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Short Communication

CDA Formulations to Make Surgery A Top Choice of Cancer Therapy

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Abstract

The objective of this article is to promote surgery as a top choice of cancer therapy. Surgery is obviously a top choice of cancer therapy when cancer stem cells (CSCs) and cancer cells (CCs) are confined to the primary site, and chemo-surveillance and immune-surveillance are still functioning to prevent the dissemination of metastasis. Surgical therapy of cancer is instant following the healing of surgical wounds which comes naturally within a week or two weeks. But if metastasis has occurred, surgery is no longer an option, because surgical wounds tend to promote dissemination of metastasis. Metastasis is the making of CSCs. If CSCs can be effectively put under control to prevent metastasis, then surgery is still a top choice of cancer therapy even metastasis has taken place. Cell differentiation agent-2 (CDA-2) is a preparation of wound healing metabolites purified from freshly collected urine by reverse phase chromatography on XAD-16, which has been approved by the Chinese FDA as an adjuvant agent for breast, non-small cell lung cancer and primary hepatomas in 2004, and as a mono-therapeutic agent for myelodysplastic syndromes (MDSs) in 2017. MDSs are diseases attributable entirely to CSCs. CDA-2 is obviously the best drug for the therapy of CSCs. The active components of CDA-2 include differentiation inducers (DIs), differentiation helper inducers (DHIs) to target abnormal methylation enzymes (MEs), and phenylacetylglutamine as an effective anti-cachexia chemical to restore chemo-surveillance. We have carried out extensive studies on natural and non-natural DIs and DHIs to make CDA formulations effective for the induction of terminal differentiation of CSCs and CCs, which are definitely helpful to promote surgery as a top choice of cancer therapy.

Introduction

Surgery is obviously a top choice of cancer therapy when CSCs and CCs are confined to the primary site, and chemo-surveillance and immuno-surveillance are still functioning to prevent the dissemination of metastasis. Surgical therapy of cancer is instant following the healing of surgical wounds which comes naturally within a week or two weeks. This was why President Biden was so enthusiastic to raise a gigantic fund to support a surgical project of Tulane University to kick off cancer moonshot initiative he brought up in 2022. The promise of surgery to save cancer patients is instant. President Biden has requested to save 50% of cancer patients in 25 years in his proposal of cancer moonshot initiative in 2022. Surgical therapy of cancer has its limitation. If metastasis has taken place, it is no longer an option because surgical wounds tend to promote the dissemination of metastasis. Metastasis is the making of CSCs [1]. If CSCs can be effectively put under control to prevent metastasis, then surgery is still a top choice of cancer therapy when metastasis has taken place. Development of drugs effective to control CSCs and CCs definitely can expand cancer patients eligible for surgical therapy to include advanced cancer patients showing evidence of metastasis.

Commentaries and Discussion

The Fundamental Basis of Cancer Evolution

To effectively solve cancer, we must understand how the problem of cancer evolves. Cancer evolves due to wound unhealing because of the collapse of chemo-surveillance. The concept of cancer evolves due to wound unhealing was first introduced by the great German pathologist Virchow in the 19th century [2], which was again brought up by Dvorak in 1986 [3]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [4]. We provided the most important details on this subject that included abnormal MEs to promote perpetual proliferation of CSCs and CCs by blocking cell differentiation [5-7]; chemo-surveillance as the nature's creation of allosteric regulation on abnormal MEs to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing, cancer being the worst consequence [8-10];

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DIs and DHIs as wound healing metabolites and also as the active players of chemo-surveillance [8-10]; hypomethylation of nucleic acids as a critical mechanism on the induction of terminal differentiation [11]; mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [12-14]; and evolution of CSCs from PSCs through a single hit to silence ten-eleven translocator -1 (TET-1) enzyme due to wound unhealing [15]. These studies very convincingly establish that cancer evolves due to wound unhealing. PSCs are the cells involved in wound healing. If wound is not healed, PSCs will be forced to evolve into CSCs to escape contact inhibition which limits the extent PSCs can proliferate. The evolution and the proliferation of CSCs are still unable to heal the wound, because the problem is the collapse of chemo-surveillance, which the nature has no mechanism to rectify. Eventually, CSCs are forced to progress to faster growing CCs through chromosomal abnormalities such as translocations to activate oncogenes, or deletions to inactivate suppressor genes. Therefore, the collapse of chemo-surveillance, the evolution of CSCs from PSCs, and the progression of CSCs to become CCs all contribute significantly to the evolution of cancer. A perfect cancer solution must be able to eliminate all contributing factors of cancer [16].

PSCs are actually the most primitive stem cells to initiate the development of organs or tissues of the fetus during embryonic stage. A small number of these cells, usually less than 2% of the organ or tissue mass, are preserved in the organs or tissues for future expansion or repair. MEs of embryonic stem cells, including PSCs, are abnormal like cancer cells to associate with telomerase [5-7]. Obviously, the seed of cancer is sawed at the very beginning of life, namely the fertilization of egg with sperm to activate the totipotent stem cell which expresses telomerase. The expression of telomerase among embryonic stem cells spreads through pluripotent stem cells, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. Therefore, abnormal MEs are a normal function of primitive stage stem cells. Disruption of the function of abnormal MEs during embryonic state of fetal development is detrimental as premature induction of terminal differentiation by thalidomide results in malformation of the limbs. Abnormal MEs do not cause the problem of normal stem cells expressing telomerase, because the normal stem cells are protected by safety mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions, and chemo-surveillance to induce terminal differentiation of cells with abnormal MEs. If such safety mechanisms become dysfunctional, then the clinical symptoms arise.

MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH), which play a pivotal role on the regulation of cell replication and differentiation. Because of pivotal role, MEs are subjected to exceptional allosteric regulation [17]. Usually, only enzymes with important regulatory roles are subjected to allosteric regulation. MEs are exceptionally to subject to double allosteric regulations: one on the individual enzymes by steroid hormone, and the other on the enzyme complex by telomerase and chemo-surveillance. SAHH is the steroid hormone receptor. In steroid hormone target tissues, MEs are under strict regulation of steroid hormone [18]. In telomerase expressing cells, ternary MEs become associated with telomerase [7]. The association of MEs with telomerase changes kinetic properties of MAT-SAHH isozyme pair and the regulation greatly in favor of cell growth. Telomerase associated MAT-SAHH isozyme pair display Km values 7-fold higher than the normal isozyme pair [5-7]. The higher Km values suggest that cells expressing telomerase have a larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). A larger pool sizes of AdoMet and AdoHcy is important to promote the growth of cells expressing telomerase as the study of Prudova et al. [19] indicated that protein associated with AdoMet could increase the stability against protease digestion, and the study of Chiba et al. [20] indicated that when cancer cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly. Obviously, MEs play an important role on cell growth.

Cancer is basically a problem of growth regulation going awry. MEs becoming abnormal is a very critical issue of cancer. Chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes are also a very critical issue of cancer. We tend to believe abnormal MEs as the most important issue of cancer [21], because abnormal MEs happen quite early and are shared by all cancers [6]. When the abnormality of MEs is corrected, cells with abnormal MEs will be induced to undergo terminal differentiation, which can also put to rest the issues of chromosomal abnormalities. Oncogenes and suppressor genes are cell cycle regulatory genes, which happen quite late and variable during carcinogenesis process. Oncogenes and suppressor genes have important roles to play when cells are in cell cycle replicating. But if cells exit cell cycle to undergo terminal differentiation, they have no roles to play. So, the correction of abnormal MEs can also put to rest the issue of chromosomal abnormalities, which are not easy to fix. Cancer establishments designated 20 years, 1976-1996 right after the failure of war on cancer declared by President Nixon, to develop gene therapy. They gave up because it was too difficult and too expensive to develop gene therapy. Cancer establishments should turn to abnormal MEs which are much easier to fix.

Chemo-surveillance and Immuno-surveillance as the Nature's Creations to Ensure Perfection of Wound Healing to Avoid Disastrous Consequences of Wound Unhealing

Whatever happens naturally is the nature's creation to benefit living organisms. Photosynthesis is a prime example that provides free oxygen to sustain the lives of living organisms. Wound healing is obviously an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance for the perfection of wound healing to avoid disastrous consequences such as tissue fibrosis, dementia, organ failure or cancer [22-27].

Chemo-surveillance heals wounds caused by toxic chemicals and physical means, whereas immuno-surveillance heals wounds caused by infectious agents. 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 [8]. DIs are metabolites capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of MEs capable of potentiating the activity of DIs. DIs and DHIs are hydrophobic metabolites produced naturally in the body. Peptides share physical-chemical properties similar to DIs and DHIs, namely the ability to be retained by C18 and recovered by resorption with organic solvent, which can be used as surrogate molecules to represent wound healing metabolites. We used the quantitative assay of

Table 1. *Collapse of Chemo-surveillance of Cancer Patients*

Plasma/Urine Peptide Ratios	CDA Levels	Number of patients	% Distribution
0.83-0.80 (Normal)	5	2	1.8
0.80-0.60	4.3	7	6.5
0.60-0.40	3.1	18	16.7
0.40-0.20	1.9	38	35.2
0.20-0.10	0.9	24	22.2
0.10-0.02	0.37	19	17.6

plasma and urinary peptides to analyze capability of chemo-surveillance of cancer patients. Peptides were initially retained onto C18 cartridge from plasma deproteinized by sulfosalicylic acid or urine. After washing with water to remove unretained chemicals, the retained hydrophobic materials were recovered with 80% Methanol. Solvent was removed by lyophilization and the residue was dissolved in a small volume of water for HPLC resolution of peptide profile on a column of sulfonated polystyrene chromatographic system developed by Glenco Scientific Inc. of Houston, TX for peptide analysis. Results of 108 cancer patients came to seek Antineoplaston therapy by

Dr. Stanislaw R. Burzynski between 1982-1986 are presented in Table 1, reproduced from the reference [28]. The unit of peptides from plasma is nmoles peptides/ml plasma and the unit of peptides from urine is nmoles/mg creatinine. It is evident that chemo-surveillance is always operated at the maximum capacity. Any pathological insult can cause the collapse of chemo-surveillance, that include physical and chemical insults to damage chemo-surveillance and infectious insults to damage immuno-surveillance. Therefore, perfection of wound healing is so important to avoid clinical symptoms to show up. Creations of wounds must be avoided to solve cancer, because patient's chemo-surveillance has been badly damaged for cancer to show up. Surgery is also creating wound, but the wound created by surgery is an acute wound easy to heal.

Wound usually triggers biological and immunological responses. Biological response involves the release of arachidonic acid (AA) by phospholipase A2 from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG syntases [29, 30]. Although PGs are very active DIs [31, 32], the induction of terminal differentiation of PSCs at the initial stage of wound is not the primary objective of PGs. Rather, the localized inflammation triggered by PGs [33] 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 build up of cells with abnormal MEs. This brake must be released for cells with abnormal MEs to build up to repair the wound. PGs are metabolically unstable [29]. 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 terminal stage of wound healing is accomplished by wound healing metabolites involved in chemo-surveillance. The stable end products of PGs, namely dicycloPGs which are not very active DIs [32], may then get involved in the induction of terminal differentiation of PSCs at the terminal stage of wound healing. Chemo-surveillance is the nature's creation for the perfection of wound healing to avoid and to cure cancer [10]. Cancer establishments put up cytotoxic agents that create wounds to destroy chemo-surveillance is contra-indication of cancer therapy. No wander, cancer mortalities keep on increasing. The restoration of chemo-surveillance is utmost important to save cancer patients [9,10,34-36].

Biological response triggered by wound is good for wound healing, but immunological response triggered by wound is bad for wound healing. Immunological response prompts the patient to produce cytokines, which are toxic proteins to cause damages to normal cells, which also constitute to the therapeutic effects of immunotherapy. Tumor necrosis factor (TNF) is particularly bad among cytokines for wound healing. TNF has another name as cachectin after its notorious biological effect to cause cachexia symptoms. TNF is toxic to stem cells, causing the apoptosis of bone mallow stem cells. It is also responsible for the leaky blood vessel [37,38], resulting in excessive urinary excretion of low molecular weight metabolites, DIs and DHIs are among such low molecular weight metabolites excreted, resulting in the collapse of chemo-surveillance. The collapse of chemo-surveillance is responsible for the evolution of cancer. Our carcinogenesis studies strongly support the validity of this concept. During challenge of animals with hepatocarcinogens, we noticed numerous tiny hyperplastic nodules in the liver displaying abnormal MEs, which must represent the process of active wound healing by PSCs [39]. Most of tiny hyperplastic nodules disappeared soon afterward, suggesting the completion of wound healing, and only a few large size carcinomas appeared later from unhealed tiny nodules. If animals were provided Antineoplaston A10 during the challenges with hepatocarcinogens, the appearance of hepato-carcinomas could be effectively prevented [40]. Antineoplaston A10 is phenylacetylglutamine effective to antagonize the effect of TNF to cause excessive excretion of low molecular weight metabolites [8]. By protecting the functionality of chemo-surveillance, Antineoplaston A10 is effective to prevent hepatocarcinogenesis induced by potent hepato-carcinogen, and to cure early stage cancer [8, 40]. It appears that DIs and DHIs are the nature's prescription of effective cancer drugs. Treatments that can boost the level of DIs and DHIs such as CDA formulations made up with DIs and DHIs and phenylacetylglutamine to antagonize TNF are good for the therapy of cancer [41-44], whereas treatments that contribute to the damage of chemo-surveillance such as chemotherapy, radiotherapy and immunotherapy [43-45] are unable to save advanced cancer patients to reduce cancer mortality. Cytotoxic cancer therapies can only benefit early stage cancer patients whose chemo-surveillance have not yet fatally damaged, most likely the patients listed in Table 1 with CDA levels above 3.1, relying on the restoration of the functionality of chemo-surveillance to subdue surviving CSCs as cytotoxic cancer therapies are ineffective against CSCs protected by drug resistance and anti-apoptosis mechanisms [46-49]. Ineffectiveness against CSCs and the contribution to the damage of chemo-surveillance are the reasons behind the failure of cytotoxic cancer therapies to win the war on cancer.

Inactivation of MEs as the Only Option to Solve the Issue of Wound Unhealing and CSCs

Myelodysplastic syndromes (MDSs) are a classic case to demonstrate the evolution of cancer due to wound unhealing.

MDSs often start with a display of immunological disorder [50], which prompts the local production of inflammatory cytokines. Among such cytokines, TNF is the critical factor related to the development of MDSs [51]. 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 notorious effect to trigger cachexia symptoms as above described in the Section 2-2, resulting in the collapse of chemo-surveillance. As a consequence, chemo-surveillance normally operating in healthy people to keep cells with abnormal MEs in check becomes dysfunctional to allow PSCs to evolve into CSCs. The propagating pathological cells of MDSs have been identified as CSCs [52]. Thus, MDSs are diseases attributable entirely to CSCs. CSCs are PSCs minus TET-1 enzyme. Morphologically and functionally CSCs and PSCs are very close. Destabilization of abnormal MEs is a critical mechanism of wound healing, which should also be a critical mechanism to take care of CSCs. In fact, inactivation of MEs is the only option for the therapy of MDSs.

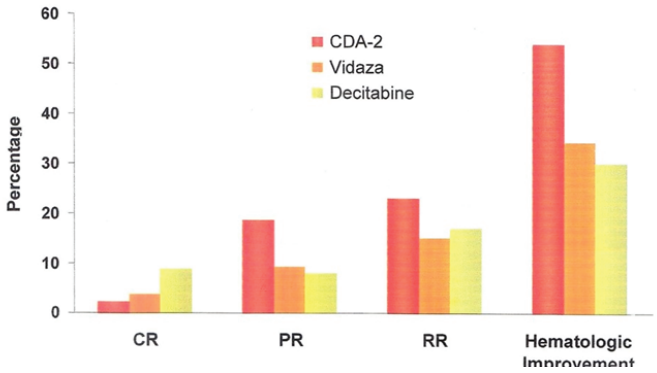

Figure 1. *Relative Effectiveness of MDSs Drugs*

Vidaza, Decitbine and CDA-2 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 carrying out clinical trials of the three MDSs drugs. According to his assessments based on two cycles of treatment protocols each 14 days, CDA-2, which was our invention of the preparation of wound healing metabolites from urine [71], 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, as shown in Figure 1, which is reproduced from the reference [53].

Therapy of MDSs require conversion of pathological CSCs to become functional cells as erythrocytes, platelets 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 restore chemo-surveillance to accomplish the therapy of MDSs as above described in the Section 2-2, whereas Vidaza and Decitabine rely on covalent bond formation between MT and 5-aza-cytosine incorporated into DNA to eliminate MEs [54]. CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [55, 56], and quite toxic to DNA [57-59]. Clearly, CDA-2 is the drug of choice for the therapy of MDSs with better therapeutic efficacy and without adverse effects. It should be considered the standard care of CSCs as CSCs are critically linked to wound unhealing and the induction of terminal differentiation of cells with abnormal MEs is the only option for the healing of wound and for the solution of CSCs [60].

CSCs, like the make up of PSCs, constitute only a small minority, less than 2% of the most popular primary tumors. Primary malignant brain tumors are exceptional to have CSCs more than 10% [61-62]. CSCs contribute the major fatal effects of cancer that include metastasis, drug resistance, resistance to apoptosis, and angiogenesis [1, 46-49]. Cancer establishments were aware of the importance of CSCs. The pharmaceutical giant GSK put up 1.4 billion, the most expensive cancer drug, to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University about 17 years ago, which failed to materialize because killing was not an option for the solution of CSCs. The composition of CSC s in the tumor can greatly affect the therapeutic effects. Cytotoxic cancer therapies kill CCs to create wounds to trigger proliferation of CSCs to heal wounds [41], thus gradually increase the proportion of CSCs. When the proportion of CSCs becomes greater than 10% as the primary malignant brain tumors, those tumors become unresponsive to further cytotoxic therapies. Only CDA formulations can offer rescue of patients with CSCs as a dominant issue [43-45]. Cytotoxic therapies of cancer are obviously wrong, thus, cancer mortality keeps on increasing to reach 10 million worldwide in 2019 with an annual increment of 5% according to NCI [63]. The USA records showed 0.61 million deaths in 2023 with an annual increment of 0.2% according to ACS [63]. Can we expect cancer establishments to turn cancer mortality around from increasing to decreasing? As long as they are obsessed on killing of cancer cells and to reduce tumor size, the cancer mortality will keep on increasing, because killing to create wounds is contra-indication of cancer therapy.

Surgeons and Cancer Patients United to Push for the Approval of CDA Formulations to Make Surgery a Top Choice of Cancer Therapy

Surgery is a perfect choice of cancer therapy at early stage when CSCs and CCs are confined to the primary site. A surgery to remove the primary tumor eliminates all causes to cancer. Healing of surgical wounds comes naturally. Surgical wounds usually heal in a week or two. Cancer can also be cured in a week or two following the completion of wound healing. So, the problem is solved instantly. President Biden was so enthusiastic to support surgical solution of cancer. Surgery has a limitation. When metastasis has taken place, it is no longer an option, because surgery tends to cause dissemination of metastasis. Metastasis is the making of CSCs [1]. If metastasis can be effectively put under control, then surgery is still a top choice of cancer therapy even metastasis has taken place. President Biden is an exceptional pollical leader to genuinely committed to solve cancer, because he lost his most accomplished son to brain cancer. He personally campaigned to raise a gigantic fund to support a promising surgical project of Tulane University. CDA formulations are the standard care of CSCs [36, 42, 44, 45, 60]. Thus, dissemination of metastasis can be effectively prevented by CDA formulations to make surgery still a top choice of cancer therapy even CSCs have spread out. The therapeutic end point of CDA formulations

Table 2. *Active DIs*

DIs	ED25 (μM)	ED50 (μM)	ED75 (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
Boline	60.1	78.8	94.2

is terminal differentiation of cancer cells, which is also the end point of wound healing. The therapy offered by CDA formulations cannot make the tumor to disappear, and is, therefore, unacceptable as a cancer drug according to the rule set up by cancer establishments. The rule set up by the cancer establishments in essence denies the success of cancer therapy, because the success of cancer therapy includes elimination of CSCs. Approval of CDA formulations to prevent dissemination of metastasis is essential for the success of surgical therapy of cancer. Surgeons and cancer patients must unite to push for the approval of CDA formulations for the perfection of surgical therapy of cancer to fulfill cancer moonshot initiative of President Biden and the war on cancer of President Nixon.

Development of CDA Formulations to Make Surgery A Top Choice of Cancer Therapy

We have carried out extensive studies on natural and non-natural DIs and DHIs for the manufacture of CDA formulations [31, 32, 41-45, 64-71]. Active DIs and DHIs are presented in Table 2 and 3. DIs and DHIs can be excellent cancer drugs. All-trans retinoic acid (ATRA) is the standard care of acute promyelocytic leukemia [72], and Gleevec is the standard care of chronic myeloid leukemia [73]. ATRA requires the expression of the receptor of ATRA, namely RAR, to activate oligoisoadenylate synthetase to achieve the therapeutic effect [74]. The product of this enzyme oligoisoadenylate is the actual DI to act on abnormal MEs. PGs are better DIs than their precursor AA and metabolic end product dicycloPGs. But PGs are metabolically unstable with half lives in minutes [29]. Unstable chemicals are not good candidates as drugs. AA and dicycloPGs are better candidates as natural DIs for the manufacture of CDA-CSCs to target against CSCs. CSCs are protected by drug resistance mechanism which may reject the access of non-natural chemicals [46-49]. BIBR1532 is the only choice of non-natural DI for the manufacture of CDA-CCs to target against CCs. Fast growing CCs are known to express a high level of degradative enzymes to salvage substrates for the syntheses of macromolecules to support their fast growth. Natural metabolites may be quickly degraded to lose activities. We recommend to manufacture two sets of CDA formulations: one against CSCs with natural DIs and DHIs for easy access to CSCs, and one against CCs with non-natural DIs and DHIs to resist degradative enzymes of CCs.

For the induction of terminal differentiation, DIs are more important than DHIs which can initiate the differentiation by the elimination of telomerase from abnormal MEs. DHIs can only provide a helping role to potentiate the activity of DIs. But the inclusion of DHIs is also crucial to achieve effective therapy. DIs alone cannot achieve differentiation to reach

Table 3. *Active DHIs*

SAHH Inhibitors	RI0.5 (μM)	STIs	RI0.5 (μM)
Pyrivinium Pamoate	0.012	Sutent	0.28
Vitamin D3	0.61	Berberine	0.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandros-terone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59	**Polyphenols**	**RI0.5 (μM)**
Pregnenolone	7.16	Tannic Acid	0.37
		EFCG	0.62
MT Inhibitors	**RI0.5 (μM)**	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	**RI0.5 (μM)**	Pyrogallol	3.18
Indol Acetic Acid	220	Silibinine	3.8
Phenylacetylvaline	500	Caffeic Acid	3.87
Phenylacetylleucine	780	Ellagic Acid	4.45
Butyric Acid	850	Gallic Acid	5.35
Phenylbutyric Acid	970	Ferulic Acid	7.41
		Phloroglucinol	38.82

completion, because DIs alone tend to induce dissociation of ternary MEs to become individual enzymes. Methyltrasferases in monomeric forms can be easily modified to become nucleases to create damages that can interrupt replication process to interfere differentiation process, which requires two cell replications to complete. The damaged cells after repair can resume replication to cause 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 DIs and DHIs can reach completion to avoid recurrence.

Inhibitors of SAHH and MT are better DHIs. This is because MAT is the most stable enzyme of the three MEs [18]. 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 [66]. Although it is not a very active DHI as shown in Table 3, we consider it a very important DHI, because 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 approximately 50 mg at 20-25 years old [75]. 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-CSCs. The finding of signal transduction inhibitors (STIs) as excellent DHIs was expected, since signal transductions always produced factors to stabilize MEs to promote cell replication. 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 polyphenol as excellent DHIs adds the credibility of polyphenols as health food.

Effective CDA formulations can be plasma dosages of ED25 of a DI + 3xRI0.5 of a DHI, or ED50 of a DI + 2xRI0.5 of a DHI, or ED75 of a DI + RI0.5 of a DHI [66]. RI0.5 of a DHI is equivalent to ED25 of a DI, which can be determined by the procedure provided in the reference [68]. 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, or 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 CCs above mentioned.

Conclusion

Surgery is obviously a top choice of cancer therapy when CSCs and CCs are confined to the primary site. The therapy of cancer is instant following the completion of healing of surgical wounds which comes naturally. However, surgery is not an option if metastasis has taken place, because surgical wounds tend to cause the dissemination of metastasis. Metastasis is the making of CSCs. If CSCs can be effectively eliminated, then surgery is still a top choice of cancer therapy of advanced cancer patients showing evidence of metastasis. CDA formulations are the best drugs to eliminate CSCs. Pretreatment to restore the functionality of chemo-surveillance with CDA formulations can prevent dissemination of metastasis for the perfection of surgical care of cancer therapy.

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Conflicts of interest

The authors declare no conflicts of interest.

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