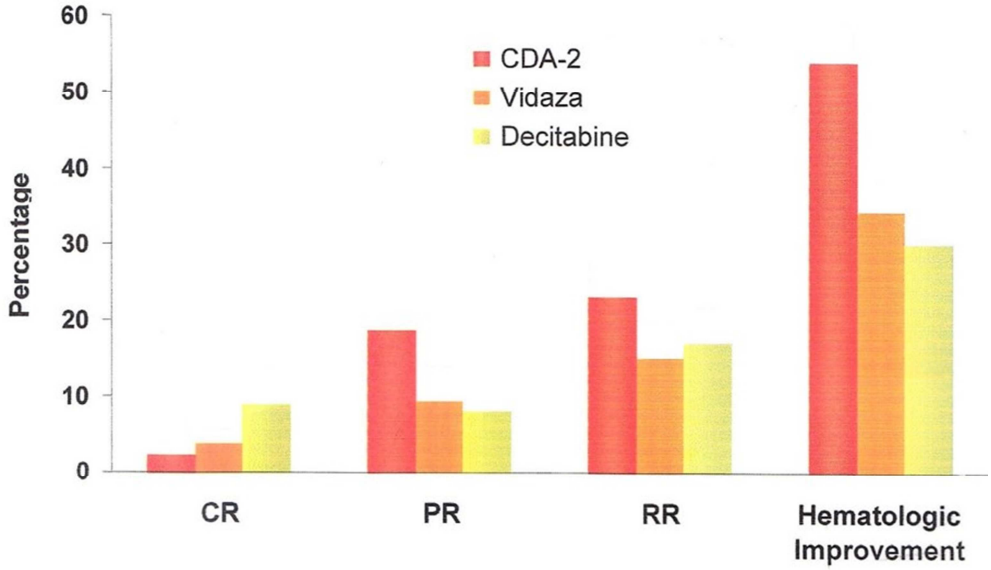

Figure 2. *Relative effectiveness of MDS drugs.*

2.5. Development of CDA Formulations as Good Cancer Drugs to Save Cancer Patients

CDA-2 has been approved by the Chinese FDA as a supplement of cytotoxic cancer drugs to improve cancer therapy and to reduce adverse effects of cytotoxic drugs to improve quality of life [62]. Cancer establishments set up the rule of tumor reduction as an exclusive criterion of acceptability as cancer drugs that can only allow the approval of bad cancer drugs and exclude good cancer drugs. Now President Biden wanted the health profession to come up solutions to reduce cancer mortality by 50% in 25 years [11]. Health profession has the obligation to develop good cancer drugs to reduce cancer mortality [9]. Approval of new drugs may take time to achieve the effect on the reduction of cancer mortality. Before good cancer drugs become available, we can modify bad cancer drugs to become good cancer drugs to achieve reduction of cancer mortality right away. The ability to induce terminal differentiation of CSCs and to restore chemo-surveillance marks the difference between good and bad cancer drugs. All we need to do right now is to search approved drugs that can induce terminal differentiation of CSCs and the agents that can restore chemo-surveillance.

Effective CDA formulations are made up by DIs and DHIs [12, 63]. All-trans retinoic acid (ATRA) is an excellent DI, which has been approved as a standard care of acute promyelocytic leukemia [64]. ATRA requires cancer cells expressing receptor of ATRA (RAR) to activate gene for the expression of oligoisoadenylate synthetase to produce oligoisoadenylate which is the active DI to achieve terminal differentiation of cancer cells [65]. ATRA is effective on acute promyelocytic leukemia cells and HL-60 cells, both are pluripotent stem cells. CSCs are also pluripotent stem cells, very likely to express RAR to respond to ATRA. Then, ATRA may be used as the DI of an effective CDA-CSC to induce terminal differentiation of CSCs to cut down cancer mortality. In case CSCs do not express RAR, then we may consider other approved drugs potentially active as DIs, which are listed in Table 2 [43, 44, 64]. ATRA is a drug approved for cancer therapy that can be prescribed for the application as a DI. PGJ2 and PGE2 are the drugs approved for the delivery. AA can be considered as a health food. BIBR1532 and boldine are the drugs approved as telomerase inhibitors. The use of PGJ2, PGE2, BIBR1532 and boldine as DIs may require permission for the change of indication, which should not take as long as the permission of new drugs. As to the selection of DHIs, pregnenolone is a major DHI of CDA-2 [63]. Pregnenolone is the master substrate of steroid hormones, which are the allosteric regulators of MEs at the individual enzymes [25, 26]. Pregnenolone must have an important role to play on chemo-surveillance. Deficiency of this important metabolite appears to have a decisive role on the development of cancer. According to Morley [66], production of pregnenolone is bell shape with a peak at 20-25 year old with a daily production of 50 mg. The very young and the very old people produce relatively smaller quantity, and these are the two age groups most vulnerable to develop cancer. Therefore, naturally deficiency of pregnenolone is at a risk to develop cancer. Supplement of pregnenolone is very likely to have a great benefit on the prevention of cancer evolution. Pregnenolone is a top choice of natural DHI. Actually we have carried out extensive studies of DHIs as presented in Table 3 [67-70], which can give us multiple choice to make effective CDA formulations as ED_{50} of a DI and $2xRI_{0.5}$ of a DHI [68]. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI. In the design of CDA formulations for particular cancer, non-cancer factors must be considered to come up more effective CDA formulations. For example, hydrophobic candidates are better for CDA-BT (brain tumors) to cross blood-brain barrier, candidates active in the inhibition of hypoxia inducible factor are better for

CDA-M (melanoma), and so on.

Table 2. *Approved drugs as potential Dis.*

DIs	ED_{25} (μM)	ED_{50} (μM)	ED_{75} (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32.0	46.5
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

Table 3. *Approved and natural drugs as potential DH.*

Signal Transduction			
SAHH-Inhibitors	**$RI_{0.5}$ (μM)**	**Inhibitors**	**$RI_{0.5}$ (μM)**
Pyrvinium-Pamoate	0.012	Sutent	0.28
Vitamin-D_3	0.61	Berberine	1.62
Dexamethasone	0.75	Votrient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59		
Pregnenolone	7.16		
		Polyphenols	$RI_{0.5}$(μM)
		Tannic-Acid	0.37
MT-Inhibitors	$RI_{0.5}$(μM)	EGCG	0.62
		Resveratrol	1.16
Hycanthone	2.10	Curcumin	1.24
Riboflavin	2.90	Kuromanin	1.43
		Coumestrol	1.95
MAT-Inhibitors	$RI_{0.5}$(μM)	Genisteine	2.16
		Pterostilbene	2.19
Indol-Acetic	Acid 220	Pyrogallol	3.18
Phenyacetylvaline	500	Silibinin	3.80
Phenyacetylleucine	780	Caffeic-Acid	3.87
Butyric-Acid	850	Ellagic-Acid	4.45
Phenylbutyric-Acid	970	Gallic-Acid	5.35

It is pertinent that two sets of CDA formulations may be necessary, one CDA-CSC to target CSCs and the other CDA-CC to target CCs to achieve effective therapy of cancer. CDA-CSC is made by natural DIs and DHIs that are natural partners of CSCs. CCs are known to express a high level of degradative enzymes to generate substrates for the syntheses of macro-molecules to support their fast growth. Natural DIs and DHIs may be degraded in CCs to lose biological activities. The employment of unnatural DIs and DHIs for the formulation of CDA-CC is a better choice to target CCs. Alternatively, relying on cytotoxic agents to target CCs may also be an effective combination.

The duty to save cancer patients falls onto conscientious oncologists. They can prescribe approved cancer drugs effective to promote terminal differentiation of CSCs as a supplement to bad cancer drugs to save cancer patients. Approval of CDA formulations to save cancer patients may not be that easy, which has been consistently blocked by cancer establishments in the past. It requires the cooperation of authority higher up than cancer establishments such as President Biden, conscientious oncologists and cancer patients to force cancer establishments to approve CDA formulations to save cancer patients. The prescription of approved cancer drugs active as DIs and DHIs and the use of natural DIs and DHIs as healthy food is legal. There are multiple choices to modify bad cancer drugs to become good cancer drugs for immediate application to save cancer patients.

3. Conclusion

Good cancer drugs can selectively destabilize abnormal MEs to induce terminal differentiation of CSCs and CCs, and to restore chemo-surveillance to save cancer patients. Bad cancer drugs can kill CCs, but cannot affect CSCs, which also can destroy chemo-surveillance to contribute to the fatality of a majority of advanced cancer patients. The ability to induce terminal differentiation of CSCs and to restore chemo-surveillance constitutes the difference between good and bad cancer drugs. The development of good cancer drugs takes time. At present, we can rely on approved drugs active as DIs and DHIs to modify bad cancer drugs to become good cancer drugs to save cancer patients.

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Abbreviations

AA: Arachidonic Acid
AdoHcy: S-adenosylhomocysteine
AdoMet: S-adenosylmethionine
CA: Cytototoxic Agent
CC: Cancer Cell
CDA: Cell Differentiation Agent
CR: Complete Remission
CSC: Cancer Stem Cell
DI: Differentiation Inducer
DHI: Differentiation Helper Inducer
ED: Effective Dosage
MAT: Methionine Adenosyltransferase
MT: Methyltrsnsferase
MDS: Myeloid Dysplastic Syndrome
PG: Prostaglandin
PR: Partial Remission
RI: Reductive Index
RR: Relative Response
SAHH: S-adenosylhomocysteine Hydrolase
TET-1: Ten Eleven Treanslocator-1

TNF: Tumor Necrosis Factor

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Conflicts of Interest

The authors declare no conflicts of interest.

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