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Combination Treatment with BEC and Cisplatin Synergistically Augments Anticancer Activity and Results in Increased Absolute Survival

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Abstract

Plant-derived BEC with its main component solamargine possesses anticancer activities via its effect on a variety of biological pathways in a wide range of human cancer cells. High cure rates with BEC therapy have been obtained in animals with deadly cancers, and, in humans with terminal cancers promising results have been reported. At a clinical level, optimal concentrations of BEC have been established in a topical cream formulation Curaderm, for effective removal of skin cancers, but optimal concentrations of BEC have not been reported for other cancers. The objective of this study was to determine whether combination therapy of Cisplatin with BEC would result in synergism using cure rates as end points. BEC on its own cures Sarcoma 180 in mice, whereas, Cisplatin on its own has no effect on Sarcoma 180 activity. A combination of BEC and Cisplatin shows synergism, resulting in higher cure rates than BEC and Cisplatin at comparable individual concentrations.

Keywords

BEC, Solamargine, Cisplatin, Curaderm, Anti-Cancer

1. Introduction

Cytotoxic chemotherapy remains one of the premier treatment options to combat cancer. However, the efficacy of chemotherapy is limited by the fact that not all tumors respond optimally. Single modality chemotherapy with existing drugs is rarely curative. In addition, drug-resistant tumor cells and cancer stem cells, that represent a small subpopulation of dormant cancer cells within numerous tumors, escape chemotherapy. For this reason, combination chemotherapy has become the standard treatment for advanced cancers. Evidence supporting the

benefit of combination chemotherapy is mixed. Despite some encouraging responses with combination chemotherapy, significant toxicities occur, and, there is no evidence of overall beneficial survival between these treatment strategies. Importantly, most anticancer drugs enter the market without evidence of benefit on survival or quality of life [1].

Most standard chemotherapies act on all rapidly dividing normal and cancer cells and were originally identified because they kill cells in general by a process known as indiscriminate cytotoxicity. Consequently, the currently used standard chemotherapies are indiscriminate and have low safety profiles.

Targeted therapies that induce apoptosis are currently the focus of much anticancer drug development. Targeted chemotherapy blocks the growth and spread of cancer by interacting with molecular targets that are involved in the pathways relevant to cancer growth, progression, and spread.

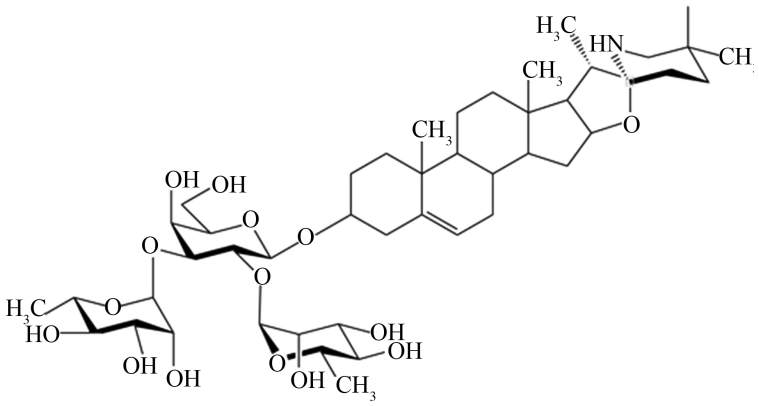
Our original reports on the plant genus *Solanum* showed that BEC steroidal glycoalkaloids, in particular, solamargine and solasonine have anticancer properties [2]-[7].

Since then, a plethora of further investigations has taken place resulting in the placement of BEC or its individual components as very promising antineoplastic agents with vast potential to serve as targeted anticancer agents.

The main components of BEC are solamargine and solasonine together with minor components that consist of mono- and di-glycosides of solasodine [3] [8].

It was previously shown that in BEC, solamargine accounts for 86% antineoplastic activity and solasonine accounts for 9% antineoplastic activity, whereas, the mono- and di-glycosides of solasodine only contribute 5% of anticancer activity. Furthermore, the anticancer activity of these glycoalkaloids is considered to be concerted and additive [9].

Figure 1 illustrates the chemical structure of solamargine, the main active antineoplastic agent in BEC.



Solamargine

Figure 1. Chemical structure of solamargine (22 R, 25 R)-spiro-5-ene-3 β-yl-α-L-rhamnopyranosyl-(1- > 2 glu)-O-α-L-rhamnosyl-(1- > 4 glu)-β-D-glucopyranose. On average, solamargine is 9 and 19 times more effective against cancer than solasonine and mono-and di-glycosides of solasodine respectively.

BEC targets specific mutant (altered) proteins on cancer cell membranes that act as receptors. After binding to these characterised specific receptors [6]-[14], BEC is internalised into the cancer cell by receptor-mediated endocytosis followed by the anticancer sequelae of identifiable anticancer properties on a variety of biological pathways including cell survival pathways [8] [12] [14] [15], tumor suppressor pathways [8] [12] [14] [16], lysosomal pathways [8] [12] [14] [17], mitochondrial pathways [8] [12] [14] [18], caspase activation pathways [8] [12] [14] [19], death receptor pathways [8] [12] [14] [20], protein kinase pathways [8] [12] [14] [21], and signal pathways that impede invasion/migration [8] [22] and multi-drug resistance [8] [23].

BEC exhibits much higher cytotoxic effects on cancer cells when compared with a number of currently used antineoplastic agents such as vinblastine, vincristine, camptothecin, methotrexate, cisplatin, 5-fluorouracil, gemcitabine, epirubicin, cyclophosphamide, taxol and doxorubicin [24].

Furthermore, the absolute concentrations of these drugs to obtain comparable efficacy as BEC are in the order of 6 - 40 times higher [25].

Moreover, the therapeutic index (TI; also referred to as the therapeutic ratio) is much higher for BEC compared with other antineoplastics as shown with cell culture studies [26] and whole animal studies [27]. The high TI of BEC translates to high safety margins.

BEC has been shown to be active against a wide variety of cancer cells, such as ovarian cancer [28], basal cell carcinoma [29], squamous cell carcinoma [30], melanoma [31], colorectal cancer [32], bladder cancer [33], oral epidermoid carcinoma [34], breast cancer [35], myelogenous leukemia [36], prostate cancer [37], liver cancer [38], lung cancer [39], pancreatic cancer [40], gastric carcinoma [21], renal cancer [29], uterine cancer [28], mesothelioma [41], glioblastoma [42] and osteosarcoma [16].

In addition, BEC has shown to cure animals from terminal cancers [2] [7] and to eradicate skin cancers in humans [43]-[62].

The pharmacodynamics of BEC entailing specificity, efficacy, multidrug resistance, anti-metastasis and immunological effects, together with the pharmacokinetics of BEC in animals and in humans showing safety profiles, render BEC as a very promising antineoplastic agent [8] [25] [63] [64] [65] [66].

Indeed, BEC in a cream formulation Curaderm, has been approved as a topical application for the treatment of human skin cancers with curative and amazing cosmetic outcomes [43]-[62].

Although BEC, as monotherapy is very promising, its full potential is not yet realised. With the increased frequency of cancer and lack of clinical efficacy of many currently used anti-cancer drugs, novel combination treatments are sought. BEC provides an ideal entity for such studies.

The present study seeks to identify if chemotherapeutic agents, widely used in clinical settings, can be used in combination with BEC to produce an advantageous synergistic therapeutic effect. In particular, the synergistic effect of BEC together with Cisplatin is investigated using the Sarcoma 180 murine module,

whereby, a curative survival of the treated animal is the endpoint.

2. Material and Methods

2.1. Mice

Herston Whites were obtained from the Medical School, University of Queensland, Australia. Male and female mice of body weight of approximately 30 g and aged 8 - 10 weeks were randomly selected and served as recipients. Twelve mice were randomly chosen for each experimental group.

2.2. Tumor

The tumor was Sarcoma 180. It was established in the ascitic fluid of Herston Whites in 1969 at the Medical School as above, and was passaged by *i.p.* transplantation.

Sarcoma 180 cells were maintained in an ascitic form by serial transplantation every 13 days in the Herston White mice. Tumor cells (5×10^5) inoculated *i.p.* caused a mortality of 100 percent with a median survival time of 21 days in the control groups.

2.3. Drugs and Treatment Schedules

BEC was extracted from the fruit of *S. sodomaeum* essentially as described earlier [3].

In the present studies, the extract BEC containing the mixture of glycoalkaloids was investigated. A solution of 0.5 g BEC/100mL dimethyl sulfoxide (DMSO) was used.

BEC in DMSO, now referred to as BEC01, was administered *i.p.* at a concentration of 8 mg/kg animal weight. The dose of BEC01 ranged from 44.7 - 51.2 microliters of BEC01 for mice ranging from 28 - 32 g in body weight, resulting in a dose of 8 mg BEC/kg animal weight. The dose of BEC01 was given 0.5 h after administration of the Sarcoma 180 tumor cells as previously described [2]. Single doses of BEC were given on two consecutive days.

***Corynebacterium parvum* (*CP*)**

As a positive control, a killed vaccine of these bacteria (Wellcome Foundation, Sydney, Australia) was used. Thirty microliters aliquots of the suspension (7 mg/ml, dry weight) were injected *i.p.* in mice. Mice were treated *i.p.* with a single dose of *CP*, 0.5 h after tumor implantation.

2.4. Cisplatin

Cisplatin was obtained from Sigma-Aldrich, St. Louis, MO. A solution of Cisplatin at 30 mg/100mL saline was used. In the studies with Cisplatin, two doses were used. A low dose (LD) of 1.5 mg Cisplatin/kg, and high dose (HD) of 3.0 mg Cisplatin/kg animal weight were administered *i.p.* The doses of Cisplatin ranged from 140 - 320 microliters of Cisplatin solution for mice ranging from 28 - 32 g in body weight. This translates to doses of 1.5 and 3.0 mg Cisplatin/kg

animal weight. The doses of Cisplatin were given 0.5 h after administration of the Sarcoma 180 tumor cells. Single doses of low dose (LD) and high dose (HD) Cisplatin were given on two consecutive days.

The experimental protocol was approved by the Ethics Committee and the care of the animals was in accordance with the ethical standards of the University of Queensland.

2.5. Statistical Analyses

Data are expressed as means ± SD. Differences between the various groups were performed using Student's t-test. Two-tailed p value is significant when $p < 0.05$.

3. Results

Eight groups of animals were investigated. Data reported in Table 1 and partly in Figure 2 indicate that DMSO and Saline had no effects on the activity of Sarcoma 180 ($p > 0.7035$). For clarity, no graphs of the effects of DMSO and Saline were incorporated in Figure 2 since they were similar to the controls. Mice inoculated with 5×10^5 Sarcoma 180 cells alone, or Sarcoma 180 cells and 0.5h later with DMSO or Saline generally died in 2 - 3 weeks.

Administration of LD Cisplatin into Sarcoma 180 containing mice resulted in slightly increased survival time but was statistically not significant ($p = 0.1718$) and at day 25 all the mice had died. High dose of Cisplatin into Sarcoma 180 containing mice resulted in longer survival time, which was statistically significant ($p = 0.0061$) compared with untreated Sarcoma 180 containing mice. However, all the mice died at day 35 and there was no difference in complete survival when compared with untreated control animals infected with Sarcoma 180 cells. There was no statistical difference when the effects of LD and HD Cisplatin were compared ($p = 0.1431$).

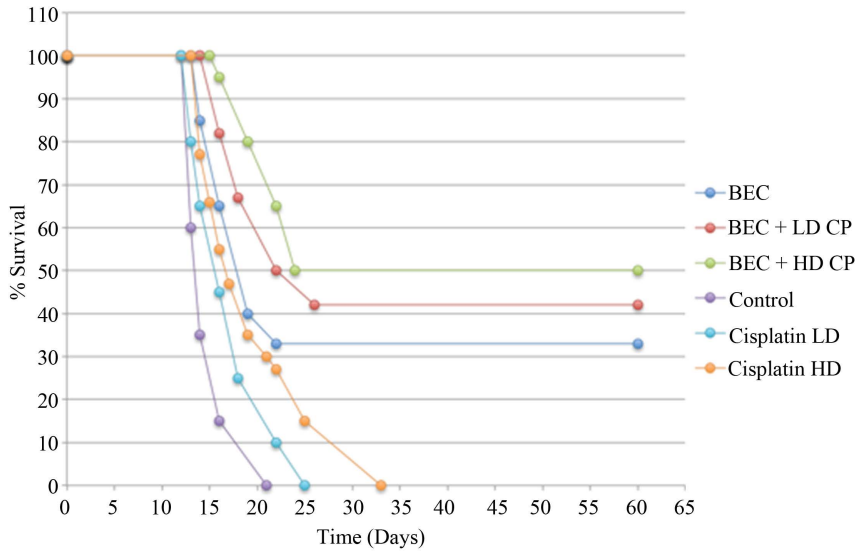


Figure 2. Effects of various compounds, single or in combination, on mouse survival with Sarcoma 180.

Table 1. Effects of tested compounds on the survival time of mice bearing Sarcoma 180.

Compound	Dose (mg)	Number doses[b]	Survival time[a]		Animals survived[d] Treated
			Days	% T/C[c]	
-	-	-	21.0 ± 6.1	-	0/12
DMSO	1.6	2	20.2 ± 3.8	96	0/12
SALINE	10	2	21.4 ± 3.4	102	0/12
BEC01	8	2	48.2 ± 7.1	230	4/12
C.parvum	8	1	42.6 ± 18.2	203	5/12
Cisplatin (LD)	1.5	2	25.2 ± 8.3	120	0/12
Cisplatin (HD)	3.0	2	30.6 ± 9.1	146	0/12
BEC01 + Cisplatin (LD)		2	42.1 ± 10.3	200	5/12
BEC01 + Cisplatin (HD)		2	56.3 ± 10.9	268	6/12

Each value is the mean ± SD obtained in groups of twelve tumor-bearing mice treated *i.p.* 0.5 h after tumor implantation (5×10^5 cells/mouse). [a]The criterion of complete survival was taken as 56 days because it was shown that if treatment was effective against Sarcoma 180 for this period, the mice then had a normal life span (approximately 3 years). [b]Doses given on consecutive days. [c]% T/C is the ratio of the average of each treated group to controls expressed as a percentage. [d]Animals surviving after eight weeks.

The immunotherapeutic agent *C. parvum* resulted in 58% inhibition of Sarcoma 180 with a complete survival rate of 42%, whereas, BEC01 inhibited Sarcoma 180 activity resulting in 33% complete survival. The criterion of complete survival was taken as 56 days because it was shown that if the treatment was effective against Sarcoma 180 for this period, the mice then had a normal life expectancy which was approximately 3 years.

Administration of BEC01 together with LD Cisplatin resulted in increased survival time and complete survival, but the increased survival time and complete survival were not significantly ($p = 0.1053$) different from treatment with BEC01 alone. BEC01 together with HD Cisplatin showed greater increases in survival time and complete survival. These survival parameters were significantly different compared to treatment with BEC01 alone ($p = 0.0422$) or HD Cisplatin alone ($p < 0.0001$).

4. Discussion

It is accepted that cancer cells can outsmart chemotherapy. The challenge is how to outmanoeuvre the cancer cells that have outsmarted chemotherapy. The answer may be revealed by studying cancer not only at a cellular level but, more so, at a molecular level. For example, there are various mechanistic molecular pathways that result in multi-drug resistance, a hallmark of failure with chemotherapy. There are many other identifiable, and to date, unidentifiable molecular mechanisms that result in failure of cancer treatment, either directly or as a consequence of increased toxicity.

Plant-derived compounds such as BEC have a high impact as therapeutic agents both alone and in combination with conventional drugs.

Previous studies have shown that single doses of BEC are effective against Sarcoma 180 in mice with an ED_{50} of 9 mg/kg and LD_{50} of 30 mg/kg, resulting in a therapeutic index of 3.3 [2] [4].

Cell culture studies with various human cancer cells and human normal cells result in similar therapeutic indexes [12] [14].

Single administrations of 8 mg BEC/kg on two consecutive days resulted in longer survival time and complete survival for 40% of the animals [2].

In the current studies 33% complete survival was obtained confirming the previous observations. The conditions to obtain a value of approximately 40% survival with BEC treatment was considered appropriate to establish whether a combined therapy of BEC and Cisplatin would result in possible potentiation, additive efficacy, synergism or antagonism. This condition was met with 2 doses of BEC at 8 mg/kg.

The immunotherapeutic agent *C. parvum* resulted in inhibition of Sarcoma 180 activity confirming other studies [2].

The extent of the impressive efficacy of BEC was shown in previous studies with the administration of three and four doses of BEC at 8 mg/kg resulting in greater than 90% complete survival [2], also, mice which are in their terminal stage with Sarcoma 180 were shown to tolerate and become symptom-free of cancer by single dose administration of BEC at concentrations of BEC three times the LD_{100} for normal mice, highlighting the selectivity and low toxicity of BEC towards cancer cells [7].

Synergy is a process in which some substances cooperate to reach a combined effect that is greater than the sum of their separate effects.

Data presented in this communication using two different concentrations of Cisplatin in combination with BEC show that there is synergism.

The mode of action of the synergy with the combination therapy of BEC and Cisplatin may impact on different targets of the cancer cell, and centers around the mechanisms by which the emergence and progression of the particular cancer exists. For example, it is known that BEC has a positive effect on drug resistant cancer cells by antagonising the development of drug resistance [8].

Cisplatin is widely used for the treatment of testicular, bladder, head and neck, small-cell and non-small cell lung cancers, but it also possesses substantial side effects such as neuro-, nephro-, and myelo toxicities. Cisplatin exerts its indiscriminate toxicity by DNA binding and downstream apoptotic signalling. Resistance of Cisplatin therapy is achievable by reducing apoptotic signalling, up-regulating DNA damage repair mechanisms, altering cell cycle checkpoints, and disrupting assembly of the cytoskeleton. Whether BEC has an effect on any of the above causes that may result in the synergism with Cisplatin is currently unknown.

It has been previously proposed that Cisplatin may serve as an effective combination regimen with BEC, especially in Cisplatin resistant breast cancer and lung cancer cells [35] [39].

It is important to appreciate that previously reported observed synergistic effects on cancer with the combination of BEC and Cisplatin entail in vitro cell culture studies. *Ex-vivo* synergistic anticancer effects of BEC when tested in combination with other chemotherapeutic agents with nuclear mechanism of action have been reported with a number of cancers [67].

The current studies show in whole in vivo animal studies that combination of BEC with Cisplatin not only increases life expectancy but very importantly, also cures cancer-affected animals.

In the current studies it was necessary to dissolve the BEC in DMSO for the *i.p.* administration of BEC. Recent studies have shown that DMSO adversely affects the antineoplastic effects of Cisplatin [68].

In the groups of animals that were studied with the combination of Cisplatin and BEC, Cisplatin would have been exposed to DMSO. However, the amount of DMSO in the peritoneal cavity was very small and unlikely would pose inhibitory effects on the activity of Cisplatin. Furthermore, in the event that Cisplatin would have been negatively affected by DMSO, this would mean that the observed synergistic effects of the combination therapy would likely result in increased synergism.

The limitation of this study is that the combination of the mixture of BEC and Cisplatin to obtain maximal synergism has not been determined in the current study and warrants further investigation. It would be interesting to study other antineoplastic agents in combination with BEC using cure rates of cancer as the outcomes.

5. Conclusion

Compelling evidence that BEC possesses vital antineoplastic activities by expressing unique modes of action with low toxicity in cell culture, animals, and humans puts this compound in a special class. Synergisms of BEC and conventional chemotherapeutics exist in human cancer cell culture. Now it can be added that in animal studies with deadly cancer, complete survival resulting in cure rates is achievable with BEC therapy and that the cure rates are improved by the action of synergism of BEC with Cisplatin.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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