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CDA Formulations to Remove Cancer as the Top Killer of the People of Asian Countries

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ABSTRACT: The objective of this article is to rectify cancer therapies which are apparently inadequate to result in cancer as the top killer of the people of many Asian countries for a very long time. Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells (CCs), which was a mistake made at a time when we did not have a complete knowledge of cancer. Cancer stem cells (CSCs) became known in 1997. The discovery of CSCs unraveled a very important issue of cancer. It became evident that, although CSCs constituted only a small subpopulation, these cells were responsible for the initiation of tumor growth and the treatment failure. Thus, the success of cancer therapy depends on the elimination of CSCs. Our studies on abnormal methylation enzymes (MEs), chemo-surveillance, wound healing and cell differentiation agent (CDA) formulations are very closely related to the issue of CSCs. Thus, we are in a unique position to offer the best solution of CSCs. Cancer evolves due to wound unhealing. Chemo-surveillance is the creation of the nature to ensure perfection of wound healing. Chemo-surveillance is specifically destroyed in cancer patients. Restoration of chemo-surveillance offers excellent therapy of cancer. CDA-2 was a preparation of wound healing metabolites purified from urine which has been approved by the Chinese FDA for the therapy of cancer and myelodysplastic syndromes (MDSs). MDSs are diseases attributable entirely to CSCs. CDA-2 was demonstrably the best drug for the therapy of MDSs. CDA formulations are the creation of the nature to remove cancer as the top killer of the people of Asian countries.

Keywords: Cancer Stem Cells, Cell Differentiation Agents, Chemo-Surveillance, Methylation Enzymes, Myelodysplastic Syndromes, Progenitor Stem Cells.

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INTRODUCTION

Every year the ministry of health and welfare of Taiwan government issues a list of top 10 Killers of the people of Taiwan. Cancer is always on the very top of the list for the last 43 years [1]. Cancer is also the top killer of the people of Japan for almost as long as Taiwan. Cancer is also the top killer of the people of China in recent 20 years after China has become the center of the world production. Asian countries are not alone, cancer mortalities are ever escalating around the world. The latest records compiled by NCI in 2019 showed cancer incidence of 19 million and cancer fatality of 10 million, which were an increment of 5.0% and 5.3% over the previous year. The inability to reduce cancer mortality is an indication of the failure of cancer therapies currently in practice. Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells. Cytotoxic chemotherapy was a tragic byproduct of the World War II. During the war, toxic sulfur mustard booms 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. Toxic chemicals were indeed very effective to kill leukemia cells. Cytotoxic chemo-therapy, thus, became a standard care of cancer, and the disappearance of cancer cells in the case of hematological cancers and the disappearance of tumor in the case of solid tumors became the standard

criteria for the evaluation of cancer therapy. Both were wrong [2, 3].

The mistakes were made at a time when cancer was not completely known. The mistakes were excusable. Cytotoxic chemotherapy and radiotherapy were the major modalities employed to combat cancer during the war on cancer declared by President Nixon during 1971-1976, which was not successful [4]. Cancer establishments started to search other cancer drugs such as drugs for gene therapy during 1976-1996, drugs to achieve anti-angiogenesis therapy during 1996-2016, and drugs to achieve immunotherapy from 2016 onward [5]. They could not find drugs better than the failed cytotoxic drugs and radiation to kill CCs to reduce the tumor size, and kept using the failed drugs to treat cancer patients. That was inexcusable. The consequence is as expected that cancer mortality keeps on escalating to remain the top Killer of the people of many Asian countries. CSCs became a known entity in 1997 [6]. The discovery of CSCs unraveled an important issue of cancer. It became evident that, although CSCs constituted only a small subpopulation, these cells were responsible for the initiation of tumor growth and the treatment failures [7-11]. Our studies on abnormal MEs [12-14], chemo-surveillance [15-17], CDA-2 [18-21], and wound healing [22-26] are closely related to CSCs, so we are in a unique position to offer the best solution of CSCs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [27]. We are clearly the winner to remove cancer as the top killer of the people of many Asian countries.

RESULT

Table 1: Chemo-surveillance Selectively Destroyed in Cancer Patients.

Plasma/Urine Ratios	CDA Level	Patient Number	% 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 (Unresponsive)	0.37	19	17.6

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

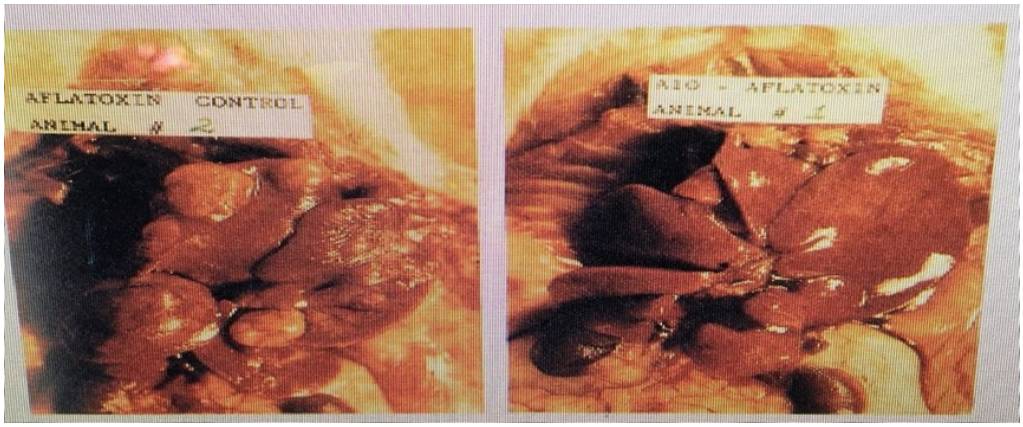

Figure 1: Phenylacetylglutamine as An Effective Chemo preventive Agent

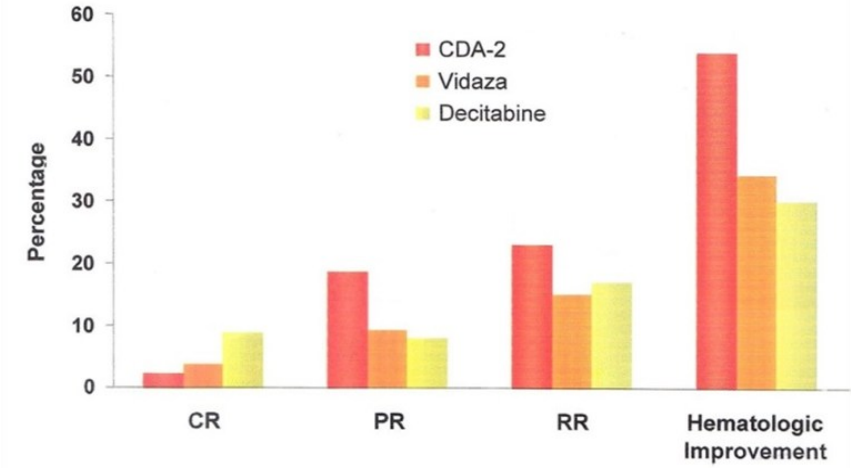

Figure 1: CDA-2 as the Best Drug for the Therapy of MDSs

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	32.0	40.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

Change Indication does not take as long as the approval of new drug for clinical application.

Table 3: Active DHIs

SAHH Inhibitor	**RI0.5 (μM)**	**STIs**	**RI0.5 (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
Dehydroepiandrosterone	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	**RI0.5 (μM)**	EGCG	0.62
Uroerithrin	1.9	Resveratrol	1.16
Hycanthone	2.1	Curcumin	1.24
Riboflavin	2.9	Kuromanin	1.43
MAT Inhibitors	**$RI_{0.5}$ (μM)**	Coumestrol	1.95
		Genisteine	2.19
		Pyriogallol	3.18
		Silibinin	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetyl valine	500	Ellagic Acid	4.45
Phenylacetyleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenyl butyric Acid	970	Phloroglucinol	38.82

COMMENTARIES AND DISCUSSION

Failure of Cytotoxic Agents to Reduce Cancer Mortality

Perpetual proliferation of CCs is the most outstanding symptom of cancer. Cancer establishments are trapped in belief that killing of CCs is the best strategy of cancer therapy. They knew cytotoxic agents were unable to put cancer away, because these agents failed to win the war on cancer during 1971-1976 of intensive effort to beat cancer [4]. They also knew that CSCs were responsible for the failure of cytotoxic agents to put cancer away. Approximately 18 years ago, the pharmaceutical giant GSK put up 14 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies against CSCs invented by scientists of Stanford University, which was not successful, because killing of CSCs was not an option to solve CSCs. Cancer establishments tend to rely on wrong approaches to solve important cancer issues. The pursuance of the cytotoxic agents for cancer therapy, the aberrant tRNA and DNA methylations, the anti-angiogenesis cancer therapy and the immunotherapy was all wrong to miss the most critical issues of abnormal MEs and CSCs to result in the failure to put cancer away [4]. The pursuance of gene therapy during 1976-1996 was a right approach, but they failed to develop a drug for gene therapy because it was too difficult to achieve. Anti-angiogenesis therapy devoted during 1996-2016 was a complete failure, because the successful therapy ended up causing the death of patients due to internal bleeding. Immunotherapy is the current effort after the failure of anti-angiogenesis attempt. It is a better version of the strategy based on cell killing, because it targeted on programmed death specific to CCs to spare the agony of excruciating adverse effects of cytotoxic agents. But immunotherapy has the same problem of cytotoxic therapy to show ineffectiveness against CSCs and to contribute to the damage of chemo-surveillance, which are the reasons to contribute to the failure of cytotoxic therapy. Immunotherapy may improve cancer mortality, but is unlikely to cut cancer mortality by half in 25 years requested by President Biden on his cancer moonshot initiative brought up in 2022 [28-30]. To effectively solve cancer, we must study how the problem of cancer arises and then to pursue solutions to eliminate the causes leading to cancer [31]. Since cancer evolved due to wound unhealing, solution of cancer according to wound healing process is the most appropriate strategy for cancer therapy [32-35]. This strategy offers therapy to target on abnormal MEs and CSCs which are the most important causes of cancer [36-47]. Drugs to target on the causes are always better than the drugs to focus on the elimination of cancer symptoms. Cytotoxic agents are primarily to eliminate cancer symptoms. CDA formulations are indeed the best cancer drugs to remove cancer as the top killer of the people of many Asian countries [36-47]. Unfortunately, drugs that can save cancer patients are blocked by cancer establishments. These drugs do not look like toxic drugs they prefer that can kill CCs to reduce tumor size. This is a difficult hurdle we have to overcome.

Chemo--surveillance Specifically 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 differentiation inducers (DIs) and differentiation helper inducers (DHIs), whereas cancer patients tended to show deficiency of such metabolites as shown in Table l, which is reproduced from the reference [15]. DIs are metabolites that can eliminate telomerase from abnormal MEs of cells expressing telomerase [12-14, 18, 37, 39]. Telomerase is a tumor factor to turn MEs into exceptionally stable and active enzymes to block differentiation, thus, enabling CCs to proliferate perpetually. Chemo-surveillance is the nature's creation as allosteric regulation on abnormal MEs to prevent the buildup of cells with abnormal MEs to become clinical symptoms such as tissue fibrosis, organ failure, dementia or cancer [40, 49]. DHIs are inhibitors of MEs that can greatly potentiate the activity of DIs [50-53]. Metabolites active as DIs and DHIs are also the active players of chemo-surveillance. DIs and DHIs are hydrophobic metabolites that can be retained by C18 from aqueous solution and recovered by organic solvent, namely a process of purification by reverse phase chromatography. Peptides share physical chemical properties similar to DIs and DHIs, thus, can be used as surrogate molecules to represent DIs and DHIs in the plasma and urine [54]. Peptides were initially purified from plasma after deproteinization with sulfosalicylic acid and from urine without deproteinization treatment by C18 cartridge, and recovered by elution with 80% methanol. After removal of the methanol solvent by lyophilization, the residue was dissolved in a small volume of water for HPLC resolution of peptide profiles on a column of

sulfonated polystyrene, and quantitative assay by Ninhydrin reaction. Results presented in Table 1 is a clear indication that chemo-surveillance that provides the protection of people from becoming cancer patients is selectively destroyed in cancer patients. Chemo-surveillance must be destroyed by inflammatory response for cancer to set in, and the progression of cancer, which by itself is a source of inflammation, further contribute to the destruction of chemo-surveillance. Cytotoxic agents are wrong drugs which create wounds to aggravate the damaged chemo-surveillance. The reduction of CDA level from 5.0 of the healthy people to 2.5 has reached a critical fatal threshold level. Above CDA 2.5, cancer patients may be responsive to the cytotoxic agents, relying on the restoration of chemo-surveillance to subdue surviving CSCs which are not responsive to cytotoxic agents [8-11]. Below CDA 2.5, the damage to chemo-surveillance is too extensive for the recovery to subdue surviving CSCs, cancer patients become unresponsive to cytotoxic treatments, or even still responsive to reach complete remission, these patients are eventually succumbed to the recurrence [41-45]. Cytotoxic therapies are actually responsible as the top killers of the people of many Asian countries. That practice must be stopped.

Antineoplastics were good cancer drugs to show effective therapy without adverse effects [54]. Patients responding favorably to Antineoplastics would show recovery of CDA level back to the healthy level 5. Those not responding favorably would continue to show decline of CDA level. CCs are known to express a high level of degradative enzymes to salvage substrates for the syntheses of macromolecules to support their fast growth. Antineoplastics are natural metabolites which may be degraded to lose activity. We recommend two sets of CDA formulations: one set CDA-CSC made by natural DIs and DHIs to get access to CSCs, and another set CDA-CC made by non-natural DIs and DHIs to resist degradation by fast growing CCs. Despite excellent therapeutic efficacy, Antineoplastics were banned by the cancer establishments around 1990, because these drugs were not the kind of drugs they liked to kill CCs and to reduce the tumor size. We were convinced that wound healing metabolites were good cancer drugs. We went to China in 1993 to develop CDA-2, which was a preparation of urinary wound healing metabolites employing XAD-16 as the adsorbent for the purification of wound healing metabolites. CDA-2 has a comparable activity to induce terminal differentiation of HL-60 cancer cells as Antineoplastic A5, although chemical compositions may not be the same. CDA-2 has been approved by the Chinese FDA as an adjuvant to cytotoxic agents for the therapy of breast, non-small cell lung cancer and primary hepatoma [20] and as a mono-therapeutic agent for the therapy of MDSs [55]. Evidently, wound healing is an important health issue, so that the nature creates chemo- surveillance and immuno-surveillance to ensure perfection of wound healing, chemo- surveillance to heal wounds arising from toxic chemicals and physical means, and immuno- surveillance to heal wounds arising from infectious agents. Chemo-surveillance and immuno-surveillance can act synergistically to heal wounds to prevent cancer from taking place. Our carcinogenesis studies support the concept of protection of chemo-surveillance to avoid cancer. During the challenges of animals with hepatocarcinogens, we noticed the appearance of numerous tiny hyperplastic nodules displaying abnormal MEs. These tiny hyperplastic nodules must represent the active wound healing by the proliferation of progenitor stems cells (PSCs), which are the primitive stem cells expressing abnormal MEs involved in the 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 unhealed tiny hyperplastic nodules [56]. If A10, namely phenylacetyl-glutamine, was provided during the challenges of animals with potent hepatocarcinogen aflatoxin B1, the appearance of carcinomas could be effectively prevented as shown in Figure 1, which is reproduced from the reference [57]. Phenylacetylglutamine is a major chemical composition of CDA-2. It is biologically inactive. However, it is effective to reverse excessive urinary excretion of low molecular metabolites [15]. By the protection of chemo-surveillance, phenylacetylglutamine is effective to prevent cancer even under the challenge with a potent carcinogen [57]. It appears that chemo-surveillance is an important protection mechanism created by the nature to ward off cancer. Chemicals such as phenylacetylglutamine that can effectively prevent cancer evolution under the challenge of potent carcinogens should be considered as the best cancer drugs. It is the wisdom of oriental medicine that stresses the importance of the drugs to prevent diseases and to target on the causes of diseases. Oriental medicine considers the drugs that can

prevent diseases from taking place as the best drugs and the drugs to target on the causes of diseases as the second-best drugs. The drugs focusing on the elimination of symptoms are ordinary drugs. We are seeking to develop the best and the second-best drugs to save cancer patients. Cancer establishments prefer ordinary cancer drugs that can make tumor to disappear. The ordinary cancer drugs they have developed so far are unable to save advanced cancer patients [2, 3] to result in cancer as the top killer of the people of many Asian countries.

Cancer Evolves Due to Wound Unhealing

The concept of cancer evolves due to wound unhealing was introduced by the great German pathologist Virchow in the 19th century [58]. It was again brought up by Dvorak in 1986 [59]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [60]. We provided the most important details on this subject that included abnormal MEs to promote perpetual proliferation of CCs by blocking differentiation [12-14]. Chemo-surveillance as the nature's creation of allosteric regulation on abnormal MEs to ensure perfection of wound healing to avoid cancer [15-17]; DIs and DHIs as wound healing metabolites and as the active players of chemo-surveillance [19, 50-53, 61-64]]; hypomethylation of nucleic acids as a critical mechanism of wound healing [65] and the evolution of cancer due to wound unhealing [22-26]. These studies very convincingly establish the validity of the concept that cancer evolves due to wound unhealing. Our carcinogenesis studies above described confirm the validity of this concept. Myelodysplastic syndromes (MDSs) are diseases to illustrate the evolution of cancer due to wound unhealing. MDSs often start with a display of immunological disorder, which prompts the production of inflammatory cytokines [66]. Among such cytokines, TNF is the critical factor related to the development of MDSs [67]. 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 and neutrophils. TNF is also named cachectin after its notorious effect to cause cachexia symptom, which is a symptom commonly shared by cancer and inflammatory patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites resulting in the collapse of chemo-surveillance as above described. TNF causes vascular hyperpermeability of blood vessels [68, 69] to result in the collapse of chemo-surveillance, leading to wound unhealing. PSCs are then forced to evolve into CSCs to escape contact inhibition, which is a mechanism to limit the extent that PSCs can proliferate. It takes a single hit to silence TET-1 enzyme to convert PSCs to become CSCs, that is easy for PSCs to accomplish because these cells are equipped with abnormally active MEs. The evolution of CSCs still cannot solve the problem, because the problem is the collapse of chemo- surveillance. CSCs are then forced to progress to faster growing CCs by the chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes, eventually pushing CSCs to become full blown CCs as acute myeloid leukemia. MDSs are diseases at the stage of CSCs. The propagating pathological cells have been identified as CSCs [70]. Therapy of MDSs requires the terminal differentiation of CSCs to become functional erythrocytes, platelets and neutrophils. Cytotoxic agents aimed to kill CSCs are not an option for the therapy of MDSs.

Vidaza, Decitabine and CDA-2 were the three drugs approved by the Chinese FDA for the therapy of MDSs. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs. Professor Ma, the Director of the Harbin Institute of Hematology and Oncology, was instrumental in conducting the clinical trials of all three MDSs drugs. According to his assessments, 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 the hematological improvement evaluation, meaning becoming independent on blood transfusion to stay alive, as shown in Figure 1, which is reproduced from the reference [55]. Inactivation of abnormal MEs of CSCs to achieve terminal differentiation of CSCs is the only option for the therapy of MDSs. CDA-2 achieve destabilization of abnormal MEs by the elimination of tumor factor telomerase [12-14], which is a selective pharmacological action on abnormal MEs, whereas Vidaza and decitabine inactivate MEs by covalent bond formation between methyltransferase (MT) and aza-cytosine incorporated into DNA [71], that is non-selective toward abnormal MEs. Thus, CDA-2 is free of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [72, 73], and very toxic to DNA [74-76]. Clearly CDA-2 is demonstrably the best drug for the therapy of MDSs to display superior

therapeutic efficacy and without adverse effects. Thus, we are in a position to remove cancer as the top killer of the people of many Asian countries.

Cancer is basically a problem of growth regulation going awry. Abnormal MEs and chromosomal abnormalities are most critically involved to mess up the growth regulation, abnormal MEs to block differentiation and chromosomal abnormalities to accelerate cell replication. Abnormal MEs play a pivotal role on the regulation of cell replication by virtue of the fact that DNA methylation controls the expression of tissue specific genes [77] and rRNA methylation controls the production of ribosome [78], which in turn controls the cell to initiate cell replication [79]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [80]. Because of this important role on the regulation of cell replication, MEs are subjected to exceptional allosteric regulation [40]. In telomerase expressing cells, MEs become associated with telomerase [14]. The association with telomerase changes the kinetic properties of MAT-SAHH isozyme pair and the regulation greatly in favor of cell growth [12-14]. Km of telomerase associated isozyme pair are 7-fold higher than the normal isozyme pair. The increased Km values suggest that telomeres expressing cells have a larger pool size of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). The larger pool sizes of AdoMet and AdoHcy are important for the growth of cells with abnormal MEs as the study of Prudova *et al* [81] indicated that association with AdoMet could stabilize protein against protease digestion, and the study of Chiva *et al.,* [82] indicated that when cancer cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly. Therefore, abnormal MEs are very critical for the promotion of the growth of cells with abnormal MEs.

Abnormal MEs are found in cells expressing telomerase. Embryonic cells express telomerase. 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 the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells during embryonic development of the fetus, but secedes when pluripotent stem cells undergoing lineage transition to reach unipotent stem cells. Abnormal MEs carry out functions important for the development of the fetus. Interruption of the function of abnormal MEs is harmful to the development of the fetus. Interruption of abnormal MEs by thalidomide results in malformation of limbs. Abnormal MEs do not cause problems of normal stem cells, because there are safety mechanisms such as contact inhibition, TET-1 enzyme and Chemo-surveillance to safeguard cells with abnormal MEs. If such safety mechanisms become dysfunctional, then clinical symptoms arise. Abnormal MEs are a far more important cause of cancer than chromosomal abnormalities [39]. Abnormal MEs happen very early at the beginning of life and shared by all cancers [12-14]. When the abnormality of MEs is solved, cells with abnormal MEs will exit cell cycle to undergo terminal differentiation to terminate malignant growth. That can also put to rest the problems arising from chromosomal abnormalities. 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 the replicating cells exist cell cycle to undergo terminal differentiation, abnormal oncogenes and suppressor genes have no roles to play. Thus, induction of terminal differentiation is an easy solution of chromosomal abnormalities, which are otherwise very difficult to solve. Cancer establishment devoted 20 years, 1976-1996, on gene therapy, but failed to come up a gene therapeutic drug. Of course, killing of CCs can also put to rest abnormal MEs and chromosomal abnormalities, that has been tried, but failed. Solution of abnormal MEs is the only hope to remove cancer as the top killer of humans.

Development of CDA Formulations

We have carried out extensive studies of natural and non-natural DIs and DHI for the manufacture of CDA formulations [18, 19, 50-53, 61-64]. Active DIs and DHIs are summarized in Table 2 and 3. ED25, 50, 75 of DIs and RI0.5 of DHIs are included to facilitate the manufacture of CDA formulations. RI0.5 of a DHI is equivalent to ED25 of a DI, which can be determined by the procedure presented in the reference [51]. DIs and DHIs can be excellent cancer drugs. ATRA is the standard care of acute promyelocytic leukemia [83]. 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 [84]. Therefore, only cancer cells expressing RAR can benefit from the treatment with ATRA. The rest of DIs presented in

Table 2 act directly on abnormal MEs. AA and its metabolites PGs are natural DIs involved in chemo-surveillance. BIBR1532 and boldine are non-natural DIs, which have been approved as telomerase inhibitors for cancer therapy PGs are also approved drugs to help delivery. Inhibitors of SAHH and MT are better DHIs than inhibitors of MAT. The stability of three MEs is related to the mass [48]. SAHH is the smallest enzyme of the three, which is also the most unstable enzyme of the three to require a steroid hormone as a stabilizing factor. SAHH has a high affinity to form dimer complex with MT. The MT-SAHH dimer has a mass similar to MAT. MAT is the largest enzyme of the three MEs, and is also the most stable enzyme. The association with telomerase further increases its stability. It takes large amounts of inhibitors of MAT to function as effective DHIs. Although pregnenolone is not the most active DHI of SAHH inhibitors. We consider it a valuable DHI. It is a major DHI of CDA-2 [19]. It is the master substrate of all biologically active steroids. It is a single metabolite to have profound influence on the development of cancer. According to Morley [85], the production of pregnenolone is bell shape with a peak production of around 50 mg daily at 20-25 years old. The youngest and the oldest people produce the least amounts of pregnenolone, and these two age groups are the most vulnerable to develop cancer. It is our top choice of DHI to make CDA-CSC formulations.

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 tends causes 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 [83]. The addition of SAHH or MT inhibitors can keep MT-SAHH intact to prevent modification of monomeric MT to become nuclease to disrupt differentiation process. It is a good idea to have both DIs and DHIs to make CDA formulations. The finding of signal transduction inhibitors (STIs) as excellent DHIs is expected, since signal transductions always lead to the production of factors to stabilize MEs. Therefore, STIs can function as DHIs. Gleevec is an excellent cancer drug. It is the standard care of chronic myeloid leukemia [84]. The finding of polyphenols as excellent DHIs is unexpected, but is a pleasant finding. Polyphenols are regarded as healthy foods. The finding of polyphenols as excellent DHIs increases their credibility as healthy foods. The manufacture of CDA formulations can be the following formula to reach plasma concentration as 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 [19]. We recommend to make two sets of CDA formulations: one set CDA-CSCs made by AA + pregnenolone to get access to CSCs, and another set CDA-CC made by BIBR + pyrvinium pamoate to resist enzymatic degradation of the active components. The application of phenylacetylglutamine is also recommended to prevent excessive excretion of low molecular weight metabolites often associated with cancer patients. The application of phenylacetyl- glutamine can be independently done with capsule, and monitor the effect independently by peptide assay as above described. A therapeutic endpoint of CDA formulations has to be established. These are all new endeavors. A lot of work remains to be done to overcome the difficult hurdles.

CONCLUSION

Cancer evolves due to wound unhealing. Cytotoxic agents creating wounds are contraindication of cancer therapy to result in cancer as the top killer of the people of many Asian countries for a very long time. CDA formulations healing wounds are the right cancer drugs to remove cancer as the top killer of the people of many Asian countries.

Recommendation

Eliminating DNA interacting drugs as cancer drugs.
Approval of CDA formulations as effective cancer drugs.
Establishing a simple test for chemo-surveillance.
Establishing therapeutic end point of CDA formulations.

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