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Research Article

Effect of Salvestrol as an Adjunct in the Treatment of Head & Neck, GIT, Ovary, Breast and Lung Malignancies Undergoing Conventional Treatment in an Indian Population

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Abstract

Background: Previous studies have elucidated that Salvestrols are a class of phytonutrients that, function through an extremely targeted mechanism that hinges on their metabolism by the universal cancer marker CYP1B1, causing cell apoptosis. Unfortunately, modern-day cultivation practices have severely limited the obtainability of these specific phytonutrients in the modern food regime. These phytonutrients are all phytoalexins and are not induced in abundance until the plants are exposed to predation or infection as a part of their defense mechanism. Hence this investigation aims to study the effect of Salvestrol as an adjunct to routine cancer therapy on five different types of malignancies and to assess its impact on survival and quality of life has been studied.

Patients and methods: This are a two-arm study comprising of a cohort of 102 patients having cancers of the head and neck, lung, ovary, breast, and GIT. The patients in both the arms were randomized to receiving chemotherapy, radiotherapy and surgery or in combination. The test group received the above along with Salvestrol (6000 salvestrol units as leader dose for 1 month followed by maintenance 4000 salvestrol units till death or discontinuation). The control arm received the same treatment as the test arm minus the salvestrol. Vitamin C and B complex was given to both groups.

Results: The mean overall survival in the head and neck cancer salvestrol arm was 15.91 ±10.73 months and that of the controls was 8.0 ± 5.83 months, which was statistically significant (P=0.0441). The mean overall survival in the lung cancer salvestrol arm was 8.708 ± 9.006 months and in the controls was 2.292 ±1.484 months, which was statistically significant (p=0.0234). The mean overall survival in the GIT salvestrol arm was 10.000 ± 10.317 months and that in the control arm was 3.550 ± 3.700 months which was statistically significant (p=0.0792). The mean survival in the ovary salvestrol arm was 17.63 ± 7.19 months and in the control, the arm was 6.63 ± 7.56, which is very statistically significant (p=0.0099). The mean survival in the breast salvestrol arm was 21.80 ± 6.96 months and that of the control group was 22.10 ± 4.01 months (p=0.9073), which was statistically insignificant.The overall survival among the

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salvestrolpatients was 14.480 ± 10.036 months as compared to 8.333 ± 8.507 months in the control arm (p=0.0012). The mean ECOG score was 1.12 ± 0.773 in the salvestrol arm (n=60) and 1.58 ± 0.8593 in the control arm (n=60), which was statically significant (p=.00591). The HAM-A scores were 2.4314 ± 2.9138 in the salvestrol arm (n=60) and 3.0612 ± 3.4666 in the control arm (n=60), which was statically insignificant (p=0.97). The mean PGSGA scores in the salvestrol arm (n=60) were 6.4688 ± 2.8959 and that in the control arm (n=60) was 7.625 ± 5.7291, which was also statistically insignificant (p=.312209).

Conclusion: To date, there have been a case or series of reports on the efficacy of salvestrols in cancer. No randomized control trial has been undertaken with conventional treatment and salvestrol. Hence it was imperative to study the role of salvestrol in a randomized controlled fashion. This study was designed to compare the survival of 102 patients with five types of cancer by adding salvestrol in the prescribed treatment regime to one arm. As the results of the study showed improved overall survival in cancers of the head and neck, lung, GIT and ovary, it may consider that salvestrols have played a role in survival, as both groups, received the same TNM based treatment. Salvestrols improved ECOG scores but not HAM –A or PGSGA. The use of salvestrol as an adjunct to surgery, radiotherapy and chemotherapy in GIT, lung, Head & neck and ovarian malignancies may prolong the overall survival and improve the ECOG status. CYP1B1 pathways and salvestrol were found to be promising solutions to improve cancer treatment with no added side effects or toxicity. Larger randomized studies are required to further confirm the role of salvestrols.

Keywords: Salvestrol, CYP1B1, polyphenol, phytoestrogen, Cytochrome P450, Diet and Stress, Piceatannol, Chemotherapy, Surgery, Radiation.

Introduction

Salvestrols are specific common food-based compounds that act as natural cancer-specific nutritional rescue mechanisms against cancer cells, identified and outlined by Gerry Potter in 2002 [1,2]. The rescue mechanism hinged on the metabolic activity of a certain cytochrome P450 enzyme, CYP1B1 [3,4]. Importantly, this enzyme was found to be expressed by all cancers, regardless of oncogenic origin, while being absent from healthy tissue [5-7. It is now widely regarded as a universal cancer marker [8]. When Salvestrols are metabolized by CYP1B1, they create compounds that cause apoptosis of the cancer cell. In this way, Salvestrols operate as natural prodrugs, completely targeted to killing diseased cancer cells without any toxicity to normal cells. This CYP1B1 mechanism could operate prophylactically killing microscopic cancer cells after mutation or gross tumors in a therapeutic setting.

Each salvestrol capsule (approximately 450 mg) is a proprietary blend of Citrus, Pumpkin (Cucurbita maxima), and Grape Seed (Vitis vinifera) and many other compounds in various proportions depending on availability. Unlike drugs, they are not measured in milligrams but rather points. Salvestrol points indicate the potency of the molecule [9]. Salvestrols are synthesized by the plants as a part of a defense mechanism and are harmless to humans.

Salvestrols operate as natural prodrugs, completely targeted to kill cancer cells causing no harm to normal cells[10]Pineatannol, which is stilbene plant extract, is also known to have tyrosine kinase inhibitory activity [11].

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Piceatannol (3,4,3', 5'-tetrahydroxy-trans-stilbene) is a naturally occurring protein-tyrosine kinase inhibitor [12]), including the MAP kinases [13] involved in cell proliferation. It is also known that resveratrol (similar to salvestrol) is converted to the anticancer agent piceatannol by cytochrome P450 family. The only difference between the stilbenes and piceatannol is the addition of a hydroxyl group in one of its aromatic rings. CYP1B1 enzyme in turn belongs to the cytochrome P450 family [14]. According to the analysis by the Institute of health metrics and Evaluation, Washington (Indian express Sunday 28th February 2021) India is ranked tenth at 106.6 new cancer cases in 2016 per 1,00,000.

The study aimed to determine the positive effect of salvestrol; a nutritional approach to the already existing conventional treatment of cancer patients could provide added benefits. The toxins produced through the metabolism of Salvestrols by CYP1B1 are reported to be confined to the cancer cells and are exhausted through the destruction of the cell. This natural defense mechanism of salvestrol could have beneficial effects on the patients by being non-toxic. These substances can give new hope to cancer patients by initiating a cascade of events, which can have extremely positive effects on the human body.

Patients and Methods

The study was done in a regional cancer center (MNJIO & RCC, Hyderabad-Telangana –India) where the patients were presented in locally advanced or metastatic malignancies were chosen as they formed the bulk of outpatient in our regional cancer center (Head and Neck, GIT, Lung, Ovary and Breast). A cohort of 102 patients with biopsy-confirmed malignancies was selected for the study. All patients were enrolled after obtaining written informed consent and the approval of the institutional ethics committee. Most of the patients had either locally advanced or metastatic disease.

Inclusion criteria

1. Biopsy confirmed Head & Neck, GIT, Ovary, breast and lung malignancies.
2. Only recently diagnosed patients were included
3. Age group from 18-70 years
4. ECOG performance status 0 -2.
5. Patients must receive surgery, radiation, chemotherapy or all as the standard management of cancer.
6. Cancer from stage I to IV.

Exclusion criteria

1. Patients who have received prior chemotherapy or radiotherapy
2. Patients with prior malignancy
3. ECOG 3 and 4 were excluded.

Methods

The test medication contained Salvestrol weighing 280mg of extract, which is equivalent to 2000 points (Salvestrol units). Salvestrol treatment commenced in the treatment arm with a leader dose of 6000 points in three divided doses per day for

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the first month, followed by 4000 points in two divided doses till study completion or death. The doses were administered on an empty stomach on waking and just before going to bed. Both cohorts were administered a single daily dose of 500mg of Vitamin C, biotin and cofactor Q10 which are required for the better absorption of salvestrols. The above three were supplemented with a standard formula of commercially available B-Complex containing the requisite RDA. The study commenced in November 2014 and ended in July 2016 (21 months). The control arm received a combination of surgery, radiotherapy and chemotherapy according to TNM status. The Salvestrol arm received the same above-mentioned treatment along with Salvestrol. All patients had a complete staging workup including imaging, histological or cytological confirmation, tumor markers, biochemistry and hematological tests. The lesions sizes were recorded both clinically and radiologically, both initially and after 3 months of completion of treatment. The endpoints of the study were overall survival, quality of life and ECOG status. The ECOG status was recorded at the time of inclusion/randomization, end of treatment, every follow-up visit and end of the study. An overall ECOG score was created for every patient by averaging all the ECOG values hence making him or her comparable. The Quality of Life (QOL) was analyzed using HAM-A scale and the PGSGA scale. These two parameters were also assessed at the time of inclusion/randomization, end of treatment and follow-up visits. Higher HAM-A and PGSDA scores indicated more stress and lesser scores indicating better QOL.

Randomization

The process of randomization was done in the outpatient department of MNJIO & RCC, Hyderabad. Suitable patients were selected from the outpatient and randomized first to the salvestrol arm. The controls were selected from the same outpatient within one month. All were staged on TNM basis radiologically and clinically. The controls were matched for TNM stage age and ECOG status. Gender matching was not done. The process of randomization began in November 2014 and ended in February 2015. RECIST 1.1analysis could not be attempted as all patients had advanced disease with short expected survival. Both groups received similar treatment regimens. The duration and intensity of therapy varied according to tolerance and dropout rates.

Results

Head & neck group

Twenty-two patients with advanced and inoperable head and neck malignancies were randomized into 2 sets of 11 patients. All had squamous cell histopathology. This included: Buccal Mucosa (8/22-36.3%), tongue (8/22-36.3%), the floor of mouth (1/22-4.5%), hypopharynx (4/22 - 18.1%) and hard palate (1/22-4.5%) matched for anatomically and for TNM.

Four patients underwent surgery followed by adjuvant radiotherapy without chemotherapy. Eighteen received radical chemoradiation for inoperable disease with concurrent chemotherapy @ 50mg/week. The prescribed dose of radiation was 66Gy @ 2Gy/day for all the patients.The mean dose of radiation received by the control

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group was 56Gy ± 13.89 and for the salvestrol, arm was 59.45Gy ± 17.09, which was not statistically significant (P=0.6086). 2 patients in the control arm discontinued treatment due to toxicity. The mean dose of weekly cisplatin was90.91 ± 86.08 mg in the salvestrol arm versus 95.45 ± 108.29 mg in the control arm, which was not statistically significant (P=0.9143). The mean age in the salvestrol arm was 48.36 ± 16.39 years and in the control,the group was 53.55 ± 8.81 years, which was not statistically significant (P=0.3668). The mean survival in the salvestrol arm was 15.91 ±10.73 months versus that in controls was 8.0 ± 5.83 months, which was statistically significant (P=0.0441) (Figure 1A)(Table 1) (Represented by Kaplan Meier curve). At the end of 36 months of follow up 4 patients in the salvestrol arm were still alive. All controls were dead by 19 months. The mean ECOG score for the salvestrol arm was 1.318 ± 0.717 and the control arm was 1.182 ± 0.603 which was statistically insignificant (P=0.6344). The mean HAM –A score in the salvestrol arm was 1.91 ± 2.26 and in the control arm was 4.27 ± 3.13, which was not significant (p=0.0558). Similarly, the PG-SGA scale in the salvestrol arm was 7.00 ± 2.90 and that in the control arm was 8.45 ± 3.62, which was also insignificant (p=0.3103).

Table 1: Overall Survival Data in months along with mean and standard deviation.

S. No.	Head and Neck		GI		Lung		Breast		Ovary	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
1	3	13	29	2	4	0.5	24	24	7	1
2	28	1	28	0.5	16	4	24	15	13	6
3	30	2	5	5	7	2	2	24	24	2
4	21	9	9	4	2	1	24	14	15	4
5	5	11	4	1	1	3	24	24	24	9
6	6	5	13	13	2	1	24	24	24	24
7	27	10	5	1	0.5	5	24	24	10	6
8	5	2	3	5	4	3	24	22	24	1
9	19	19	2	2	22	1	24	24	0	0
10	4	13	2	2	2	1	24	24	0	0
11	24	3	0	0	22	4	0	0	0	0
12	0	0	0	0	22	2	0	0	0	0
Total mean ±SD	15.90±10.22	8±5.55	10±9.78	3.55±3.51	8.70±8.62	2.29±1.42	21.8±6.6	21.9±3.75	17.62±6.72	6.62±7.06

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Lung group

This group constituted 24 patients with inoperable stage IIIA/IIIB/IV lung cancer with 12 in each arm. 12/22(54.6% had stage IV disease requiring palliative local radiation ± chemotherapy. Among them, 6/22 (27.2%) had bone metastasis, and 6/22 (27.2%) had malignant effusion and 2/22 (9%) had brain metastasis. 10/22 (45.4%) had stage IIIA/IIIB lung cancer. All 24 patients were equally matched for stage and metastatic status. Those having brain and bone metastasis received palliative radiation of 30 Gy/10#. All stage 4 patients received chemotherapy with cisplatin @ 75mg/m2 (D1) and etoposide 120mg/m2 (D1, D2, D3). Zoledronic acid 4mg was added for those who had bone metastasis. IIIA/IIIB were treated with radical radiation @ 66Gy/33# without chemotherapy.

The mean age in the salvestrol arm was 57.92 ±12.36 and in the control arm was 57.50 ±10.10, which was not statistically significant (p=0.9288). The mean survival in the slavestrol arm was 8.708 ± 9.006 months and in the controls was 2.292 ±1.484 months which was statistically significant (p=0.0234) (Figure 1B)(Table 1) (Represented by Kaplan Meier curve). Three patients in the salvestrol arm were alive 12 months after the conclusion of the study. All the patients in the control arm expired within the 5th month.

The mean cycles of chemotherapy received by the stage 4 patients in the salvestrol arm was 2.167 ± 1.946 and that in the control arm was 2.292 ± 1.484, which was not statistically significant (p=0.8612) The mean ECOG performance status in the salvestrol arm was1.167 ±0.389 and that in the control arm was 1.542 ± 1.033 which was not statistically significant (p=0.2517). The mean HAM-A scores in the salvestrol arm were 4.75 ± 4.11 and that in the control arm was 4.25 ± 2.63, which was not statistically significant (p=0.7263). The mean PGSGA scores in the salvestrol arm were 5.92 ± 1.88 and that in the control arm was9.00 ± 3.13, which was statistically significant (p=0.0079).

Figure 1: Represents survival data of various groups (1A: H&N, 1B: Lung, 1C: Gastrointestinal tract, 1D: Ovary, 1E: Breast). (A) Survival data of Head and neck group in months. The hazard rates differ z=2.24, p=0.0252 (Confidence levels 95%). (B) Survival data of Lung group in months. The hazard rates differ z=2.25, p=0.0242 (Confidence levels 95%).(C) Survival data of Gastrointestinal track in months. The hazard rates differ z=1.89, p=0.059 (Confidence levels 95%). (D) Survival data of Ovary group in months. The hazard rates differ z=2.55, p=0.0106 (Confidence levels 95%). (E) Survival data of Breast group in months. The hazard rates differ z=0.55, p=0.58 (Confidence levels 95%).

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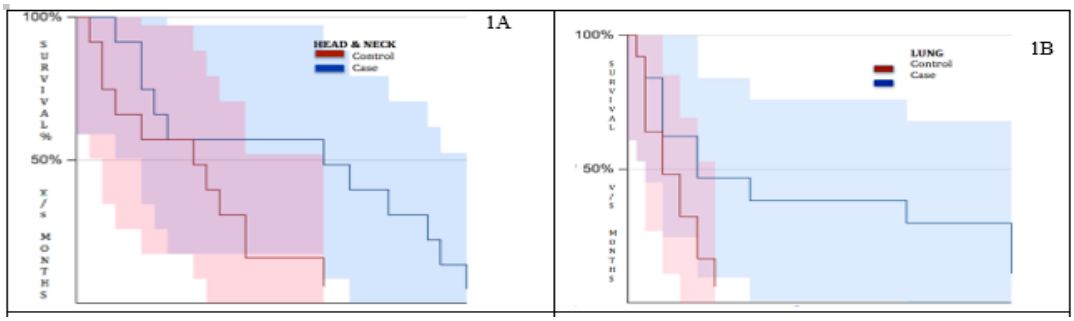

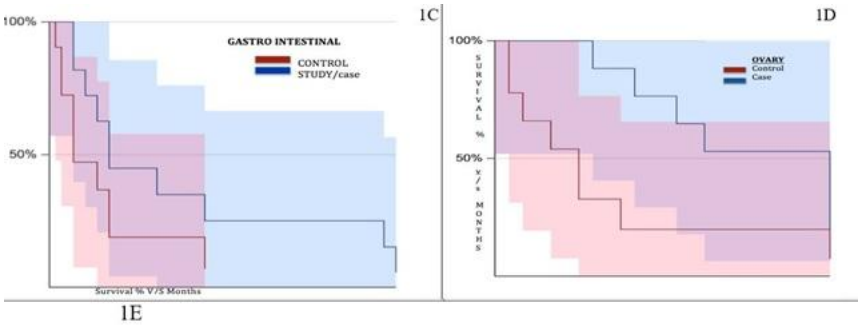

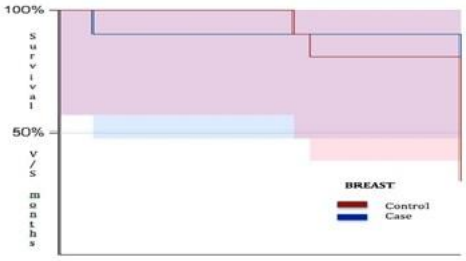

GIT

A total 20 patients were recruited with 10 patients randomized to each arm (Table 1). 8 (40%) had Ca stomach, 8 (40%) had colorectal and 4 (20%) had esophageal cancers.

Ca esophagus patients were inoperable and treated with radical radiation. Among the 4 patients, 2 received 40Gy one received 60Gy and one received the best supportive care. The average survival in the esophagus was 4 months in the Salvestrol group and 3 months in controls. The 8 patients with ca stomach received palliative radiation @ 40Gy/20#, followed by chemotherapy with Mc Donald's regimen (Ca Leucovorin @ 20mg/m2 day 1 to 5 and 5FU @ 425mg/m2 day 1 to 5). 8 patients with ca rectum received palliative radiation @ 50Gy/25# followed by chemotherapy with Mc Donald's regimen. The majority of the patients could not complete the entire course of prescribed radiation or chemotherapy due to deterioration of the ECOG status. The mean dose of radiation received by the Salvestrol group was 31.70 ± 23.92 Gy and that received by the control

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group was 24.80 ± 22.69 Gy was not statistically different (p=0.5164). The mean number of cycles of Mc Donald's regime in the Salvestrol arm was 2.78 ± 1.86 and that received by the control arm was 2.80 ±2.39 cycles, which was not statistically significant (p=0.9824). The mean age of the patients in the salvestrol group was 63.00 ± 18.62 and that in the control group was 53.50 ± 18.46, which was not statistically significant (p=0.2669). The mean ECOG score in the salvestrol arm was 1.40 ± 1.17 and that in the control group was 2.10 ± 0.99 which was statistically insignificant (p=0.1673). The mean HAM–A scores in the salvestrol arm was 0.50 ± 1.08 and that in the control arm was 1.30 ± 0.95, which was statistically insignificant (p=0.0954). The mean PGSGA scores in the salvestrol arm were 6.50 ± 3.81 and that in the control arm was 11.00 ± 4.78, which was statistically significant (p=0.0318). The mean overall survival in the salvestrol arm was 10.000 ± 10.317 months and that in the control arm was 3.550 ± 3.700 months which was statistically significant (p=0.0792) (Figure 1C) (Table 1) (Represented by Kaplan Meier curve).

Ovary group

Among the16 patients in the ovary group 12 patients had stage IIIC disease, 2 had stage IIIA and 2 had stage IV disease (liver metastasis). All the patients were matched for stage, age and ECOG. As all the patients had the inoperable disease, they were treated uniformly with neoadjuvant chemotherapy with paclitaxel@175 mg/m2 and Carboplatin @ AUC 6 every 21 days for a total of 6 cycles. The mean number of chemotherapy cycles received by the salvestrol arm was 5±2.1 cycles and the control group was 4±2.20, which was not significant (p=0.0867). All patients underwent CT scans of the abdomen after 3 cycles and 6 cycles to assess operability. Only 8 patients underwent cytoreductive surgery (4 from each arm). The patients were followed up for a total period of 36 months (15 months post-trial) and it was observed that 4 patients from the salvestrol arm and 1 patient from the control arm were still alive.

The mean age in the salvestrol group was 58.50 ±10.23 years and the mean age in the control group was 51.38 ± 11.76 years, which was statistically insignificant (p=0.2169). The mean ECOG status score in the salvestrol arm was 1.00 ± 0.53 and that in the control group was 1.75 ± 0.89 which is considered to be not quite statistically significant (p=0.0596). The mean HAM-A score in the salvestrol arm was 4.38 ± 3.02 and that of the control arm was 6.75 ± 5.39, which was statistically insignificant (p=0.2954). The mean PG-SGA score in the salvestrol group was 5.63 ±2.20 and that in the control group was 8.13 ± 2.90, which was statistically insignificant (p=0.0725).The mean survival in the salvestrol arm was 17.63 ± 7.19 months and the meansurvival in the control arm was 6.63 ± 7.56 months and this difference is considered to be very statistically significant (p=0.0099) (Figure 1D) (Table 1) (Represented by Kaplan Meier curve).

Breast

A total of 20 patients with breast cancer were randomized into 10 patients in each arm. All the patients who were selected had already undergone a modified MRM and post-operative staging. The patients

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were matched for their age and TNM status. All the patients who were ER/PR positive received Tamoxifen in addition to their adjuvant chemotherapy. All the patients received adjuvant chemotherapy with either the FAC regime (6 cycles) for low-risk patients or the AC-T regime (8 cycles) for node-positive patients except for one patient in the control arm due to refusal of chemotherapy. All patients received adjuvant radiation with 50 Gy/ 25 # to the chest wall and drainage areas except for 2 patients in the study arm and 2 patients in that salvestrol arm as they had T1/T2 node-negative lesions.

The mean age of the patients in the salvestrol arm was 52.50 ± 11.96 years and that of the control arm was 54.50 ± 7.23 years, which was statistically insignificant (p=0.6562). The mean survival in the salvestrol arm was 21.80 ± 6.96 months and that of the control group was 22.10 ± 4.01 months, which was not significant (p=0.9073) (Figure 1A) (Table 1) (Represented by Kaplan Meier curve). There was no statistical difference in the survival of both groups as the duration of follow-up was not sufficient. At the end of 36 months of follow (15 months post-study), 9 patients from the salvestrol arm and 7 from the control arm were alive. There were no deaths in the study period. The mean HAM –A score in the salvestrol group was 1.40 ± 1.84 and that in the control group was 2.30 ± 2.31, which was statistically insignificant (p=0.3480). The mean PG-SGA scores in the salvestrol group were 2.10 ± 2.18 and that in the control group was 3.70 ± 1.49 which was statistically insignificant (p=0.0719). The mean ECOG performance scores in the salvestrol group were 0.650 ± 0.580 and that in the control group was 1.350 ± 0.669 which was statistically significant (p=0.0223). The mean number of cycles of chemotherapy received by the salvestrol arm was 7.40 ± 1.07 cycles and that received by the control group was 7.60 ± 3.47 cycles, which was statistically insignificant (p=0.8637).

Overall Result (n=102)

The overall data on the 102 patients was analyzed using ANOVA thereby accounting for the 5 diverse groups. The overall survival in the salvestrol arm was 14.480 ± 10.036 months versus 8.333 ± 8.507 months in the control arm (Figure 2) (Table 1) (Representation by Kaplan Meier curve), which was statistically significant (p=0.0012). The mean PGSGA scores in the salvestrol arm were 6.4688 ± 2.8959 and that in the control arm was 7.625 ± 5.7291 which was not statistically different (p=.312209) (Figure 3). The mean HAM-A scores in the salvestrol group were 2.4314 ± 2.9138 and that in the control group was 3.0612 ± 3.4666 which was not statistically significant (p=0.97) (Figure 4). The mean ECOG scores in the salvestrol group were 1.12 ± 0.773 and that in the control group was 1.58 ± 0.8593 which was statistically significant (p=.00591) (Figure 4).

Figure 2: Overall survival data of all groups. Hazard rates differ z=4.88, p < 0.001 (Confidence levels 95%).

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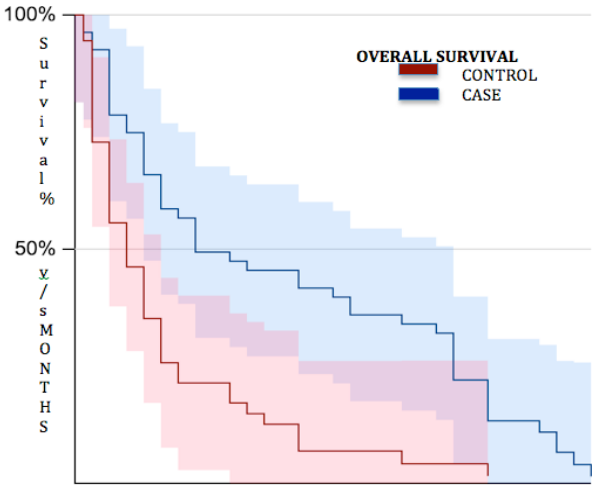

Figure 3: Overall PG-SGA data of all groups. Hazard rates differ z=3.03, p=0.00244.

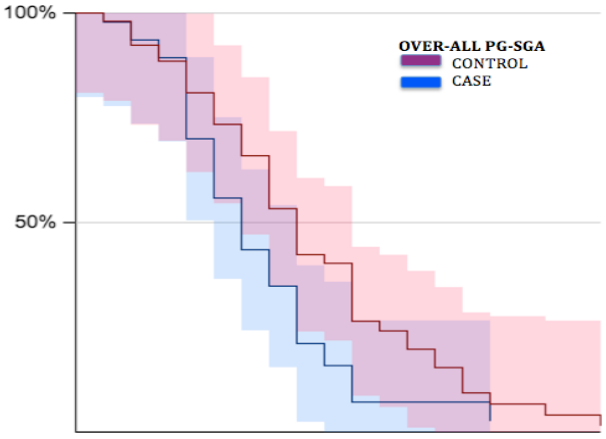

Figure 4: Overall HAM-A data of all groups. No Significant difference z=0.038, p=0.97.

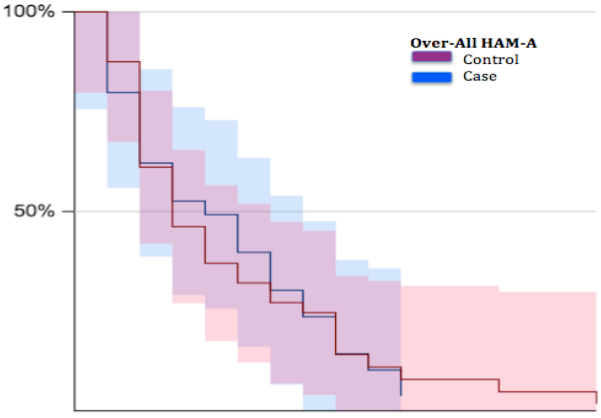

Figure 5: Overall ECOG data of all groups. Hazard rates differ z=2.67, p=0.00768.

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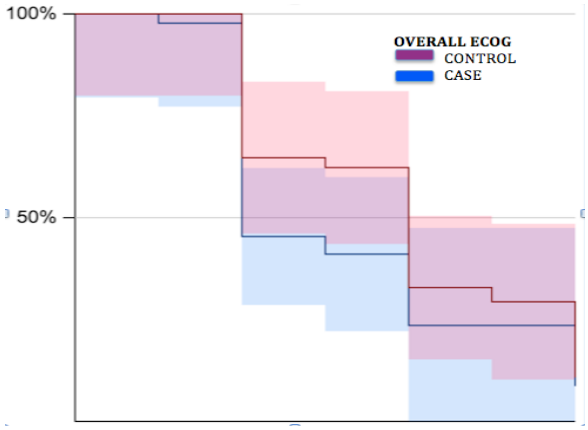

Discussion

The discussion on salvestrol as anti-cancer nutritional components can be disputed. The reason for this is that all the studies published to date are either study on the molecular in vivo behavior of these classes of molecules, case studies or case series reports, showing some promising outcome in cancer patients [15,16,17]. However, to date, no randomized controlled study has been performed to assess more precise responses. In most of the case studies, conventional cancer medication and surgery were offered to make the benefit of salvestrols non-fathomable as there was no control group. These studies are insufficient to assess the effect or efficacy of salvestrol in cancer. This study attempted to broaden the indication of a nutrition-based product, salvestrol[16], which uses the unique metabolic properties of CYP1B1. This is probably the first randomized clinical trial that has been done on salvestrol along with conventional treatment in Regional cancer hospitals. The process of randomization and the selection of controls have added to the level of evidence and enabled a more precise assessment of the response of salvestrol in a cancer setting.

In most of the previously reported case studies, the patient was either receiving conventional cancer therapy concurrently with salvestrol or no mention whatsoever is made of any concurrent or past conventional cancer therapy, making any efficacy judgment difficult [15,16,14].

To shed some light on the combination of the CYP1B1 pathway and conventional cancer therapy, a randomized clinical trial was undertaken in a Regional Cancer Centre. Every patient received evidence-based treatment according to his/her TNM staging. The addition of salvestrol in one arm was the only additional intervention. Most patients had advanced or terminal cancers; hence the study was completed in 21 months. Multi-modality treatment is the norm for most cancers. Hence, the addition of any intervention of possible benefit needs to be incorporated into the evidence-based treatment and patients duly randomized without bias.

However, using the same principles it was observed that the salvestrol group had a statistically significant overall survival (p=0.0012). Salvestrols have not been able to improve the quality of life as seen in the HAM-A and PGSGA scores. However, a significant improvement in the ECOG

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status may be attributed to the possible contribution of salvestrol as the ECOG was matched at the time of randomization. The results of the study were compelling to give this molecule a new look as an adjunct in the treatment of cancers of the Head& Neck, Lung, GIT and Ovary.

These results indicate that there may be a role of CYP1B1 induced pathways in several cancers (1,2,16). The addition of salvestrol probably stimulates these pathways leading to an additional gain from surgery, radiotherapy and chemotherapy. A modest improvement in overall survival and ECOG status deserves a closer look at polyphenols and phytoestrogens like salvestrols in contributing as an adjunct to modern treatment or even as part of palliative care when no further cancer treatment can be offered. Hence there is a need for larger randomized trials that may shed light on the role of polyphenols, phytoestrogens and salvestrols in cancers.

Conclusions

The cases presented here were from a cross-section of cancers such as head & neck, lung, GIT, breast and Ovary. Hopefully, the data obtained from this study may be useful to the patients and their physicians to incorporate salvestrol into their treatment plans for a cure, regardless of their choice of intervention. These cases provide a further indication on the unique metabolic properties of CYP1B1 that can bring about a very favorable outcome for cancer sufferers. Some of these cases outline the experience of individuals that were in the third or fourth stage of cancers. These cases help to highlight the beneficial role that salvestrol can play. These cases provide new hope to cancer sufferers and their physicians with the confidence to explore nutritional approaches before, or concurrent with, conventional procedures to achieve a beneficial outcome. The use of salvestrols as an adjunct to surgery, radiotherapy and chemotherapy in GIT, lung, Head & neck and ovarian malignancies may prolong the overall survival and improve the ECOG status. CYP1B1 pathways and salvestrol are promising solutions to improved cancer survivals with no added toxicity.

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Ethical approval letter

Given 21 January 2014.

Consent for publication

Consent letter available.

Conflict of Interest

There is no conflict of interest.

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Authorship

Dr. Gayathri Bathoju (Medical Director of Prayus) designed the study, Patient studies and Data acquisition, Statistical analysis and Manuscript preparation. Dr. Raghu Raman selection of patients, Conventional treatment and Manuscript Preparation. Dr. Vijay Kumar Conventional treatment.

References

1. Potter GA. The role of CYP1B1 as a tumour suppressor enzyme. InBritish Journal of Cancer. Macmillan Building, 4 Crinan St, London N1 9XW, England: Nature. 2002;86:S12-S12.

2. Potter GA, Patterson LH, Wanogho E, Perry PJ, Butler PC, Ijaz T, et al. The cancer preventative agent resveratrol is converted to the anticancer agent piceatannol by the cytochrome P450 enzyme CYP1B1. Br J Cancer. 2002;86(5):774-8.

3. Potter GA, Burke MD. Salvestrols-natural products with tumour selective activity. J Orthomol Med. 2006;21(1):34-6.

4. Tan HL, Butler PC, Burke MD, Potter GA. Salvestrols: a new perspective in nutritional research. J Orthomol Med. 2007;22(1):39-47.

5. Murray GI, Taylor MC, McFadyen MC, McKay JA, Greenlee WF, Burke MD, et al. Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res. 1997;57(14):3026-31.

6. McFadyen MC, Melvin WT, Murray GI. Cytochrome P 450 CYP1B1 activity in renal cell carcinoma. Br J Cancer. 2004;91(5):966-71.

7. McFadyen MC, Cruickshank ME, Miller ID, McLeod HL, Melvin WT, Haites NE, et al. Cytochrome P450 CYP1B1 over-expression in primary and metastatic ovarian cancer. Br J Cancer. 2001;85(2):242-6.

8. Dana-Farber. Cancer Institute: Cytochrome P450 1B1 is a Universal Tumor Antigen Eliciting Cytotoxic TCell Responses. 2007.

9. Schaefer BA, Dooner C, Danny Burke M, Potter GA. Nutrition and cancer: further case studies involving Salvestrol. J Orthomol Med. 2010;25(1):17.

10. Schaefer BA, Tan HL, Burke MD, Potter GA. Nutrition and cancer: salvestrol case studies. J Orthomol Med. 2007;22(4):177-82.

11. Ware WR. Nutrition and the prevention and treatment of cancer: association of cytochrome P450 CYP1B1 with the role of fruit and fruit extracts. Integr Cancer Ther. 2009;8(1):22-8.

12. Ware WR. P450 CYP1B1 mediated fluorescent tumor markers: A potentially useful approach for photodynamic therapy, diagnosis and establishing surgical margins. Med Hypotheses. 2009;72(1):67-70.

13. Murray GI, Taylor MC, McFadyen MC, McKay JA, Greenlee WF, Burke MD, et al. Tumor-specific expression of cytochrome P450 CYP1B1. Cancer Res. 1997;57(14):3026-31.

14. Sutter TR, Tang YM, Hayes CL, Wo YY, Jabs EW, Li X, et al. Complete cDNA sequence of a human dioxin-inducible mRNA identifies a new gene subfamily of cytochrome P450 that maps to chromosome 2. J Biol Chem. 1994;269(18):13092-9.

15. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997;275(5297):218-20.

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16. Bavaresco L, Fregoni MA, Trevisan MA, Mattivi F, Vrhovsek U, Falchetti R. The occurrence of the stilbene piceatannol in grapes. 2002;41(3):133-136.

17. Geahlen RL, McLaughlin JL. Piceatannol (3, 4, 3′, 5′-tetrahydroxy-trans-stilbene) is a naturally occurring protein-tyrosine kinase inhibitor. BiochemBiophys Res Commun. 1989;165(1):241-5.

18. Fleming I, Fisslthaler B, Busse R. Calcium signaling in endothelial cells involves activation of tyrosine kinases and leads to activation of mitogen-activated protein kinases. Circ Res. 1995;76(4):522-9.

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