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Healing the Unhealed Wounds as the Top Priority to Save Cancer Patients

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ABSTRACT

The objective of this article is to rectify the inadequate cancer therapies focusing on the killing of cancer cells (CCs). Cancer is evolved due to wound unhealing because of the collapse of chemo-surveillance. Healing the unhealed wound should be the most appropriate strategy of cancer therapy. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs). Chemo-surveillance is the nature's creation of allosteric regulation to ensure perfection of wound healing. The collapse of chemo-surveillance caused by pathological assaults including carcinogens results in wound unhealing that forces PSCs to proliferate. The proliferation of PSCs is limited by contact inhibition. PSCs are then forced to evolve into cancer stem cells to escape contact inhibition. It takes a single hit to silence ten-eleven translocator-1 enzyme (TET-1) to convert PSCs to become cancer stem cells (CSCs), which is a task easily accomplished by PSCs equipped with abnormally active methylation enzymes (MEs). The proliferation of CSCs is still unable to heal the wound, because the problem is the collapse of chemo-surveillance unable to achieve terminal differentiation of PSCs, not the deficiency of PSCs. So, chromosomal abnormalities set in such as translocations to activate oncogenes or deletions to inactivate suppressor genes eventually forcing CSCs to become full blown cancer cells (CCs) with much faster replication capability than CSCs.

Since cancer is caused by wound unhealing. The process of wound healing is most appropriate to solve cancer. Induction of terminal differentiation of PSCs is a critical mechanism of wound healing, which is accomplished by the destabilization of abnormal MEs. MEs in cells expressing telomerase are abnormal, because MEs tend to associate with telomerase to turn these enzymes abnormal in favor of cell growth that is the most critical issue of cancer. The solution of abnormal MEs is very critical to the success of cancer therapy. When abnormal MEs is solved, replicating cells with abnormal MEs will be induced to undergo terminal differentiation. By completion of terminal differentiation, chromosomal abnormalities important for speeding up cell replication can also be put to rest. Oncogenes and suppressor genes are cell cycle regulatory genes, which have important roles to play when cells are in cell cycle replicating, but when cells exit cell cycle to undergo terminal differentiation they have no roles to play. CSCs are critically linked to wound unhealing. Destabilization of abnormal MEs is the only option to solve the issue of CSCs. It can also solve the issue of CCs by turning these cells into terminally differentiated cells unable to replicate, but it cannot make the tumor to go away. The tumor residue is harmless. If it is annoying, it can be safely removed by surgery.

Keywords

Abnormal methylation enzymes, Cancer stem cells, Cell differentiation agent, Chemo-surveillance, Differentiation inducers, Differentiation helper inducers, Progenitor stem cells, Wound healing.

Introduction

Perpetual proliferation of CCs is the most outstanding feature of cancer. Elimination of CCs naturally became a top choice of cancer therapy. Cancer therapy had a bad start to rely on toxic chemicals to kill CCs, which was a mistake committed when we did not have complete knowledge of cancer. The mistake was excusable. Cytotoxic chemotherapy was a tragic byproduct

of World War II. During the war, toxic 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. Cytotoxic chemotherapy thus became the standard care of cancer, and the disappearance of CCs in hematological cancers or the disappearance of tumor in solid cancers became the standard criteria for the evaluation of the success of cancer therapy. When President Nixon declared war on cancer as a presidential project during 1971-1976, cytotoxic chemotherapy and radiotherapy were the major treatment modalities employed to combat cancer, which were not successful [1]. When treatment modalities were drilled through as a presidential project that received unlimited support from national resources and failed, it was fair to conclude that the treatment modalities were inadequate which should be dismissed. Cancer establishments knew chemotherapy and radiotherapy were unable to solve cancer and started to search alternatives such as gene therapy during 1976-1996, anti-angiogenesis therapy during 1996-2016, and immunotherapy from 2016 onward presumably up to 2036 [2]. They did not find alternatives that could kill cancer cells better than chemotherapy and radiotherapy, and kept using failed drugs to result in escalating cancer mortalities that was inexcusable. CSCs became a known issue in 1997 [3]. CSCs are the origin of cancer evolved from PSCs. CSCs are protected by drug resistance and anti-apoptosis mechanisms, thus unresponsive to cytotoxic therapies [4-7]. Ineffectiveness against CSCs and the contribution to damage chemo-surveillance were the reasons cytotoxic therapies failed to win the war on cancer. The latest cancer statistics showed 0.61 million mortality in the USA with an annual increment of 0.2%, and 10 million mortality around the world with an annual increment of 5% [8]. Cytotoxic agents may be able to save a small minority of cancer patients in the early stage whose chemo-surveillance have not yet fatally damaged, relying on the recovery of chemo-surveillance to subdue surviving CSCs. These drugs cause the deaths of a majority of cancer patients in advanced stage whose chemo-surveillance have been fatally damaged [9-14]. Apparently solving CSCs is very critical to the success of cancer therapy [15]. Of course, cancer establishments knew the importance of CSCs. The pharmaceutical giant GSK put up 1.4 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University about 17 years ago, which did not materialize because killing of CSCs was not an option to solve the issue of CSCs. Cell differentiation agent (CDA) formulations were the drugs best for the solution of CSCs which are critically linked to wound unhealing. However, clinical developments of CDA formulations were blocked by cancer establishments because these drugs violated the commanding principle of cell killing they put up [16]. The unfortunate reality is cancer establishments are unable to solve cancer to turn around cancer mortality from increasing to decreasing. However, they are very powerful to block CDA formulations that can put cancer away to reduce cancer mortality. We call for surgeons, oncologists and cancer patients to unite to push for the approval of CDA formulations to save advanced cancer patients [13,16-18].

Commentaries and Discussion

On the Fundamental Basis of Cancer Evolution

To effectively solve cancer, we must understand how the problem of cancer evolves. Cancer is caused by multiple factors: pathological assaults to cause damages to chemo-surveillance and immuno-surveillance resulting in wounds unhealing; evolution of CSCs from PSCs due to wound unhealing; and progression of CSCs to faster growing CCs through chromosomal abnormalities to activate oncogenes or to inactivate oncogenes. Thus, the collapse of chemo-surveillance, the evolution of CSCs and the progression of CSCs to become full-blown CCs all play important roles on the development of cancer. A perfect solution of cancer must be able to deal all these contributing factors [19]. Cytotoxic therapies focusing on the killing of CCs is insufficient to solve cancer, resulting in ever-increasing cancer mortality.

The concept of cancer evolving from wound unhealing was first introduced by the great German pathologist Virchow in the 19th century [20]. It was again brought up by Dvorak in 1986 [21]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [22]. We provided the most important details on this subject that included abnormal MEs to promote perpetual proliferation of CCs and CSCs by blocking differentiation [23-25]; chemo-surveillance as the nature's creation of allosteric regulation on abnormal MEs for the perfection of wound healing to avoid disastrous consequences of wound unhealing, cancer being the worst consequence [26-29]; DIs and DHIs as wound healing metabolites and as active players of chemo-surveillance [26-29]; hypomethylation of nucleic acids as a critical mechanism of terminal differentiation [30]; mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [31-34]; and the evolution of CSCs from PSCs through a single hit to silence TET-1 enzyme [35]. These studies very convincingly establish that cancer evolves due to wound unhealing because of the collapse of chemo-surveillance. Our carcinogenesis studies also confirmed the validity of this concept. When animals were challenged with hepatocarcinogens, we noticed the appearance of numerous tiny hyperplastic nodules displaying abnormal MEs, which must represent proliferation of PSCs in the process of healing wounds created by hepatocarcinogens. Most of these tiny hyperplastic nodules disappeared shortly, indicating the completion of wound healing. Only a few large size carcinomas appeared later from a few hyperplastic nodules which did not healed [36]. If Antineoplaston A10, which is phenylacetylglutamine, was provided during the challenge with potent hepatocarcinogen aflatoxin B1, the appearance of carcinoma could be effectively prevented as shown in Figure 1, which is reproduced from the reference [37]. It is remarkable that biologically inactive Antineoplaston A10 can effectively prevent carcinogenesis induced by a potent carcinogen. Antineoplaston A10 is effective to protect the functionality of chemo-surveillance [26] through antagonization of tumor necrosis factor (TNF) to prevent urinary excretion of wound healing metabolites. Carcinogen tends to create wound to trigger immunological response, resulting in the production of TNF to lead to cachexia symptoms. TNF is also named cachectin after its effect to cause cachexia symptoms. A

manifestation of cachexia symptoms is the excessive urinary excretion of low molecular weight metabolites due to blood vessel hyperpermeability caused by TNF [38,39]. Wound healing metabolites are among low molecular weight metabolites lost. Chemo-surveillance is indeed a very important mechanism created by the nature to benefit humans. But the cancer establishments do not recognize this important mechanism of wound healing, because it violates the commanding principle of cell killing they put up to combat cancer. Cancer therapy is basically a battle between the cancer establishments who insist on killing of CCs to reduce tumor mass and the creator of the nature to protect chemo-surveillance for the perfection of wound healing. Cancer establishments are not winning the battle, but they are very powerful to block the creator of the nature to put cancer away.

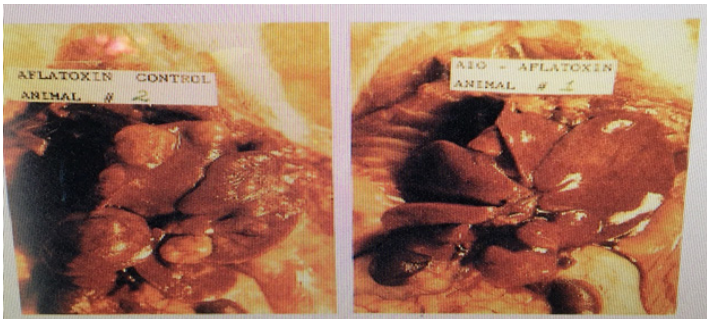

Figure 1: Prevention of hepatocarcinogenesis by the protection of chemo-surveillance.

Close Relationship between Wound Healing and Cancer

Wound healing and cancer are closely related to involve PSCs as the common elements [22, 31]. Wound healing requires the proliferation and the terminal differentiation of PSCs. PSCs are the most primitive stem cells to initiate the development of organs and tissues during embryonic stage of fetal development. A fraction of these cells, usually less than 2% of the mass, is preserved in the organs and tissues for future expansion or repair. PSCs are pluripotent stem cells capable of differentiation into various component cells of the organ or tissue. These cells are protected by drug resistance and anti-apoptosis mechanisms, and express chemokine receptors to respond swiftly to signals for expansion or repair. MEs of PSCs are abnormal due to association with telomerase like most cancer cells [25], which are the most critical issue of cancer [40]. It appears that the seed of cancer is sawed at the very beginning of life, namely the fertilization of the egg with a sperm to activate 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 functions important for the development of fetus, as premature interruption of abnormal MEs with thalidomide results in the malformation of limbs. Abnormal MEs are not a problem to normal stem cells expressing telomerase, because there are safety mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to prevent pathological buildup of cells with abnormal MEs. When such safety mechanisms become dysfunctional, then clinical symptoms arise.

Wound triggers biological and immunological responses. 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 [41,42]. Although AA and PGs are active DIs [43,44], 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 [45] 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 that 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 PSCs. This brake must be released in order for PSCs to produce enough cells for the repair of the wound. PGs are metabolically unstable [41]. 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 terminal differentiation of PSCs at the final stage of wound healing is accomplished by wound healing metabolites of chemo-surveillance. The stable end products of PGs, dicycloPGs, may then participate in the final stage of wound healing. DicycloPGs as DI are not as active as PGs. But their activity can be greatly boosted by DHIs. Pregnenolone is a good DHI to boost the activity of AA and dicycloPGs [44].

The biological response triggered by the wound is in general good for wound healing. But the immunological response triggered by the wound is bad for wound healing. Immunological response prompts the patient to produce cytokines to mediate immunological therapeutic effects. TNF among cytokines produced is particularly bad for wound healing as above described. It is the balance of biological response and immunological response to determine the outcome of wound healing. If biological response prevails, wound is healed successfully. If immunological response prevails, wound cannot be healed to produce clinical symptoms. Thus, immuno-surveillance can act synergistically with chemo-surveillance to prevent wounds caused by infectious agents or toxic chemicals, but can also act antagonistically with chemo-surveillance to trigger the production of TNF to result in the damage to chemo-surveillance. The functionality of chemo-surveillance stands out as the most important factor to dictate the success of wound healing and cancer therapy [27,28].

Chemo-surveillance Destroyed in Cancer Patients

Chemo-surveillance was a terminology we created to describe an 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 [26-28]. DIs are chemicals capable of eliminating telomerase from abnormal MEs [46,47], and DHIs are inhibitors of MEs capable of potentiating the activity of DIs [48,49]. DIs are most likely derived from the degradative products of erythrocytes that include acidic peptides, AA or dicyclioPGs as liposomal complexes with pregnenolone designated as OA-0.79, and membrane fragments containing AA designated as PP-0 [46,47,50,51]. 0.79 after OA

and 0 after PP are chromatographic coefficient Kav values of particular chromatographic system, which may vary according to the chromatographic system employed. Peptides are important active components of Antineoplastons purified from urine [46, 47] Urinary peptide profile and plasma peptide profile were exactly the same, which was also very similar to the peptide profile of spleen extract, but dissimilar to peptide profiles of other organ extracts, which led us to believe that wound healing metabolites were primarily contributed by the degradative products of erythrocytes since spleen was known to process dead erythrocytes [52]. Uroerythrin is a very active DHI, which must derive from the heme of hemoglobins, also from degradation of erythrocytes [53]. Steroid metabolites constitute major urinary DHIs, which may derive from organs involved in steroid metabolisms. DIs and DHIs are hydrophobic metabolites that can be retained by C18 or XAD-16 in aqueous solution and recovered by organic solvent. Peptides share physical-chemical properties similar to DIs and DHIs. Therefore, peptides can be used as surrogate molecules to represent DIs and DHIs. We have used peptide analysis to study the status of chemo-surveillance of cancer patients. Peptides were initially purified from plasma deproteinized with sulfosalicylic acid or urine without deproteinization process by C18 cartridge and recovered by elution with 80% methanol. Solvent was removed by lyophilization and the residue was dissolved in a small volume of water for HPLC resolution of peptides on a column of sulfonated polystyrene. Results of 108 patients came to seek Antineoplaston therapy by Dr. Stanislaw R. Burzynski during 1982-1986 are presented in Table 1, which is reproduced from the reference [26]. Results presented in Figure 1 and Table 1 are a clear indication that cancer evolves due to the collapse of chemo-surveillance. Cachexia is a symptom commonly share by cancer and inflammatory patients, which is caused by TNF. The damage to chemo-surveillance will get worse as the disease progresses. Treatment with cytotoxic agents that create wounds also triggers the production of TNF to damage chemo-surveillance. CDA level of 2.5 is probably the critical level to determine the responsiveness to cytotoxic therapies. Above 2.5, patients are responsive to cytotoxic therapies, and below 2.5, patients are unresponsive. Cytotoxic therapies can only save a small minority of cancer patients in the early stage, but cause the fatality of the majority of cancer patients in the advanced stage [16]. Restoration of chemo-surveillance is, therefore, very important to the success of cancer therapy [54]. Consequently, restoration of chemo-surveillance is the top priority of cancer therapy no matter what therapy the cancer patient chooses [55]. On cytotoxic therapies and immunotherapy, it can promote unresponsive patients to become responsive patients [9, 10, 12, 14, 16]. On surgery, it can make metastatic patients to become eligible patients for surgery by blocking dissemination of metastasis [13]. On differentiation therapy and therapy based on wound healing, it is the right indication [10, 35, 48, 49, 54, 55]. It appears that restoration of chemo-surveillance is the best way to save cancer patients. Indeed, cancer therapy by Antineoplaston [52] or CDA2 [14] was very encouraging. Patients responding to Antineoplaston therapy all showed CDA levels increasing to approach normal level of CDA-5.0. If not responding, CDA levels continued to decline. Obviously, not all patients responded positively to therapies of Antineoplastons or CDA-2. CCs are known to express a high level of degradative enzymes to salvage substrates for macromolecule syntheses to support their faster growth. Antineoplastons and CDA-2 are natural wound healing metabolites purified from urine, which may be quickly degraded in some very fast growing CCs. We recommended two sets of CDA formulations: one set made by natural DIs and DHIs for easy access to CSCs and another set made by non-natural DIs and DHIs to resist enzymatical degradation by CCs [9,10].

Table 1: Chemo-surveillance destroyed in cancer patients.

Plasma/Urine Ratios	CDA Level	Patient Numbers	% Distribution
0.83-0.80 (Normal)	5.0	2	1.0
0.80-0.60	4.3	7	6.5
0.60-0.40 (Responsive)	3.1	18	16.7
0.40-0.20	1.8	38	35.2
0.20-0.10	0.9	24	22.2
0.10-0.02 (Unresponsive)	0.37	19	17.6

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

Abnormal MEs as the Most Critical Issue of Cancer

Cancer is basically a problem of growth regulation going awry. Abnormal MEs and chromosomal abnormalities to activate oncogenes and to inactivate suppressor genes are the most critically issues to mess up growth regulation. MEs play a pivotal role on the regulation of cell replication and differentiation by virtue of the fact that DNA MEs control the expression of tissue specific genes [58], and rRNA MEs control the production of ribosome [59], which in turn dictates the commitment of cells to enter cell cycle [60]. When the enhanced synthesis of ribosome is locked in place, it becomes a factor to drive carcinogenesis [61]. Therefore, abnormal MEs are a critical issue of cancer, which give rise to aberrant nucleic acid methylation.

Aberrant tRNA methylation was aggressively pursued in a few years span around 1966 and aberrant DNA methylation was aggressively pursued in a few years span around 1985, just before and after the war on cancer of President Nixon [2]. The cancer establishments could identify the important issues of cancer, but missed the critical target of abnormal MEs to focus on the studies of methylated nucleic acids. Had they focused the studies on abnormal MEs, cancer was solved in these two periods. Identification of the critical issue is really important to the solution of the problem.

MEs are ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosyl-homocysteine hydrolase (SAHH) [62]. MEs play a pivotal role on the regulation of cell replication and differentiation. Because of this pivotal role, MEs are subjected to exceptional allosteric regulation: on the individual enzymes, MEs are regulated by steroid hormones, and on the enzyme complex, MEs are regulated by telomerase and chemo-surveillance [29]. Allosteric regulation is the most pervasive biological regulation. Only enzymes involved in important biological function are subjected

to allosteric regulation. Doble allosteric regulations must be an indication of the exceptional role of MEs on growth regulation [25,62]. Whatever happens naturally is the creation of the nature to benefit living organisms. Photo synthesis is a prime example that produces oxygen free to sustain the lives of living organisms. Immuno-surveillance is another example, which is well accepted by the health profession. Chemo-surveillance is also an example of the creation of the nature to benefit living organisms. But chemo-surveillance is not accepted by the health profession, because it violates the commanding principle of cell killing to combat cancer put up by the cancer establishments. The commanding principle of cell killing is wrong as cancer mortality keeps on increasing [8]. Solution of abnormal MEs is obviously the top priority of cancer therapy [55], since these enzymes play very important role on the regulation of cell growth [40,59,62]. MEs are regulated by steroid hormone to promote the formation of stable and active ternary MEs. The association of ternary MEs with telomerase further increase the stability and the activity of MEs [25]. The association of MEs with telomerase changes the kinetic properties of MAT-SAHH isozyme pair and the regulation greatly in favor of cell growth. Telomerase associated isozyme pair display Km values 7-fold higher than the normal isozyme pair [23-25]. The higher Km values suggest that cells expressing telomerase have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are important for the promotion of the growth of cells with abnormal MEs as the study of Prudova et al. [63] indicated that protein associated with AdoMet could increase stability against protease digestion, and the study of Chiva et al. [64] indicated that when cancer cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly. Obviously, abnormal MEs play an important role on the growth of cells expressing telomerase, and the expression of telomerase commences at the very beginning of life. Abnormal MEs are shared by all cancers [24]. Once this target is hit, other important cancer targets will also fall. Oncogenes and suppressor genes are cell cycle regulatory genes which have important roles to play when cells are in cell cycle replicating. But if abnormal MEs are corrected by CDA formulations to exit cell cycle to undergo terminal differentiation, oncogenes and suppressor genes have no roles to play. So, abnormal MEs are the bullseye of cancer target [65]. Cytotoxic agents can also put to rest abnormal MEs and chromosomal abnormalities, which have been tried but failed. The failure for cytotoxic agents to solve cancer is inability of cytotoxic agents to kill CSCs and the contribution of cytotoxic agents to cause damage to chemo-surveillance. Immunotherapy has the same problem to show ineffectiveness against CSCs and to trigger the production of TNF to damage chemo-surveillance. It appears that CDA formulations are the only drugs able to fulfill cancer moonshot initiative of President Biden and to win the war on cancer of President Nixon [66,67].

CDA Formulations as the Best Drugs to Solve the Issue of CSCs

CSCs evolve from PSCs due to wound unhealing. The appearance of CSCs in the primary site is an indication of unhealed wounds which have to be healed to solve the problem. Myelodysplastic syndromes (MDSs) are a unique case to demonstrate the evolution of cancer due to wound unhealing at the stage of CSCs. MDSs often start with a display of immunological disorder, which prompts the local production of inflammatory cytokines [68]. Among such cytokines, TNF is the critical factor related to the development of MDSs [69]. 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 responsible to trigger cachexia symptoms resulting in the collapse of chemo-surveillance as above described. As a consequence, chemo-surveillance normally operating in healthy people to keep cells with abnormal MEs in check becomes dysfunctional to force the evolution of CSCs from PSCs. The propagating pathological cells of MDSs have been identified as human CSCs [70]. Therefore, MDSs are diseases of cancer development at the stage of CSCs.

Vidaza, Decitabine and CDA-2, which is a drug of our invention of the preparation of wound healing metabolites purified from urine [50], are the three drugs approved by the Chinese FDA for the therapy of MDSs. Vidaza and Decitabine are also the two drugs approved by the US FDA for the therapy of MDSs. Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental in conducting clinical trials of all three MDSs drugs. According to his assessments based on two cycles of treatment protocols each 14 days, CDA-2 had a noticeable better therapeutic efficacy based on the cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy based on hematological improvement evaluation, namely becoming independent on blood transfusion to stay alive as shown in Figure 2, which is reproduced from the reference [71]. Therapy of MDSs requires the conversion of pathological CSCs to become functional erythrocytes, platelet or neutrophils.

Killing of CSCs cannot cure MDSs. Therefore, induction of terminal differentiation of CSCs is the only option for the therapy of MDSs. CDA-2 employs wound healing metabolites to destabilize abnormal MEs and phenylacetylglutamine to antagonize TNF to restore chemo-surveillance to accomplish the therapy of MDSs, whereas Vidaza and Decitabime rely on the covalent bond formation between MT and 5-aza-cytosine incorporated into DNA to inactivate MEs [72]. The action of CDA-2 is selective on the tumor factor of abnormal MEs, whereas the action of Vidaza and Decitabine is non-selective that can also affect normal stem cells. Thus, CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [73,74], and very toxic to DNA [75-77]. Clearly, CDA-2 is the best drug for the therapy of MDSs. The difference between CDA-2 and Vidaza and Decitabine is very convincing that if you mess up DNA structure, the consequence is very serious, very frequently fatal. DNA modifying agents even showing promising therapeutic efficacy are not trust worthy, because the adverse effects may result in the fatality at later time. Radiotherapy is very effective to achieve complete remission of nasopharynx carcinoma, but the patients in remission cannot survive very long. Most of the surviving patients are succumbed to adverse effects such as cardiovascular breakdown. DNA inter

acting agents should be banned as cancer therapeutic agents. Cancer establishments hold on to such agents to solve cancer. That is the problem to cause ever-increasing cancer mortality.

Solution of CSCs is very critical to the success of cancer therapy, because CSCs are responsible for the major fatal effects of cancer such as metastasis, drug resistance, angiogenesis, unresponsiveness and recurrence [35, 51, 78]. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapy [15]. Apparently, the winner is CDA formulations as induction of terminal differentiation of CSCs is the only viable option to solve the issue of CSCs [11]. Surgeons, oncologists and cancer patients must unite to push for the approval of CDA formulations to save desperate advanced cancer patients [78].

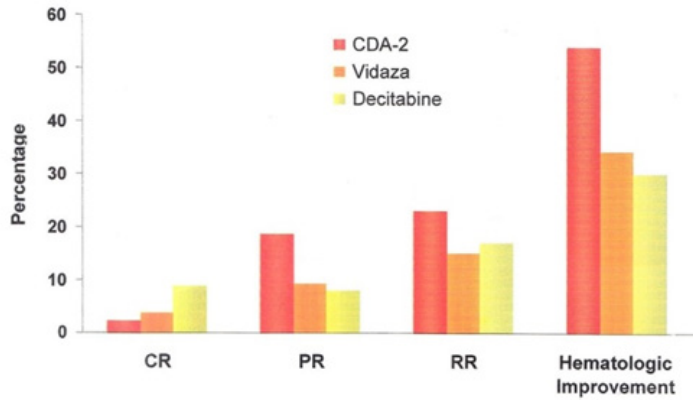

Figure 2: Relative Effectiveness of MDSs Drugs.

CDA Formulations to the Rescue of Advanced Cancer Patients

Cytotoxic agents and immunotherapeutic agents put up by cancer establishments are unable to save advanced cancer patients. CDA formulations are the only hope to save advanced cancer patients whose chemo-surveillance have been fatally damaged [12]. We have carried out extensive studies on natural and non-natural DIs and DHIs for the manufacture of CDA formulations [9-15,31-35,43,44,46-50,53,54,66,67,79]. Active DIs and DHIs are summarized in Table 2 and 3. $ED_{25, 50, 75}$ of DIs and $RI_{0.5}$ of DHIs are included to facilitate the manufacture of CDA formulations. $RI_{0.5}$ of a DHI is eqivalent to ED_{25} of a DI, which can be determined by the procedure presented in the reference [49]. ATRA is the standard care of acute promyelocytic leukemia [80]. It requires the expression of the receptor of ATRA to activate oligoisoadenylate synthetase to achieve the therapeutic effect. The product of this enzyme oligoisoadenylate is the actual DI [81]. Therefore, only cancer cells which express RAR can benefit from ATRA. The rest of DIs presented in Table 1 work directly on abnormal MEs. AA and its metabolites PGs are natural DIs involved in chemo-surveillance. BIBR1532 and boldine are approved cancer drugs as telomerase inhibitors. PGs are approved drugs for the delivery. The request for the change of indication will not be as long as the request of new indication. PGs and telomerase inhibitors can be switched quickly as DIs to save cancer patients.

Inhibitors of MEs are excellent DHIs. As shown in Table 3, SAHH and MT inhibitors are much better DHIs than MAT inhibitors. MAT is the most stable enzyme of the three MEs [62]. The association with telomerase further increases its stability. It is very hard to shake loose of this enzyme. Thus, inhibitors of MT and SAHH are better choice of DHIs. Pregnenolone is not a very active DHI as shown in the Table 3. We consider it as a very valuable DHI. It is a major DHI of CDA-2 and Antineoplastons. It is the master substrate of all 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 according to Morley [82]. The youngest and the oldest people produce the least amount of pregnenolone, and these two age groups are the most vulnerable to develop cancer. Thus, pregnenolone is a single metabolite to have a great influence on wound healing and health issues related to wound healing. It is our top choice of DHI for CDA-CSC formulations.

Table 2: Active Dis.

DIs	ED25 (μM)	ED50 (μM)	ED50 (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32	40.5
DicycloPGE2	21	43.5	-
AA	21	42	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

Table 3: Active DHIs.

SAHH Inhibitor	$RI_{0.5}$ (μM)	STIs	$RI_{0.5}$ (μM)
Pyrvinium Pamoate	0.012	Sutent	0.28
Vitamin D3	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
Uroerithrin	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)	Pyriogallol	3.18
		Silibinin	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ellagic Acid	4.45
Phenylacetyleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	Phloroglucinol	38.82

The findings of signal transduction inhibitors (STIs) as good DHIs are expected, because signal transductions tend to produce factors that can promote the activity of MEs. The findings of polyphenols as excellent DHIs are unexpected, but are pleasant findings. Since polyphenols are recognized good for health, the activity as excellent DHIs can increase their credibility as health food.

DIs are more important than DHIs on the induction of terminal differentiation. But DIs alone cannot achieve differentiation to reach completion. Because elimination of telomerase allows MEs to dissociate into individual enzymes. MT as a monomer has a tendency to be modified to become nuclease which can create damage to disrupt differentiation process. The damage can be repaired to cause recurrence. The therapy of acute promyelocytic leukemia with ATRA is excellent, but the majority of patients recur within a year [80]. The addition of DHIs can keep MT-SAHH in dimmer to prevent modification of MT to become nuclease. The inclusion of DHI is essential to reach completion of differentiation.

The manufacture of CDA formulations can be ED_{25} of a DI + $3xRI_{0.5}$ of a DHI, or ED_{50} of a DI + $2xRO_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [51]. We recommend to make two sets of CDA formulations: one set CDA-CSC made up by AA + pregnenolone, and another set CDA-CC made up by BIBR1532 + pyrvinium pamoate. The schedule of administration must be decided by clinical trial. The inclusion of phenylacetylglutamine as anti-cachexia agent definitely help, which can be administered as capsules. The schedule of administration should be monitored on the status of chemo-surveillance. These are all new endeavors. A lot of hard work remain to be done to overcome the hurdles.

Conclusion

Cancer is evolved due to wound unhealing, because of the collapse of chemo-surveillance, which is the creation of the nature for the perfection of wound healing. Wound unhealing forces PSCs to evolve into CSCs to escape contact inhibition which limits the extent of PSCs proliferation. The proliferation of CSCs is still unable to heal the wound, which are then forced to progress to faster growing CCs by activation of oncogenes or inactivation of suppressor genes. Thus, the collapse of chemo-surveillance, the evolution of CSCs and the progression of CSCs to become faster growing CCs all contribute to the development of cancer. An effective cancer therapy must deal all these contributing factors. Focusing alone on CCs cannot solve cancer. Inability to eliminate CSCs and the contribution to the damage of chemo-surveillance are the reasons behind the failure of cytotoxic agents to solve cancer, which include chemotherapy, radiotherapy and immunotherapy. CDA formulations offer the best solution of cancer, which can eradicate CSCs, CCs by inducing these cells to become terminally differentiated cells unable to replicate, and restore chemo-surveillance. Residual tumor mass is harmless. If it is annoying, it can be safely removed by surgery.

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