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CDA Formulations as the Only Option Capable of Reducing Cancer Mortality

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ABSTRACT

The objective of this article is to develop CDA formulations to reduce cancer mortality. In 2022, President Joe Biden of the USA asked the health profession to reduce mortality of cancer patients by 50 % in the following 25 years which was a modest request in comparison to the war on cancer declared by President Nixon in 1971. Cancer is a giant issue of national interest for presidents to get involved. The health profession is hapless to solve this issue. The incidence and the mortality of cancer continued to increase since these statistics became public records. Cancer mortality in the USA has reached 0.61 million in 2023 and around the world has reached 10 million in 2019. The ever increasing records of cancer mortality are an indication of the failure of the health profession to solve cancer.

Cancer is caused by wound unhealing due to the collapse of chemo-surveillance. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs), which are the embryonic stem cells to initiate the development of organs or tissues, and also the cells responsible for wound healing. Methylation enzymes (MEs) of embryonic stem cells are abnormal due to association with telomerase, which gives cells with abnormal MEs a great advantage on cell growth. Cell growth is, obviously, needed for the development of fetus and wound healing. The nature creates safety mechanisms such as contact inhibition, ten eleven translocator-1 (TET-1) enzyme to direct lineage transitions and chemo-surveillance to prevent the buildup of cells with abnormal MEs to become clinical problems. When such safety mechanisms fail, clinical symptoms evolve. Cancer is one of these clinical problems. So, the correct solution of cancer is to heal wound, which we advocate. The cancer establishments preferred cell killing to eliminate tumor mass, which is opposite to healing wound by creating wounds to aggravate the already bad situation to result in ever increasing cancer mortality. Cancer mortality is the ultimate judgment on the success of cancer therapy. Cytotoxic agents approved by cancer establishments can cure cancer patients in the early stage relying on the restoration of chemo-surveillance to subdue surviving CSCs, but contribute to the deaths of advanced cancer patients whose chemo-surveillance have been fatally damaged, whereas cell differentiation agent (CDA) formulations can save all cancer patients to reduce cancer mortality. Therefore, CDA formulations are the only viable option to fulfill President Biden's order to save cancer patients.

Keywords

Cancer moonshot, CDA formulations, Chemo-surveillance, Cancer stem cells, Differentiation inducers, Differentiation helper inducers, Methylation enzymes, Wound healing.

Introduction

Cancer therapy had a bad start relying on toxic chemicals to kill cancer cells (CCs). Cytotoxic chemotherapy was a tragic byproduct of World War II. During the war, toxic sulfur mustard gas bombs were used. Victims of toxic gas displayed depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Cytotoxic chemotherapy became the standard care of cancer therapy, and the disappearance of cancer cells or tumor became the standard criteria for the evaluation of therapeutic efficacy. Cytotoxic chemotherapy and radiotherapy were the choice of cancer establishments to combat

cancer during the war on cancer declared by President Nixon during 1971-1976, which was not successful to reduce cancer mortality [1]. If treatment modalities were drilled through as a presidential project to receive unlimited support of national resources but failed, it was fair to conclude that those treatment modalities were inadequate for cancer therapy. Apparently, cancer establishments agreed with this conclusion and searched for other options. The emphasis on the development of new cancer therapies shifted from cytotoxic agents to gene and targeted therapies during 1976-1996 [2]. It was the right move, since chromosomal abnormalities were a critical issue of cancer, partly responsible for the perpetual proliferation of CCs which was the most outstanding feature of cancer. Gene therapy was simply too difficult and too expensive, so the cancer establishments gave up. The focus was then turned to anti-angiogenesis strategy during 1996-2016, which was deemed unsuccessful as patients died from bleeding as a consequence of effective blockade of angiogenesis. After this, the cancer establishments turned to immunotherapy from 2016 and onward as the cancer establishments failed to reduce cancer mortalities with chemotherapy, radiotherapy, and anti-angiogenesis therapy. Can they succeed on immunotherapy? It is very unlikely as the commanding principle of cell killing is basically wrong. Killing CCs cannot eradicate cancer stem cells (CSCs). Immunotherapy definitely is a better version of cytotoxic therapies to target on cell surface antigens that can avoid adverse toxic effects of cytotoxic chemicals and radiation, but immunotherapy has the same problem of cytotoxic chemotherapy and radiotherapy to show ineffectiveness against CSCs and to cause the damage to chemo-surveillance which are responsible for the failure of chemotherapy and radiotherapy to end cancer. We have to get to the very basis to find out the causes of cancer in order to search for the right solution. Cytotoxic chemotherapy, radiotherapy, anti-angiogenesis therapy and immunotherapy are piecemeal solutions that can only solve a fraction of cancer problems that is not very helpful to save cancer patients. That is the reason why cancer mortality continues to rise. It has reached 0.61 million annually in the USA in 2023 with an annual increment of 0.2%, and 10 million annually around the world in 2019 with an annual increment of 5% [3]. In 2022, President Biden of the USA asked the health profession to save 50% of cancer patients in the following 25 years. That means the health profession must come up with a plan to reduce 2% of cancer mortality annually [4]. In order to reverse cancer mortality from increasing to decreasing, it will require the development of new drugs which certainly takes time to develop. There are no hopeful new drugs on the horizon to reduce cancer mortality. CDA formulations are a hopeful prospect, which, however, were rejected by the cancer establishments because CDA formulations could not make tumor to disappear. They set up a rule of tumor reduction to deny the approval of cancer drugs that could not make tumor to disappear. It is the decision of President Biden to support the development of CDA formulations which are the only viable option to fulfill his moonshot initiative.

Commentaries and Discussion

The Very Basis of Cancer Evolution

Cancer mortality is the ultimate judgment of the success of cancer therapy. Cancer incidence and mortality have continued to increase since these statistics became public records. Cancer incidence has reached 1.96 million and cancer mortality has reached 0.61 million in 2023, which were 2% and 0.2% above the statistic records of 2022. The world cancer statistics were worse. The latest statistics of 2019 showed cancer incidence has reached 19 million and cancer mortality has reached 10 million, which were 5.3% and 5.0% above the statistic records of 2018. The ever increasing cancer records are an indication of the failure of the health profession to solve cancer. Is cancer such a difficult problem to solve? Actually, cancer is an easy problem. It becomes a difficult problem because the cancer establishments did not focus on the correct solution. To solve a problem correctly, we have to get to the very basis on how the problem evolves.

Cancer is caused due to wound unhealing. The concept of cancer evolving due to wound unhealing was introduced by the great German scientist Virchow in the 19th century [5]. It was again brought up by Dvorak in 1986 [6]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [7]. We provided the most important details on this subject that included abnormal MEs to block differentiation for the perpetual proliferation of CCs [8-10]; 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 [11-13]; differentiation inducers (DIs), which are chemicals capable of eliminating telomerase from abnormal MEs, and differentiation helper inducers (DHIs), which are inhibitors of MEs capable of potentiating the activity of DIs, as wound healing metabolites and also as the active players of chemo-surveillance [11-13]; hypomethylation of nucleic acids as a critical mechanism on the induction of terminal differentiation [14]; mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [15-18]; and the evolution of CSCs from PSCs due to wound unhealing [19]. These studies very convincingly establish that cancer evolves due to wound unhealing because of the collapse chemo-surveillance. Our carcinogenesis studies confirm the validity of this concept. During challenges with hepatocarcinogens, we noticed the appearance of numerous tiny hyperplastic nodules displaying abnormal MEs, which must represent proliferation of PSCs in active wound healing [20]. Most of these tiny hyperplastic nodules disappeared shortly afterward, which was an indication of the completion of wound healing. Only a few large size carcinomas appeared later from unhealed tiny nodules. If during the challenges with hepatocarcinogens, the animals were provided with Antineoplaston A10, which was a major metabolite phenylacetylglutamine present in the plasma, hepatocarcinogenesis could be effectively prevented as shown in Figure 1, reproduced from the reference [21]. Antineoplaston A10 is a biologically inactive metabolite. It is, however, very effective to protect the functionality of chemo-surveillance [11]. By keeping the functionality of chemo-surveillance intact, wounds can be efficiently repaired to avoid disastrous consequences of cancer evolution [15-18].

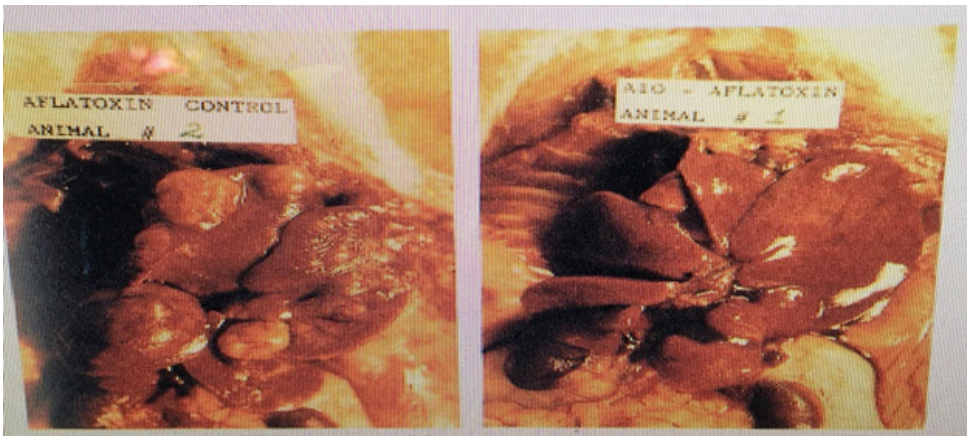

Figure 1: Effective Chemoprevention of Hepatocarcinogenesis by Antineoplaston A10.

Chemo-surveillance as the Nature's Creation of Allosteric Regulation on Abnormal MEs to Ensure Perfection of Wound Healing

Whatever happens naturally is the nature's creation to benefit humans. Photosynthesis is a prime example. All living creatures depend on photosynthesis to stay alive. Chemo-surveillance is also a creation of the nature. We are only a few to appreciate the creation by the nature of chemo-surveillance. Cancer establishments do not recognize chemo-surveillance, because most cancer drugs they put up destroy chemo-surveillance. Chemo-surveillance was a term we created to describe the observation that healthy people could maintain a steady level of metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites [11]. Peptides share physical chemical properties similar to active DIs and DHIs, therefore, can serve as surrogate molecules to represent DIs and DHIs in the plasma and urine. We have quantitatively analyzed plasma and urinary peptides of 107 cancer patients during 1980-1989, results are presented in Table 1, reproduced from the reference [11]. Peptides were initially purified by C18 cartridge from the plasma deproteinized by sulfosalicylic acid or the urine, and then analyzed by HPLC on a column of sulfonated polystyrene, followed by Ninhydrin assay. Results presented in Table 1 show only 1.8% of cancer patients had a CDA level as high as the level 5 of healthy people, 25% of cancer patients had CDA levels above 3, and 75% of cancer patients had CDA levels below 3. It is clear that the collapse of chemo-surveillance is responsible for cancer to evolve and the progress of cancer and the administration of treatments further cause the CDA levels to decrease. Obviously, chemo-surveillance is the nature's creation of protection mechanisms to prevent clinical symptoms to occur, including the evolution of cancer. The breakdown of chemo-surveillance is attributable to the creation of cachexia symptoms resulting in excessive excretion of metabolites essential for the protection of health. Tumor necrosis factor (TNF) is a cytokine triggered to produce in response to immunological responses. It is also named cachectin after its effect to cause cachexia symptoms. TNF can cause blood vessel hyperpermeability to result in excessive excretion of low molecular weight metabolites, which is a typical manifestation of cachexia symptoms [22,23]. TNF is primarily responsible for the occurrence of myelodysplastic syndromes (MDSs), because the antibody to TNF can prevent the progression of symptoms to lead to MDSs [24]. MDSs are a classic case on the evolution of cancer due to wound unhealing. Wound unhealing creates pathological conditions which triggers the production of TNF leading to the evolution of cancer. Chemo-surveillance is in essence the creator's prescription to prevent and to cure cancer [13]. Antineoplastons were the creation of Dr. Stanislaw R. Burzynski for cancer therapy since 1976 [25]. They are the preparations of active players of chemo-surveillance, namely DIs and DHIs, purified from urine by reverse phase chromatography on C18. The active components include acidic peptides, organic acid-0.79 (OA-0.79), pigment peptide-0 (PP-0) as DIs [26,27]. OA-0.79 is the liposomal complex of arachidonic acid (AA) or dicycloprostaglandins with pregnenolone, and PP-0 is membrane fragments containing OA-0.79 [28]. AA and its metabolites prostaglandins (PGs) constitute the major natural DIs [29,30]. Natural DIs are most likely the degradative products of erythrocytes. Steroid metabolites, uroerythrin, amino acid derivatives and fatty acids constitute the active natural DHIs [31-34]. Abnormal MEs are the target of Antineoplaston therapy. Since abnormal MEs are a selective cancer target responsible for the blockade of differentiation to cause perpetual proliferation of cancer cells [35,36], Antineoplastons targeted on abnormal MEs produced excellent therapeutic efficacy [37]. Patients responding favorably to Antineoplaston therapy generally showed restoration of CDA levels back to the level 5 of healthy people. If not, CDA levels continued to decline. Evidently, not all cancer patients responded favorably to Antineoplaston therapy. Cancer cells, particularly very fast growing cancer cells, are known to express a high level of degradative enzymes to salvage substrates for the syntheses of macromolecules to support the fast growth. Natural DIs and DHIs may be quickly degraded to lose activities. We recommend production of CDA formulations to include two sets, one CDA-CSC made up by natural DIs and DHIs that can easily access CSCs to target CSCs and one CDA-CC made up by non-natural DIs and DHIs that can resist degradative enzymes to target CCs. We strongly need to focus on the restoration of chemo-surveillance as a top priority to save cancer patients, since the collapse of chemo-surveillance is the primary cause for cancer to evolve [38].

Table 1: Status of Chemo-surveillance of Cancer Patients.

Plasma/Urine Peptide Ratio	CDA Level	Number of Patients	% Distribution
0.80-0.83	5	2	1.8
(Normal)			
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	0.4	19	17.6

The plasma peptides are nmoles/ml and the urine peptides are nmoles/mg creatinine.

Antineoplastons are effective to cure cancer, but chemical compositions of Antienoplastons purified from urine are unknown. Effective Cancer drugs with unknown chemical compositions are not acceptable in the USA. Antineoplastons were banned in the early 1990's. We were convinced that Antineoplastons were good cancer drugs to target on abnormal MEs we discovered [8-10,35,36]. We went to China in 1993 to develop CDA-2 using XAD-16 instead of C18 to recover urinary DIs and DHIs. Antineoplastons are very much like Chinese herbal medicines, which are therapeutic efficacy oriented medicines while chemical compositions are largely unknown. We were very certain that cancer drugs such as Antineoplastons could be accepted in China. CDA-2 and Antineoplastons both contain DIs and DHIs as active components, though not exactly the same. Acidic peptides are the major active DIs of Antineoplastons, which are not present in CDA-2. XAD-16 cannot retain peptides. PP-0 is a major active component of CDA-2, which is only a minor active component of Antineoplastons. Other active components are present in both preparations. CDA-2 and Antineoplastons are basically similar anti-cancer drugs based on destabilization of abnormal MEs. It turns out that destabilization of abnormal MEs is the only option for the solution of CSCs [39], which were an unknown issue before 2000, but are now recognized as the most important unsolved issue of cancer.

Close Relationship between Cancer and Wound Healing

Cancer and wound healing are closely related to involve PSCs as the common elements. Wound healing is an effortless production of the human body. For example, suture and the application of antibiotics on surgical wounds are subsidiary to speed up and to prevent infections. Since wound healing comes naturally, nobody cares to know how wound is healed. Actually, wound healing is an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing to avoid disastrous consequences such as tissue fibrosis, dementia, organ failure or cancer [15-18]. We need to study the natural factors of wound healing more closely. Wounds triggers biological and immunological responses. The biological response involves the release of AA from membrane bound phosphatidylinositol through phospholipase A2 for the synthesis of PGs by cyclooxygenases and PG synthases [40,41]. Although AA and PGs are active as DIs, the induction of terminal differentiation of PSCs at the initial stage of wound is not the primary objective of AA and PGs. Rather, the localized inflammation caused by PGs [42] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors in the wound resulting in edema response. Chemo-surveillance mediated through DIs and DHIs functions as a brake to prevent the buildup of cells with abnormal MEs, which must be released for PSCs to proliferate. The primary objective of PGs is to release the brake for the buildup of PSCs to heal the wound. PGs are metabolically unstable with very short half lives measured by minutes. Therefore, terminal differentiation of PSCs at the final stage of wound healing must rely on the functionality of chemo-surveillance [12]. The stable end products of PGs may then get involved in the promotion of terminal differentiation of PSCs. It appears that the biological response of wound is good for wound healing by promoting the proliferation of PSCs at the initial stage and the terminal differentiation of PSCs at the final stage. The immunological response of wound prompts the production of cytokines. TNF among the cytokines produced is particularly bad for wound healing. It is a toxic protein to cause apoptosis of normal stem cells to invite the proliferation of PSCs to work on the repair. It also causes membrane hyperpermeability to trigger excessive excretion of low molecular weight metabolites [22,23] leading to the collapse of chemo-surveillance to result in wound unhealing. Wound unhealing in most instances is caused by the collapse of chemo-surveillance which the nature does not have a mechanism to detect and to rectify. Instead, the nature forces PSCs to proliferate. The extent of the buildup of normal stem cells is subjected to contact inhibition. PSCs are then forced to evolve into CSCs to escape the limitation of contact inhibition. It takes a single hit to silence TET-1 enzyme to achieve the conversion, which is an easy task for PSCs to accomplish because these cells are equipped with exceptionally active MEs. The evolution of CSCs is an indication of wound unhealing. Therefore, the appearance of CSCs is to heal the wound. Terminal differentiation of CSCs becomes the only option to solve the problem related to CSCs [39]. If CSCs can be effectively induced to undergo terminal differentiation, the problem of wound unhealing is solved. The restoration of chemo-surveillance becomes the top priority to put away the cause forcing the evolution of CSCs [38]. If the breakdown of chemo-surveillance persists, the proliferation of CSCs still cannot heal the wound. Chromosomal abnormalities will set in to force slow replicating CSCs to become fast replicating CCs. The activation of oncogenes or the inactivation of suppressor genes are the final events of the process of carcinogenesis.

It appears that the biological response of the wound is good for wound healing, but the immunological response can be good for wound healing by eliminating infectious agents that cause wounds, and can also be bad for wound healing by triggering the production of TNF to cause cachexia symptoms leading to the collapse of chemo-surveillance. The protection of chemo-surveillance is utmost important to avoid damage arising from wounds.

Abnormal MEs as the Most Critical Issue of Cancer

Perpetual proliferation of CCs is the most outstanding feature of cancer. Cancer is basically a problem of growth regulation going awry. Abnormal MEs are a contributing factor by blocking

differentiation and activation of oncogenes or inactivation of suppressor genes are another important factor to promote proliferation. Abnormal MEs and chromosomal abnormalities are the two issues most critically related to the evolution of cancer, however, which is more important, the blockade of differentiation or the activation of proliferation? Most people, including cancer establishments bet on the activation of proliferation. Studies of oncogenes, suppressor genes, and signal transductions received all the attention and glory. Nobel prizes went to scientists in these areas. Cancer establishments even designated gene therapy to replace failed chemotherapy during 1976-1996. They gave up, simply because it was too difficult and too expensive to develop gene therapy. Besides, it was not feasible. A difficult gene problem might be solved, only to find another gene problem popped up to negate the previous effort. We were the only few to insist on abnormal MEs as the most important issue of cancer [43]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [44]. MEs play a pivotal role on the regulation of cell replication and differentiation [35,36]. Enzymes playing important regulatory roles are often subjected to delicate biological regulations. Allosteric regulation is the most pervasive regulation that is created by the nature to maintain biological optimum to avoid extreme often resulting in the display of clinical symptoms. MEs are exceptional to subject to double allosteric regulations: one on individual enzymes and one on the enzyme complex [45]. On the individual enzymes, SAHH is the steroid hormone receptor in steroid hormone target tissues. SAHH requires steroid hormone to assume a stable configuration in order to form a dimeric enzyme complex with MT. MT-SAHH dimer has a molecular size similar as MAT to form ternary MEs. The ternary MEs is the stable and active functional enzymes. In the absence of steroid, the ternary enzyme complex dissociates into individual enzymes to lose activity. In the monomeric state, MTs have a tendency to be modified to become nucleases to trigger damages to cause the involution of steroid hormone target tissues. In telomerase expressing cells, MEs are associated with telomerase [10]. The association with telomerase changes kinetic properties of MEs and the regulation greatly in favor of cell growth [8-10,35,36]. K_m values of telomerase associated MAT-SAHH isozyme pair are 7-fold higher than those of the normal isozyme pair. The increased K_m values are an indication that MEs of telomerase expressing cells bind larger amounts of S-adenosylmethionine (AdoMet) and cells with abnormal MEs have much larger pool sizes of AdoMet and S-adenosylhomocysteine (AdoHcy). Evidently, stable MEs and larger pool sizes of AdoMet and AdoHcy are important for the growth of cells with abnormal MEs as the study of Prudova et al. showed that AdoMet could protect protein against protease digestion [46] and the study of Chiba et al. showed when HL-60 cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly [47]. Thus, abnormal MEs are a very critical issue of cancer. Embryonic stem cells (ESCs) including PSCs express telomerase, MEs of these cells are also abnormal. Evidently, abnormal MEs are important for the development of fetus and wound healing. Disruption of abnormal MEs in ESCs can result in disastrous consequences. Administration of thalidomide during pregnancy can result in malformation of limbs. Abnormal MEs in normal stem cells do not seem to create problem, because normal stem cells have protection mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to keep cells with abnormal MEs under control. When such safety mechanisms become dysfunctional, the clinical symptoms arise. It is exceedingly important to protect safety mechanisms of cells with abnormal MEs.

We consider abnormal MEs as the most critical issue of cancer, because MEs are very important enzymes on the regulation of cell growth. Abnormal MEs are shared by all cancers [9]. Abnormal MEs happen quite early on totipotent stem cells, namely the fertilized eggs and also the very beginning of the life, and spread to ESCs including PSCs, and then pass on to CSCs and then to CCs. Most importantly, once MEs are solved, cells exit the cell cycle to undergo terminal differentiation that can also solve the issue of chromosomal abnormalities. Oncogenes and suppressor genes are cell cycle regulatory genes. They have important roles to play when cells are in the cell cycle replicating. However, if replicating cells are forced to undergo terminal differentiation, they have no roles to play. Obviously, abnormal MEs are the bullseye of cancer target [48]. Killing of CCs can also solve the issues of abnormal MEs and chromosomal abnormalities. It has been tried, but has failed [1].

CDA Formulations as the Best Drugs for the Eradication of CSCs

The evolution of cancer proceeds from PSCs to CSCs due to wound unhealing, and then to CCs. Myelodysplastic syndromes (MDSs) are a classic case to demonstrate the validity of this concept. MDSs often start with a display of an immunological disorder [49], which prompts the local production of inflammatory cytokines. Among cytokines produced, TNF is the critical factor related to the development of MDSs [24]. 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 or neutrophils. TNF is also named cachectin after its nortorious effect to cause cachexia symptoms which are commonly shared by inflammatory and cancer patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites leading to the collapse of chemo-surveillance described in the section 2-2. The high level of telomerase in the peripheral and bone marrow leukocytes in MDSs patients is an indication of the widespread multiplication of malignant cells [50,51]. The propagating pathological cells have been identified as human CSCs [52]. So, MDSs represent cancer development at the stage of CSCs. Further development through chromosomal abnormalities eventually pushes MDSs patients to become acute myeloid leukemia patients.

MDSs are ideal to test the drugs effective against CSCs, which are responsible for the fatal effects of cancer. Fatal effects such as metastasis, drug resistance, angiogenesis, unresponsiveness and recurrence are the making of CSCs. CSCs are notoriously

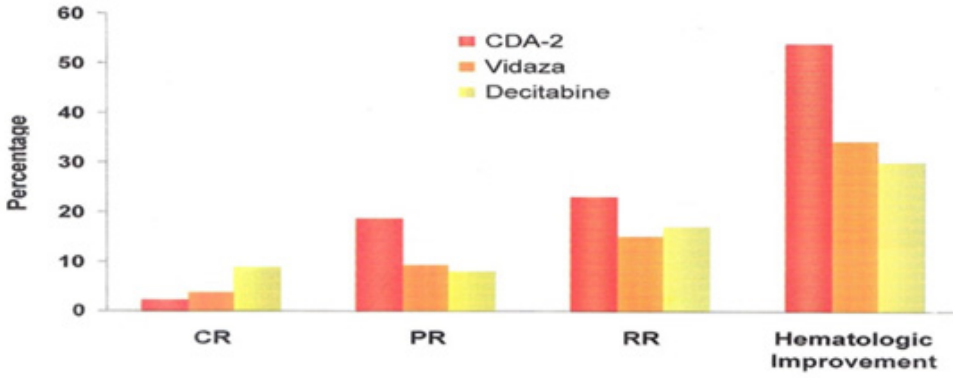

Figure 2: Response rates of CDA-2 in comparison to Vidaza and Decitabine.

tenacious because these cells are protected by drug resistance and anti-apoptosis mechanisms [53-56]. The best and the only way to handle CSCs is the prescription of the nature, namely chemo-surveillance above described in the section 2-2.

Vidaza, Decitabine and CDA-2 are the three drugs approved for the therapy of MDSs by the chinese FDA. CDA-2 is our creation [57]. Vidaza and Decitabine are also approved for the therapy of MDSs by the US FDA. Professor Jun Ma, Director of the Harbin Institute of Hematology and Oncology, was instrumental in conducting clinical trials of all three MDSs drugs in China. According to his assessments based on two cycles of treatment protocols each 14 days, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission, and markedly better therapeutic efficacy based on hematological improvement evaluation, namely on the dependency of blood transfusion, as shown in Figure 2, which is reproduced from the reference [58].

All three MDSs drugs achieve therapeutic effects by inactivation of MEs, Vidaza and Decitabine by covalent bond formation between DNA methyltransferase and 5-aza-cytosine base incorporated into DNA [59], whereas CDA-2 by the elimination of the tumor factor telomerase of the abnormal MEs [10,19,35,36,39,57]. CDA-2 selectively eliminated the tumor factor of abnormal MEs, whereas Vidaza and Decitabine by a non-selective mechanism affecting also methylation of normal stem cells. Therefore, CDA-2 was devoid of adverse effects, whereas Vidaza and Decitabine were proven carcinogens [60,61] and very toxic to DNA [62-64]. Obviously, CDA-2 is the drug of choice for the therapy of MDSs with superior therapeutic efficacy and devoid of adverse effects. Evidently, induction of terminal differentiation of CSCs is the only option for the therapy of MDSs. It is also the only option for wound healing. Killing of CSCs cannot cure MDSs. Cancer establishments must recognize this fact. Commanding principle of cell killing is basically an inappropriate strategy, particularly with respect to CSCs. Solution of CSCs is essential to the success of cancer therapy. Cancer establishments tend to dismiss CSCs as unimportant small minor issue. CSCs may be a very small minority of the tumor mass. They contribute the most damaging effects of cancer. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [65]. Apparently, the winner is CDA formulations.

CDA Formulations to Fulfill the Supreme Commander's Order of Saving Cancer Patients

Effective solution of cancer must take into consideration all factors involved in the evolution of cancer. A piece meal approach dealing only with an incomplete issue of cancer cannot solve cancer. Cytotoxic chemotherapy, radiotherapy, anti-angiogenesis therapy and immunotherapy are all piece meal approaches. Chemotherapy, radiotherapy and anti-angiogenesis therapy were therapies unable to reduce cancer mortality. Gene therapy was abandoned because it was too difficult and too expensive to develop. Immunotherapy is an ongoing project, which is a better version of cell killing to target on cell surface antigens that can avoid adverse effects. However, it has the same problem of cytotoxic agents to show ineffectiveness against CSCs and to cause damage to chemo-surveillance. A perfect cancer drug must be able to take out CSCs and CCs, and to restore the functionality of chemo-surveillance [66]. Based on these arguments, we can compare different cancer therapies to make an assessment of the therapies most promising to save cancer patients. Effects of cancer therapies on CSCs, CCs, normal stem cells (NSCs), on the protection mechanisms of chemo-surveillance and immune-surveillance, on the tumor shrinkage and the patient survival are listed in Table 2. Survival of cancer patients is our major concern as the objective of this article is to save cancer patients, which is also President Biden's order. Obviously, therapies able to take care of CSCs by the induction of terminal differentiation are the best strategy to save cancer patients [39,67-69]. Afterall, cancer evolves due to wound unhealing, destabilization of abnormal MEs to induce terminal differentiation of CSCs is the only option to take care of CSCs [39]. CDA is better than Vidaza and Decitabine to spare the bad adverse effects on NSCs and immuno-surveillance, thus, CDA is able to save more cancer patients. The wound healing strategy is the right approach of cancer therapy [39,67-69].

Cancer therapies based on the killing of CCs are favored by cancer

Table 2: A Comparison of Cancer Therapies on the Survival of Cancer Patients.

Cancer Therapy	CSCs	CCs	NSCs	Chemo- surveillance	Immuno- surveillance	Tumor Shrinkage	Patient Survival
CDA	+	A	-	+	0	-	+
Vidaza							
Decitabine	+	A	+	+	-	-	+
Chemo	-	B	+	-	-	+	+ Early
							- Late
Radio	-	B	+	-	-	+	+ Early
							- Late
Immuno	-	B	-	-	+	+	+ Early
							- Late
Gene	-	A	-	+	0	-	+
Target	-	A	-	+	0	-	+
Anti-							
Angiogenesis	-	B	-	-	0	+	-

On the effect toward CSCs, + can induce terminal differentiation, - cannot; on CCs, A means induction of terminal differentiation, B means cell killing; on NSCs, - means no effect, + means damaging effect; on chemo-surveillance, + means improving, - means damaging; on immune-surveillance, 0 means no effect, + means improving, - means damaging; on tumor shrinkage, + can cause shrinkage, - cannot cause shrinkage; on patient survival, + means can, + Early means can help survival of early stage patients, - Late means cannot help survival of late stage patients.

establishments. CSCs are the most tenacious stem cells to be killed. Cell killing strategies cannot affect CSCs. Cancer patients undergoing cell killing strategies must rely on the recovery of chemo-surveillance to subdue surviving CSCs. Therefore, only the early stage cancer patients whose chemo-surveillance have not yet fatally damaged have the chance to recover the functionality of chemo-surveillance to stay alive. The late stage cancer patients whose chemo-surveillance have been fatally damaged are either killed by becoming unresponsive to further therapy, or successfully reach complete remission and then succumbed to recurrence. Cytotoxic cancer therapies tend to increase the proportion of CSCs in the tumor mass [67]. Killing of CCs invite the proliferation of CSCs to repair the damages, eventually boosting the proportion of CSCs from less than 2% in most popular primary cancers to reach more than 10% to become unresponsive to further treatments. Primary malignant brain tumors have CSCs greater than 10% which are unresponsive to cytotoxic cancer therapies [70,71]. Thus, cancer therapies base on cell killing cannot save late stage cancer patients harboring greater proportions of CSCs and with their chemo-surveillance fatally damaged. It is still too early to make a final judgement on immunotherapy. It has 12 more years to prove it can turn cancer mortality around from increasing to decreasing. In case it cannot turn the cancer mortality around as expected, it can rely on CDA formulations to achieve this goal. Immunotherapy and CDA therapy can make a perfect combination therapy, relying on CDA to eradicate CSCs and to restore chemo-surveillance to save cancer patients which immunotherapy cannot accomplish, and relying on immunotherapy to eliminate residual tumor mass which CDA therapy cannot accomplish. Residual tumor mass from CDA therapy is terminally differentiated cells which are harmless, albeit annoying, which can be safely removed by surgery without complication of metastasis because the functionality of chemo-surveillance has been restored to the healthy level of CDA-5.

Gene therapy is a fascinating cancer therapy, receiving support and expectation. It is a legitimate cancer therapy and duly supported during 1976-1996. Cancer establishments gave up, because it was too difficult and too expensive to develop gene therapy. Signal transduction inhibition (STI) is closely related to gene therapy, and is technologically not as difficult as gene therapy. STIs are excellent DHIs. The therapeutic endpoint of DHIs is terminal differentiation, which cannot make tumor to disappear. They are not the favorite of cancer establishments. Gene therapy and target therapy cannot affect CSCs directly. But gene therapy and target therapy by eliminating CCs without creating wound do not have the tendency to increase CSCs population. These therapies do not cause damage to chemo-surveillance. Therefore, chemo-surveillance can be restored to subdue surviving CSCs even though gene therapy and target therapy cannot affect CSCs directly. The restoration of chemo-surveillance is the key to save cancer patients, as in the cases of chemotherapy, radiotherapy and immunotherapy on the early stage cancer patients [38].

Anti-angiogenesis is also based on cell killing strategy. It does not have the bad effects on normal stem cells. The failure to save cancer patients is due to bleeding.

It appears that CDA, gene and target therapies are best to save cancer patients. Gene therapy is too difficult and too expensive to pursue. CDA and target therapies are basically the same approach to target on abnormal MEs. CDA formulations have the advantage to be able to eradicate CSCs directly, whereas target therapy must rely on the recovery of chemo-surveillance to subdue CSCs.

Development of CDA Formulations to Save Cancer Patients

We have carried out extensive studies on natural and non-natural DIs and DHIs for the manufacture of CDA formulations [26-34,57,67-69]. Active DIs and DHIs are presented in Table 3 and 4. DIs and DHIs can be excellent cancer drugs. All trans-retinoic acid (ATRA) is the standard care of acute promyelocytic leukemia [72]. It requires the expression of the receptor of ATRA, namely RAR, to activate oligoisoadenylate synthetase to achieve the therapeutic effect [73]. The product of this enzyme oligoisoadenylate is the actual DI to act on abnormal MEs. PGJ2 is the most active DIs of PG derivatives. The half life of PGJ2 is very short [40]. It is a

good idea to use the more stable AA or dicycloPGE2 as the natural DIs for the manufacture of CDA formulations to target CSCs. BIBR1532 is the only choice of non-natural DI for the manufacture of CDA formulations to target CCs.

Table 3: Active 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	46.5
DicycloPGE2	21	43.5	-
AA	21	42	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

Table 4: Active DHIs.

		Signal Transduction	
SAHH Inhibitors	$RI_{0.5}$ (μM)	Inhibitors	$RI_{0.5}$ (μM)
Pyrivinium Pamoate	0.012	Sutent	0.28
Vitamin D_3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22	-	-
Hydrocortisone	4.59	Polyphenols	$RI_{0.5}$ (μM)
Pregnenolone	7.16	-	-
-	-	Tannic Acid	0.37
MT Inhibitors	$RI_{0.5}$ (μM)	EGCG	0.62
-	-	Resveratrol	1.16
Uroerythrin	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestrol	1.95
-	-	Genisteine	2.19
MAT Inhibitors	$RI_{0.5}$ (μM)	Pyrogallol	3.18
-	-	Silibinine	3.8
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ellagic Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	Phloroglucinol	38.82

For the induction of terminal differentiation, DIs are more important than DHIs, which are able to eliminate telomerase from abnormal MEs. But the inclusion of DHIs is also crucial to achieve effective therapeutic efficacy. DIs along cannot achieve differentiation to reach 100%, because DIs alone tend to induce dissociation of ternary MEs to become individual enzymes, allowing monomeric MTs to be modified to become nucleases to create damages to interrupt replication process to complete terminal differentiation. The damaged cells after repair can result in recurrence. The addition of DHIs can prevent the dissociation of MT-SAHH dimer or the modification of monomeric MTs to become nucleases, so that induction of differentiation in the presence of both DI and DHI can reach 100% to avoid recurrence.

Inhibitors of SAHH and MT are better DHIs. This is because MAT is the most stable enzyme of the three MEs. The association with telomerase further increases its stability. It is very difficult to shake loose of this enzyme in the abnormal MEs configuration. SAHH and MT inhibitors are better DHIs, because these inhibitors can keep MT in dimeric complex to prevent the modification of MTs to become nucleases to create damages to interrupt the differentiation process, resulting in incomplete induction of terminal differentiation. Pregnenolone is a major DHI of CDA-2. It is the least active DHIs listed in Table 4, we consider it the most important steroid metabolite of natural DHIs, because it is the master substrate of all metabolically active steroids. 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 [74]. The youngest and the oldest people produce relatively the smallest amounts, and these are the two age groups most vulnerable to develop cancer. Pregnenolone is, therefore, a single metabolite to exercise profound influence on the evolution of cancer. It is our choice of natural DHI to make CDA-CSC formulations. The finding of signal transduction inhibitors as excellent DHIs is expected, since signal transducers always produce factors to stabilize MEs. The elimination of such stabilizing factors naturally will potentiate the induction of terminal differentiation. Gleevec is an excellent cancer drug as the standard care of chronic myeloid leukemia [75]. The finding of polyphenols as excellent DHIs was a surprise, but was a pleasant surprise. Polyphenols are generally considered good for health. The finding of polyphenols as excellent DHIs adds the credibility of polyphenols as health food.

Effective CDA formulations can be ED_{25} of a DI + $3xRI_{0.5}$ of a DHI, or ED_{50} of a DI + $2xRI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [28]. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI. $RI_{0.5}$ can be determined by the procedure provided [32]. 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 bring up in the section 2-2 [74,75].

Conclusion

Cancer mortality keeps on increasing, which is an indication that cancer therapies have not been handled right. Cancer evolves due to wound unhealing, progressing from PSCs to CSCs, and then from CSCs to faster growing CCs. CSCs are critically linked to wound unhealing. The induction of terminal differentiation of CSCs is the only option to solve the issue related to CSCs. Elimination of CSC is essential to the success of cancer therapy. CDA formulations, made up by DIs and DHIs, can destabilize abnormal MEs to induce terminal differentiation of CSCs and CCs. CDA formulations are, therefore, the only option best to save cancer patients to reduce cancer mortality.

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