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Creation of Wounds is Incorrect for Cancer Therapy

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ABSTRACT

The objective of this article is to correct the mistake of cytotoxic cancer therapies based on the creation of wounds to kill cancer cells (CCs). Perpetual proliferation of CCs is the most outstanding symptom of cancer. Naturally, killing of CCs with cytotoxic agents was a choice which became a commanding principle of cancer establishments to direct cancer therapies. Apparently, this commanding principle was incorrect to result in the escalation of cancer mortality to reach 10 million annually worldwide. It is necessary to establish a valid concept of cancer to confront cancer successfully. Cancer evolving due to wound unhealing was a valid concept introduced by the great Germany pathologist Virchow in 1858. Our studies of carcinogenesis, abnormal methylation enzymes, chemo-surveillance and the mechanism of wound healing strongly supported the validity of Virchow's concept of cancer evolving due to wound unhealing. Thus, perfection of wound healing is the right indication of cancer therapy. Creation of wounds is definitely contra-indication of cancer therapy clearly in violation of the valid concept of cancer introduced by Virchow. Cancer establishments became a very difficult issue of cancer to damage the reputation of health profession as a profession unable to achieve the Presidential Project to Win the War on Cancer and to contribute to the ever-escalation of cancer mortalities. A game change in oncology therapeutics from creation of wounds to perfection of wound healing is necessary to turn around cancer mortality from escalation to deceleration. Cell differentiation agent (CDA) formulations are our creation to achieve this turn around to win the war on cancer.

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Introduction

Cytotoxic cancer therapy was a tragic byproduct of world war II. During the war, toxic sulfur mustard gas bombs were used. Victims of toxic gas all displayed depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Indeed, toxic chemicals were very effective to eliminate leukemia cells to relief the symptom. Elimination of cancer cells by toxic agents thus became a standard care of cancer, and the disappearance of tumor became a standard diagnosis on the success of cancer therapy. Both were incorrect which violated the concept of cancer evolving due to wound unhealing introduced by Virchow in 1858 [1]. Virchow was a very respected pioneer on cancer from German. His concept of cancer evolving due to wound unhealing may be too ancient to remain in the memory of oncologists after World War II to influence their decision on cancer therapy. Cytotoxic agents were the major drugs employed during the War on Cancer declared by President Nixon in 1971-1976, which was not successful to reduce cancer mortality [2]. If the drugs have been drilled through as a Presidential Project to receive unlimited national support and failed to achieve cancer therapy, it was fair to conclude that these drugs were not good for cancer therapy and should be removed right away. It was inexcusable that the cancer establishments kept using the failed drugs to treat cancer patients to result in ever-escalation of cancer mortality to reach 10 million annually world-wide [3]. Virchow's advice may be too ancient to remain in the memory of recent people. Virchow's concept on cancer was brought up again recently by Dvorak in the very privileged N Engl J Med in 1986 [4]. Again, it was ignored by the cancer establishments. Apparently, cancer establishments preferred to take up the position in opposition to Virchow and Dvorak. Creation of wounds and perfection of wound healing are mutually antagonistic. Only one of these two is the correct approach of cancer therapy.

Cancer stem cells (CSCs) became known in 1997 [5]. The discovery of CSCs unraveled CSCs as the cells to initiate tumor growth, and the cells to cause most fatal effects of cancer [6-10]. Fatal effects of cancer such as metastasis, drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence are all attributable to CSCs. Therefore, CSCs are the most critical battle field to decide the outcome of cancer therapy [11-13]. Our studies of abnormal methylation enzymes (MEs) [14-16], chemo-surveillance [17-19], wound healing [20-23] and CDA formulations [3, 24-28] are closely related to the issue of CSCs, thus, we are in a unique position to offer solution of CSCs to save cancer patients [3, 29-34].

Creation of Wounds is Incorrect for Cancer Therapies and Discussions

Creation of Wounds is Incorrect for Cancer Therapies

Creation of wounds is the commanding principle adopted by the cancer establishments to direct cancer therapies, which has failed to win the war on cancer as a presidential project during 1971-1976 [2]. They knew cytotoxic agents were unable to solve cancer and started to search for the replacements. Their first choice was gene therapy during 1976-1996. It was a legitimate

approach because chromosomal abnormalities were a pivotal cause to promote the perpetual proliferation of CCs, the most outstanding symptom of cancer. They wasted 20 years to learn the difficulty of gene therapy. They gave up without producing a gene therapeutic agent. Anti-angiogenesis attempt was their second choice during 1996-2016, which was also a legitimate approach because tumor relied on angiogenesis to thrive. The development of anti-angiogenesis therapy was a failure because successful termination of angiogenesis ended up causing the death of patients due to internal bleeding. This echoes the failure of cytotoxic chemotherapy to cause the death of patients due to adverse effects of toxic therapy or recurrence. Radiotherapy of nasopharyngeal carcinoma was instant to achieve complete remission. But the patients often succumbed to stroke within a short time. The successful elimination of tumor by cytotoxic agents also results in the death of patients due to adverse effects or recurrence within a short time. Adverse effects, ineffectiveness against CSCs and the contribution to the damage of chemo-surveillance are the reasons to fail cancer therapy by the cytotoxic approach. Immunotherapy was their third choice during 2016-2036. It has the merit of targeting programmed death antigen which was a remarkable achievement of immunologists to eliminate pathological cells marked with programmed death antigen. This remarkable scientific achievement is awarded with Novel prize this year. Immunotherapy is a better version of cytotoxic therapy to spare adverse effects on normal stem cells. But immunotherapy has the same problems of cytotoxic therapy to show ineffectiveness against CSCs and to contribute to the destruction of chemo-surveillance which are the two main reasons to cause the failure of cytotoxic therapy. Toxic agents cannot affect CSCs because these cells are protected by drug resistance and anti-apoptosis mechanisms [6-10]. These cells express aldehyde dehydrogenase and MGMT, an DNA repair enzyme, to effectively detoxify toxic chemicals and to repair DNA damages. CSCs are very much like progenitor stem cells (PSCs) to tolerate immuno-surveillance. Immunotherapy tends to trigger the production of cytokines which are very damaging to chemo-surveillance, particularly tumor necrosis factor (TNF) [17]. Immunotherapy may be a better way to kill CCs, but it is not likely to reduce cancer mortality. Cancer mortalities during the past few years in the USA are still in a trend of escalation at a rate of 0.1 to 0.3% annually according to the statistics reported by American Cancer Society [35]. It appears that immunotherapy now in development is also not promising to put cancer away. It can be concluded that creation of wounds is incorrect to direct cancer therapies.

It is necessary to establish a valid concept of cancer to confront cancer successfully [36]. Cancer evolving due to wound unhealing was a valid concept introduced by the great Germany pathologist Virchow in 1858 [1], which was brought up again by Dvorak in 1986 [4]. Both Virchow and Dvorak were extremely talented to comprehend the logic of wound healing to cancer at a time neither cancer nor wound healing were completely known. We unknowingly pursued cancer therapy following the guidance of Virchow's concept of cancer evolving due to wound unhealing by the discoveries of abnormal methylation enzymes (MEs) [14-16], chemo-surveillance [17-19] and the mechanism of wound healing [20-23]. Our studies strongly supported the validity of the concept of cancer introduced by Virchow. Therefore, we were also extremely talented to decode the logic of wound healing to cancer. The solution of cancer is a contest between the perfection of wound healing promoted by Virchow, Dvorak and Liau et al. and the creation of wounds promoted by cancer establishments. Creation of wounds dominated the cancer therapies in the past, but did not have a winning record to turn around cancer fatality from escalation to deceleration. Cancer therapy based on the promotion of wound healing can be very successful. All trans-retinoic acid (ATRA), a differentiation inducer (DI) capable of eliminating telomerase from abnormal methylation enzymes (MEs) [16], is the standard care of acute promyelocytic leukemia [37], and gleebec, a differentiation helper inducer (DHI) which is an inhibitor of tyrosine kinase to affect MEs capable of greatly potentiating the activity of DI, is the standard care of chronic myeloid leukemia [38]. The therapeutic efficacies of these two drugs are excellent to be qualified as the standard care of particular cancer. Antineoplastons were wound healing metabolites purified from urine initiated by Burzynski during 1976-1990 to also produce excellent cancer therapy [39, 40]. Unfortunately, Antineoplastons were blocked by the cancer establishments because they were not cytotoxic to induce tumor shrinkage. We were convinced that Antineoplastons were excellent cancer drugs to target abnormal MEs we discovered before joining Burzynski [14-16], thus we went to China in 1993 to develop CDA-2, which was also a preparation of wound healing metabolites purified from urine [24]. We used XAD-16-ethanol as the reverse phase chromatographic purification system instead of C18-80% methanol of Burzynski' privileged method. Chemical compositions of CDA-2 and Antineoplaston A5 are not exactly the same [24, 25], but both have comparable activity to induce terminal differentiation of HL-60 cells. CDA-2 has been approved by the Chinese FDA for cancer therapy as an adjuvant agent to supplement cytotoxic therapy [41], and as a mono-therapeutic agent for the therapy of myelodysplastic syndromes (MDSs) [42]. MDSs are diseases attributable entirely to CSCs [43]. Drugs effective against CSCs are extremely valuable. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [11-13]. Of course, cancer establishments knew the value of the drugs effective against CSCs. Approximately 18 years ago, the pharmaceutical giant GSK put up an outrageous 1.4 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University. They made a big noise on the possibility to solve CSCs, the most important issue of cancer. It was very strange that there was no follow-up, not even the mention of the failure of clinical trial as if it has never happened. It failed, because killing of CSCs was not an option to solve CSCs. Induction of terminal differentiation, the critical mechanism of wound healing, was the only option to deal with CSCs as the therapy of MDSs demonstrated [42]. Antineoplastons and CDA-2 are obviously the best drugs for the solution of CSCs. Cancer establishments put up a rule of tumor shrinkage to deny these excellent cancer drugs [44]. The same rule also blocks their mission to win the war on cancer as these excellent cancer drugs are the only option to solve CSCs. Therefore, cancer establishments are the culprits to damage the reputation of health profession as a profession unable to achieve a presidential project [2], and to hurt cancer patients to result in cancer mortality to reach 10 million annually around the world with an annual increment of 5% according to the cancer statistics of National Cancer Institute and 0.61 million annual mortality with an annual increment of 0.2% in the USA according to the statistics of American Cancer Society [35]. The ever-escalation of cancer mortality is a verdict of the failure of cancer therapies based on the creation of wounds.

The Logic of Wound Healing to Cancer

The concept of cancer evolving due to wound unhealing was introduced by Virchow in 1858 [1], which was supported by Dvorak [4]. The close relationship of wound healing to cancer was also noticed by MacCarthy-Morrough and Martin [45]. Our studies of carcinogenesis [46, 47], abnormal MEs (14-16) and chemo-surveillance (17-19) strongly supported the validity of cancer

evolving due to wound unhealing. We were the first to notice that MEs were abnormal in cancer cells [14]. The abnormality of MEs was due to the association of a tumor factor to change the kinetic properties and the regulation of MEs. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [48]. MEs play a pivotal role on the regulation of cell growth and differentiation. Because of this important role, MEs are subjected to exceptional allosteric regulation [49]. Km values of abnormal MEs increase 7-fold and the regulation of growth is greatly tilted in favor of growth. The increased Km values suggest that cells with abnormal MEs have greater pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are necessary to promote the exceptional growth of cells with abnormal MEs as the study of Chiva el al. showed when HL-60 cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly [50]. Exceptional growth promoted by abnormal MEs is needed for the development of the fetus as the interruption of abnormal MEs by thalidomide results in the malformation of the body parts, noticeably limbs. Maternal wound healing metabolites if getting into fetal circulation may also affect fetal development. Placenta must play a role to limit the entry of maternal wound healing metabolites into fetal circulation. The nature has its way to organize delicate regulations. The nature also creates contact inhibition, ten-eleven translocator-1 (TET-1) enzyme and chemo-surveillance to guard the operation of cells with abnormal MEs safely. When such safety mechanisms become dysfunctional, the growth of cells with abnormal MES may become problematic to display clinical symptoms. Abnormal MEs are commonly associated with all human cancers [15]. Later, we identified the tumor factor as the catalytic subunit of telomerase [16]. So, MEs of telomerase expressing cells are all abnormal. Telomerase is recognized as an oncogenic protein. The association with MEs promote malignant growth is an important factor for the characterization of telomerase as an oncogenic protein. Apparently, the seed of cancer is sown at the very beginning of life, namely the fertilization of the egg with a sperm to activate the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. Abnormal MEs carry out normal functions to develop fetus. Wound healing involving PSCs is an extension of embryonic activity, which is also an act of normal function by abnormal MEs. Functions of abnormal MEs in CSCs and CCs are abnormal because of the collapse of safety mechanisms to safe guard the operation of abnormal MEs. The discovery of abnormal MEs is a very important contribution to cancer to reveal a very important cause of cancer responsible for the perpetual proliferation of CCs. Cancer is basically a problem of growth regulation going awry. Abnormal MEs is an important factor to mesh up growth regulation. Abnormal oncogenes and suppressor genes are also an important factor to mesh up growth regulation which receive a great deal of attention including Nobel prizes. The attention on oncogene and suppressor genes did not produce any benefit to help cancer patients. Cancer establishments wasted 20 years from 1976 to 1996 to learn the difficulty of gene therapy. Actually, gene therapy is not feasible. One chromosomal abnormality may be solved, there may soon pop another chromosomal abnormality to negate the previous effort. A better way to solve chromosomal abnormality is to solve abnormal MEs which is much easier to achieve. Afterall, oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cells are in cell cycle replicating. But if replicating cells exit cell cycle to undergo terminal differentiation through destabilization of abnormal MEs, these genes have no roles to play. So, the solution of abnormal MEs can also put to rest the issue of chromosomal abnormalities. Killing of CCs can also put to rest the issues of abnormal MEs and chromosomal abnormalities. That has been tried, but failed, because killing of CCs can only solve part of cancer problem. CSCs are very tough to be killed. They can be killed with monoclonal antibodies, but killing is not an option to solve the issue of CSCs. Destabilization of abnormal MEs is the only option to achieve cancer therapy. The discovery of abnormal MEs also make a great contribution to support the validity of cancer evolving due to wound unhealing.

Wound healing requires the proliferation and the terminal differentiation (TD) of PSCs. Wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol through phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [51, 52]. Although AA and PGs are active DIs [27, 28], the induction of TD of PSCs at the initial stage of wound is not the primary objective of PGs. Rather the localized inflammation caused by PGs [51] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound resulting in edema response which is the primary objective of PGs to orchestrate the healing process. Chemo-surveillance mediated through DIs and DHIs normally functions as a brake to prevent the buildup of cells with abnormal MEs such as PSCs. The brake provided by DIs and DHIs must be released for PSCs to proliferate to produce enough cells to heal the wound. PGs are metabolically unstable [51]. Their biological effects are most likely brief and confined to the wound area. Thus, the promotion of the proliferation of PSCs is the primary objective of PGs on wound healing, whereas the induction of TD of PSCs at the final stage of wound healing is accomplished by chemo-surveillance. The stable end products of PGs may participate in the final stage of wound healing, which are also active as DIs, although not as active as PGs [28]. Wound healing is an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance to achieve perfection of wound healing, chemo-surveillance to heal the wounds created by chemical and physical means, and immuno-surveillance to heal the wounds created by infectious agents. Thus, chemo-surveillance and immuno-surveillance can act synergistically on wound healing to prevent disastrous consequences of wound unhealing.

The immunological response triggered by wound is not good for wound healing. Immunological response tends to trigger the production of cytokines, which are toxic proteins to assist immunotherapy. But these toxic proteins create wounds to aggravate wound healing. TNF among such cytokines is particularly bad for wound healing. It kills stem cells to create wound. It also causes hyperpermeability of blood vessel to result in the collapse of chemo-surveillance [54, 55]. TNF is also named cachectin after its notorious effect to cause cachexia symptoms. It is blamed to cause myelodysplastic syndromes (MDSs) [56, 57]. TNF has been reported as an oncogenic protein [58]. It appears that immuno-surveillance can also act antagonistically to chemo-surveillance. It is the balance of biological response and immunological response to dictate the outcome of wound healing. If biological response prevails, wound is healed. If immunological response prevails, wound cannot be healed to display clinical symptoms such as tissue fibrosis, organ failure, dementia, neurological disorders and cancer [22, 23, 59]. The clinical symptoms due to wound unhealing may also include cardiovascular diseases [60]. Aberrant DNA methylation is implicated in atherosclerosis, heart failure and cardiac arrhythmias. Vital reds is a food supplement produced by

the famed cardiologist Steven Gundry, which contains primarily polyphenols as the major ingredients. The efficacy of vital reds to clear blocked blood vessel may be attributable to wound healing targeting on abnormal methylation enzymes of unhealed wound just the same as the wound healing metabolites displaying activity as DHIs. Polyphenols are excellent inhibitors of signal transduction (STI) to function as DHIs [26, 38]. It appears that perfection of wound healing can eliminate two giant killers of humans, cancer and cardiovascular diseases [34].

Wound unhealing in most instance is due to the collapse of chemo-surveillance. Chemo-surveillance was a terminology we created to describe an 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 [17]. Peptides share physical-chemical properties similar to DIs and DHIs. As a matter of fact, acidic peptides are the major DIs of Antineoplastons [61, 62]. Therefore, peptides can be used as surrogate molecules to represent DIs and DHIs in the plasma and urine. Quantitative analyses of plasma and urinary peptides of 108 cancer patients showed that chemo-surveillance was selectively destroyed in cancer patients as shown in Table 1, which is reproduced from the reference 17. As above described, the decline of CDA level is necessary for the promotion of the proliferation of PSCs. If wound healing proceeds perfectly, CDA level is likely to return to the normal level of 5.0. But if the CDA level is damaged by pathological assaults producing TNF to affect terminal differentiation of PSCs, the symptom of tissue fibrosis such as the white lung of COVID-19 infection, or liver cirrhosis of hepatitis, or hypertension of cardiovascular diseases will show up. CDA level is always operating at the maximum capacity. Once it is damaged, it takes a long time to restore. The nature responds to the inability of terminal differentiation of PSCs to heal wound by forcing PSCs to proliferate. The proliferation of PSCs is limited by contact inhibition. So, PSCs are forced to evolve into CSCs to escape contact inhibition. It takes a single hit to silence TET-1 to turn PSCs into CSCs. So, CSCs are PSCs minus TET-1. The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. CSCs are considered normal cells like PSCs to not respond to immunotherapy. The problem of wound unhealing is the collapse of chemo-surveillance, so the proliferation of CSCs is not helpful to heal the wound. The pressure is then building up to force the proliferation of CSCs by the activation of oncogenes or the inactivation of suppressor genes through chromosomal abnormalities. This is the valid concept of cancer evolution promoted by the alliance of Virchow, Dvorak and Liau et al [36].

Table 1: Chemo-Surveillance Selectively Destroyed in Cancer Patients

Plasma/Urine Peptide Ratios	CDA Levels	Number of Patients	% 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 (Unresponsiive)	0.37	19	17.6

Plasma peptides : nmoles/ml ; Urine peptides : nmoles/mg creatinine

During our studies of hepatocarcinogenesis, we noticed the appearance of numerous tiny hyperplastic nodules soon after the application of carcinogens, which displayed abnormal MEs [46]. These tiny hyperplastic nodules must represent the proliferation of PSCs in the process of wound healing. Most of these tiny hyperplastic nodules disappeared soon afterward, indicating the completion of wound healing. Only a few large size carcinomas appeared later from tiny hyperplastic nodules which did not heal. If the animals were given Antineoplaston A10 after the application of hepatocarcinogen aflatoxin B1, the appearance of carcinomas could be effectively prevented as shown in Figure 1, which is reproduced from the reference [47]. Therefore, if wound healing proceeds perfectly, cancer can be prevented. Cancer evolving due to wound unhealing is a valid concept.

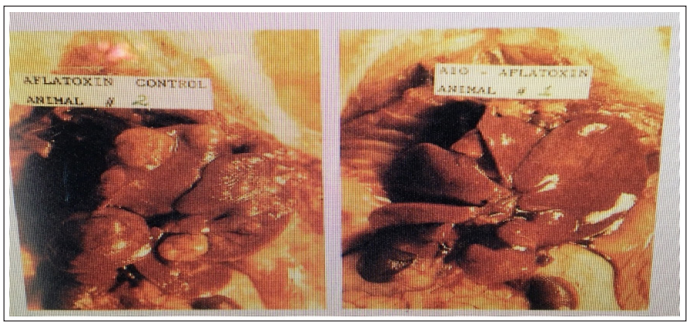

Figure 1: Effective Chemoprevention of Hepatocarcinogenesis by Antineoplaston A10

CDA Formulations as the Best Drugs to Solve CSCs

MDSs are a classic case of diseases to illustrate the evolution of cancer due to wound unhealing. The oncogenic protein TNF plays an important role to cause MDSs [54-58]. It is responsible for the collapse of chemo-surveillance [54, 55], the critical mechanism to lead to wound unhealing. It causes the apoptosis of bone marrow stem cells to trigger the proliferation of PSCs to repair the wound it created. The inability of wound healing due to the collapse of chemo-surveillance forces PSCs to evolve into CSCs to escape contact inhibition. The propagation of pathological cells of MDSs have been identified as CSCs [43]. So, MDSs are a perfect model of cancer evolving due to wound unhealing. CSCs are critically linked to wound unhealing. Induction of terminal differentiation, a critical mechanism of wound healing [20], is the only option to solve the issue of CSCs. Thus, drugs effective to inactivate MEs to accomplish terminal differentiation of CSCs are the only drugs effective for the therapy of MDSs. Vidaza and Decitabine which inactivate MEs by covalent bond formation between methyltransferase and 5-azacytosine incorporated into DNA [61] are the choice of cancer establishments. CDA-2 which destabilizes abnormal MEs by targeting on the telomerase of abnormal MEs [16] is our choice. Professor Jun Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of these three drugs for the approval by the Chinese FDA. According to his assessments, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation and a markedly better therapeutic efficacy based on hematological improvement evaluation, namely becoming independent on blood transfusion to stay alive, as shown in the Figure 2, which is reproduced from the reference [42]. Obviously, CDA-2 is a better drug for the therapy of MDSs, displaying a superior therapeutic efficacy and without adverse effects. Vidaza and Decitabine may be effective, but they are proven carcinogens [64, 65] and very toxic to DNA [66-68]. These adverse effects may cut down the life span of the patients. We are the clear winner

of the contest to eradicate CSCs. But our winner's status was denied by the cancer establishments, because CDA-2 was unable to make tumor to disappear. Vidaza and Decitabine also cannot make tumor to disappear. They approved these two cancer drugs. They had no reasons to reject CDA-2. Yes, they had a good reason to reject CDA-2 because the chemical compositions of CDA-2 were not clear. We knew the active DIs and DHIs of CDA-2, we could make CDA formulations patterned after the active ingredients of CDA-2 [24-29, 61, 62, 69, 70]. Still, CDA formulations are not allowed because of the ideological conflict.

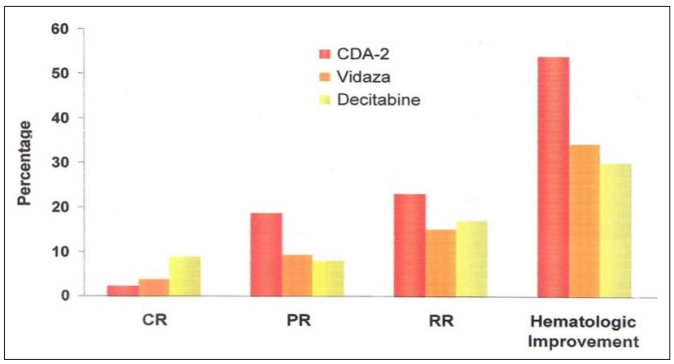

Figure 2: CDA-2 as the Best Drug for the Therapy of MDSs

Creation of Wounds is Incorrect for Cancer therapy Because It Cannot Eliminate CSCs, the Root of Cancer Problems

Creation of wounds to kill CCs and the perfection of wound healing to promote terminal differentiation of CSCs and CCs are two approaches of cancer therapies. Creation of wounds was favored by the cancer establishments and the perfection of wound healing was the choice of Virchow, Dvorak and Liau el al. A comparison of these two approaches on important parameters of cancer such as CSCs, CCs, unipotent stem cells (USCs), chemo-surveillance, immuno-surveillance, tumor shrinkage and life-long survival is presented in Table 2.

Table 2: A Comparison of Creation of Wounds and Perfection of Wound Healing on Important Cancer Parameters

Cancer Therapies	CSCs	CCs	USCs	Chemo-surveillance	Immuno-surveillance	Tumor Shrinkage	Life-long Survival
Creation of Wounds : Chemo	-	A	+	-	-	+	+ Early - Late
Radio	-	A	+	-	-	+	+ Early - Late
Immuno	-	A	-	-	+	+	+ Early - Late
Perfection of Wounds Healing : CDA	+	B	-	+	0	-	+
Vidaza & Decitabine	+	B	+	-	-	-	-
Targeted	-	B	-	+	0	-	+

Effects on CSCs: - means cannot induce terminal differentiation of CSCs, and + means can induce terminal differentiation of CSCs; effects on CCs: A means killing of CCs, and B means induction of terminal differentiation; effect on USCs: + means can cause damage, and - means does not have effects; effects on chemo-surveillance: - means damaging effect, and + means improving effect; effects on immuno-surveillance: - means damaging effect, + means improving effect, and 0 means no effect; effects on tumor shrinkage: + means can cause tumor to shrink, and – means cannot cause tumor to shrink; effects on life-long survival: + means can result in life-long survival.

That means the death of the patient is not related to previous cancer or its treatments, - means patient is likely to die from cancer or its treatments. + Early means early stage patients can obtain life-long survivor from the treatments, and - Late means patients are likely to die from cancer or its treatments.

The solution of CSCs is critical to the success of cancer therapy [11-13,33]. The induction of terminal differentiation is the only option to solve CSCs. CDA formulation, Vidaza and Decitabine are the only drugs able to achieve this goal. Vidaza and Decitabine are carcinogens [64, 65], and very toxic to DNA [66-68] that may cut down the life-long survival of patients receiving therapy with Vidaza and Decitabine. DNA modifying chemicals are very dangerous. These chemicals happen to be the most effective chemicals to kill CCs and to eliminate tumor. Cancer establishments became addicted to these dangerous chemicals. These chemicals eliminated tumor the cancer establishments like, but these chemicals are also responsible for the death of advanced cancer patients the cancer establishments did not want to admit [71]. Killing of CSCs is not an option to solve the issue of CSCs. That means CDA formulations are the only drugs to achieve cancer therapy for life-long survival. Gene therapy and targeted therapy are the same approach of cancer therapy. Gene therapy is to correct the chromosomal abnormalities to activate

oncogenes or to inactivate suppressor genes. Targeted therapies are to target on the oncogene products. Since cancer establishments have abandoned gene therapy because of the difficulty, we do not want to include gene therapy in the discussion.

Proliferation of CCs is the most out standing feature of cancer. CCs constitute the majority mass of tumor. The evolution of CCs is caused by wound unhealing, but is not critically linked to wound unhealing as CSCs. So, CCs can be eliminated by induction of terminal differentiation or cell killing. Cell killing can result in the shrinkage of tumor that is the requirement of cancer establishments. Terminal differentiation can stop the proliferation of CCs, but cannot cause the tumor to shrink. Terminal differentiation is the critical mechanism of wound healing. It is the only option to solve CSCs which are critically linked to wound unhealing. Since CCs are not critically linked to wound unhealing, killing is also an option. But killing of CCs creates wounds to promote the proliferation of CSCs to heal the wound [72]. The loss of CCs and the increase of CSCs will increase the percentage of CSCs in the tumor. The percentage of CSCs in astrocytoma is less than 1%, which is responsive to cytotoxic chemotherapy, whereas the percentage of CSCs in glioblastoma is greater than 3%, which is unresponsive to cytotoxic chemotherapy [73], so that if CSCs arise to greater than 3% of the tumor mass, that tumor becomes unresponsive to cytotoxic therapies. Ineffectiveness of cytotoxic therapy on CSCs and the contribution to the damage to chemo-surveillance are the reasons cytotoxic chemotherapy failed to win the war on cancer [2]. Chemotherapy, radiotherapy and immunotherapy all have the same problem of ineffectiveness against CSCs and the contribution to damage chemo-surveillance to fail cancer therapy. These therapies can only benefit early stage cancer patients whose chemo-surveillance have not yet fatally damaged, relying on the restoration of chemo-surveillance to subdue surviving CSCs which are not responsive to cytotoxic therapies. The success of cytotoxic cancer therapies heavily relies on the restoration of chemo-surveillance. Therefore, cancer therapies based on creation of wounds can only benefit early stage cancer patients that include CDA levels above 2.5, cancer stage I & II without evidence of metastasis, Gleason score of less than 7 and CSCs count less than 1%. Cancer patients when first diagnosed are often beyond the early stage to benefit from cytotoxic cancer therapies. The cancer of King Chares of England is the metastatic cancer. The prostate cancer of President Biden was in late stage with Gleason score of 9 and bone metastasis when first diagnosed. So, many cancer patients when first diagnosed with cancer are beyond the help of cytotoxic cancer therapies. Cancer therapies damaging to USCs should be removed because the damages to USCs are always greater than the benefits. On the basis of reducing damages, immunotherapy should be accepted to replace chemotherapy and radiotherapy, although immunotherapy is also not a perfect therapy. The perfect cancer therapy is obviously CDA formulations. Inability to cause the shrinkage of tumor is a drawback of CDA formulations. Tumor shrinkage is a bad judgement [44]. We have to develop a more valid diagnosis to evaluate cancer therapy.

In final analysis, perfection of wound healing to eradicate CSCs is an absolute requirement to achieve cancer therapy to result in life-long survival. Elimination of CCs is also essential for cancer therapy. The elimination is not necessarily the killing of CCs. Induction of terminal differentiation can also achieve the goal of stopping perpetual proliferation of CCs. Elimination of residual tumor by surgery is an option to remove residual tumor mass of CDA therapy. Combination therapy with immunotherapy is another option to eliminate residual tumor mass.

Conclusion

Creation of wound is incorrect for cancer therapy to result in ever-escalation of cancer mortality. The incorrect approach damages the reputation of health profession as a profession unable to achieve a presidential project and to hurt cancer patients resulting in the ever- escalation cancer mortality to reach 10 million annually worldwide. Cancer evolves due to wound unhealing. Therefore, perfection of wound healing is the correct approach of cancer therapy. Wound healing requires CDA formulations to promote terminal differentiation of PSCs and CSCs which are cells expressing abnormal MEs. Induction of terminal differentiation of CSCs and CCs is the correct approach of cancer therapy.

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Conflicts of Interest

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