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A randomised double blind phase II study of lifestyle counselling and salicylate compounds in patients with progressive prostate cancer.

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ABSTRACT

Introduction Salicylates, via COX-2 inhibition and diet have been implicated in the aetiology of prostate cancer but less is known about their influence on its progression.

Methods A randomised, double blind, phase II study involving 110 men with progressive prostate cancer. Progression was defined as an increase in Prostate specific antigen (PSA), on 3 consecutive values, >20% over the proceeding six months. Lifestyle advice essentially consisted of eating less saturated fat, processed food, more fruit, vegetables and legumes; exercising more and stopping smoking. Patients were randomised to sodium Salicylate (SS) alone or SS combined with, vitamin C, copper and manganese gluconates (CV247). Patients took this daily, without other intervention but were withdrawn if their PSAdt shortened or their PSA rose >20% from baseline.

Results. At 12 months there was no difference in the mean change in PSA from baseline or the number still in the study between the SS or CV247 (21 v 19 p=0.92). In 40 patients (36.4%) this intervention positively influenced the rate of PSA progression for over one year. In 14 of these (12.7%) the PSA dropped below baseline and in 26 (23.7%) it progressed but at a PSAdt greater pre-study. A further 10 patients were stabilised for 10 months. The intervention was well tolerated and compliance high. Patients least likely to stabilise had received previous radiotherapy or had Gleason $\geq$7.

Conclusions A further randomised study is required to find out whether the lifestyle alone or SS combined with lifestyle has the greatest therapeutic effect. These data suggest this intervention would be a welcomed by patients as if substantiated, could potentially delay the need for more radical therapy and their associated toxicities

Keywords. Prostate Cancer, diet, Sodium salicylate, copper, manganese, vitamin C, CV247

Introduction

Several epidemiological studies have shown that people with diets high in fruit, lycopene containing vegetables and low in saturated fats have a lower prostate cancer risk {Giovannucci E, 2002 #186} {Kolonel LN, 1999 #111; Wilkinson S, 2003 #64}. Whereas populations deficient in trace elements such as selenium, copper, manganese, vitamin E and D have a higher risk {Costello AJ, 2001 #115; Miller M, 2001 #116}. Retrospective analyses have also found an association with use of salicylates and a lower incidence of prostate and other cancers {Baron JA, 2003 #100; Harris RE, 1996 #21; Sandler RS, 2003 #111;}.

The evidence for lifestyle interventions *following the diagnosis of cancer* is less robust but a source of immense interest among patients, advocacy groups, holistic organisations and websites {Schmidt K, 2004 #62}. Although, dietary intervention programmes have been shown to restore nutrition balance in patients with cancer {Brown JK, 2003 #65}, improve quality of life{Ravasco R, 2005 #66}, its influence on malignant growth is less clear {Hirsch FR, 2005 #63; Wilkinson S, 2003 #64}. Much of the emerging data regarding diet and its influence on cancer progression has evaluated patients with indolent or relapsing prostate, where slow progression allows time for alternative interventions {Thomas R, 2006 #201}. This includes a number of epidemiological and cohort studies, which have demonstrated that patients with healthy lifestyles have more indolent prostate cancers suggesting the environmental factors can mediate the transformation of latent prostate cancer into more clinically apparent phenotypes {Chan, 2005 #91; Sonn, 2005 #90; Wilkinson, 2003 #64}. Two prospective studies have also provided more convincing clinical evidence:

The first, a randomised study involved 93 volunteers with early prostate cancer, who had opted not to undergo conventional therapies. They were randomly assigned to intensive lifestyle counselling, or not. PSA levels decreased by 4% at 12-months in the intervention group, but increased by 6% in the control group; this was statistically significant. As a secondary end point, serum taken from patients from the intervention group and introduced to prostate cell lines in vitro were 8 times more likely to inhibit their growth than the control arm{Ornish, 2005 #92}. A second prospective phase two study, evaluated 48 men with PSA relapse post radiotherapy or prostatectomy. There was a significant prolongation of PSA doubling time (PSAdt) from a mean of 15-months at baseline to 54-months post consumption of approximately 200ml pomegranate juice a day. As a secondary end point, the patients' baseline oxidative state was significantly lower after pomegranate consumption compared to baseline {Pantuck AJ, 2006 #261}.

This is the first prospective study, investigating whether the intake of a salicylate compounds combined with dietary counselling could influence the progression of established early prostate cancer.

Methods

This was a randomised, double blind, phase II study involving 110 men with progressive prostate cancer attending either Bedford or Addenbrooke's Cambridge University NHS trusts, recruited between October 2003 and November 2006 and completed in November 2007. All men, average age of 75 years (range 61-87 years), gave written informed consent, had a histologically confirmed prostate cancer (Gleason ≤ 7), had no concurrent serious medical conditions, were not current receiving androgen deprivation and would normally have be considered for a watch and wait strategy within the West Anglia Cancer Network guidelines [ref-wacn.org.uk]. Unlike other surveillance studies all men in this study had established PSA progression at trial entry, defined by an increase in PSA on the previous three consecutive blood tests of greater than 20% over the preceding six months. They were also excluded if they had a contraindication to salicylates such as allergy, asthma or peptic ulcer disease or were unwilling to change their diet or lifestyle according to the trial advice. 40 patients had been managed with active surveillance but then developed unacceptable PSA progression. Sixty men had previous prostatic radiotherapy with or without neo adjuvant hormones, and 10 radical surgery and were experiencing a PSA relapse. The average PSAdt at trial entry was 9.7months (range 1.1 to 48 months) for those patients randomised to CV247, and 12.5m (range 2.3 to 48 months) on SS Patient demographics are summarised in table.1

Lifestyle advice: At trial entry, and thereafter at regular intervals, men and their relatives were given diet and lifestyle counselling in the form an interview with the trial co-ordinator. These intervals were at least monthly but could have been more at the request of the patient. A lifestyle sheet (see appendix) was also given to the men and their family which in essence advised men to stop smoking, exercise more regularly, eat less saturated fats, more fruit, berries and vegetables, preferably organic. They were asked to avoid heavily processes sweet and salty foods with high artificial colours favours and preservatives and eat more foods with high antioxidant content such as fresh, tea, prunes and pomegranates. All men were given the opportunity to discuss specific dietary concerns with a qualified dietician. Compliance to the diet was estimated by asking men to complete a linear analogue scale at each visit**.**

Trial medication. Men were randomised (50:50) to receive either sodium salicylate alone or combination known as CV247 which consisted of a bottle of solution containing purified water, and each 10mls contained manganese gluconate 20mg, copper gluconate 20mg and sodium salicylate 350mg. 400mg of ascorbic acid was provided in a separate sachet, mixed shortly before administration. Patients < 50kg took 10mls and one sachet once a day, 50-75kg twice a day and over 75kg three times a day. The sodium salicylate was administered in an identical bottle and packaging in colour matched purified water at the same concentration of 350mg per 10mls. To facilitate blinding, for this arm of the study the sachet contained sodium salicylate instead of ascorbic acid.

Trial end points. The primary endpoint was the change in mean PSA from baseline to 12 months in the double blind randomised comparison of the sodium salicylate and CV247 groups. The secondary endpoint was the percentage of patients still taking the trial medication at one year. Patients were withdrawn if their PSAdt shortened further than at baseline or if their total PSA increased by greater than 20% from the baseline. Although not used for the statistical evaluation, a simple check in clinic of the PSAdt between two points for PSA_a to PSA_b between time (t) used the simple formula:

$$\frac{PSA_a}{PSA_b - PSA_a} \times t$$

Statistical analysis: The randomisation process required the opening of individual sealed envelopes prepared independently from a computer generated randomisation schedule and delivered to the hospital pharmacy at the start of the trial. The null hypothesis was that there was no treatment difference in the change in mean PSA from baseline to 12 months in the double blind phase of the study. Statistical analysis after 12 months was performed using Analysis the Wilcoxon rank sum test. The Wilcoxon rank sum test was used to test for differences between treatments in changes from baseline. The power calculation used a two sided p test at the 0.05 level. A more accurate calculation was performed using a standard deviation derived from a blinded interim analysis of the first 46 patients and concluded that a sample size of 50 patients per group would have adequate power to detect a mean PSA change difference of 20% between the two groups

Results

The mean treatment period in the double blind study was 9.2 months for CV 247 and 8.8 months for sodium salicylate (SS) (p=0.2). There was no statistical difference in the change in mean PSA from baseline to 12 months between the patients taking CV247 and SS (p=0.23). Likewise there was no difference in the secondary endpoint, number of stabilised patients at one year, between the two groups i.e. 21(55%) randomised to SS and 19 (45%) to CV247 (p = 0.92).
Forty of the 110 (36.4%) patients recruited into the study remained on either intervention at 12 months as it was deemed they had a therapeutic effect. A total of 14 of the 40 had an overall decrease in their PSA levels from baseline (8 on sodium salicylate and 6 on CV247). The other 26 had continued to experience a PSA progression but with a PSAdt longer than baseline and an increase in PSA no greater than 20%. A further 10 patients were stabilised for 10 months (6 on CV247 and 4 on sodium salicylate).

Subgroup analysis; Patients who had received previous radiotherapy, had gleason grades ≥ 7 or who had previously been taking daily aspirin were more likely to have withdrawn before 1 year (Table3).

Tolerability The medication was well tolerated. The adverse event (AE) profile was similar for both treatments. A total of 39 patients reported 97 AEs whilst being treated with CV247, compared with 37 patient's reporting112 events on sodium salicylate. The majority were mild or moderate in severity (76% of AEs reported by patients on CV247 and 75% for those on sodium salicylate). Only 13 AEs were considered to be probably or definitely related to CV247, and 12 to sodium salicylate. An AE was the cause for patient discontinuation for 4 patients on CV247 and for 7 on sodium salicylate. Dyspepsia and nausea were the most common AEs for both treatments. Increased manganese levels were recorded for 6 patients on CV247 and for 9 on sodium salicylate, which resulted in 1 patient being withdrawn on CV247 and for 4 to be withdrawn on sodium salicylate. There were a total of 26 serious AEs, only one of which, 25 were unrelated to the medication although 1, an episode of acute pancreatitis, may have had a possible relationship.

Compliance with the diet was generally reported as enthusiastic on discussion with patients and relatives. Many patients showed an improvement in dietary compliance as the study progressed. All patients self scored greater than 70% or above throughout the study period. Compliance with the medication, measured by counting the returned sachets and measuring the volume of returned solution to the pharmacy, was greater than 95%.

DISCUSSION

Within the design of this study, the randomised comparison of CV247 and sodium salicylate showed no statistical difference between. The conclusion is drawn that the addition of copper, manganese gluconate and vitamin C to sodium salicylate in this cohort of men had no additional influence on prostate cancer progression.

Despite the results of the randomised primary endpoints, the phase two element of the study revealed that a component of this intervention appeared to have had a positive influence on the anticipated rate of PSA progression in 36% of men overall. Without a non-intervention arm however, it was possible that a prolongation in PSAdt could have happened by chance or was the consequence of an unknown external factor. The authors believe this was unlikely as a strict criterion of trial entry was for all men to have significant PSA progression. In fact, during the recruitment period of the trial, 45 patients managed with active surveillance were excluded from trial entry because the PSA was not progressing greater than 20% in 6 months. Our trial cohort had a collective mean PSAdt of 10.2 months at trial entry, which was very different from other surveillance cohorts which include patients who were not progressing at all or in some had PSAdt of over ten years{Shulman, 2004 #51. Furthermore, recent active surveillance studies have shown that patients with PSAdt < 4 years almost universally continue to sustain a PSA progression until therapeutic intervention {Choo, 2004 #46; Partin, 2004 #49; Ross PL, 2004 #59}.

Assuming this therapeutic effect was a genuine result of this intervention, this study has also not answered whether the lifestyle counselling or the addition of salicylates were responsible. To prove this, a further study is required which would ideally have to include four randomised arms; one with no intervention at all; another with lifestyle but no salicylate; another with salicylate but no lifestyle advice and another with both. A similar design was initially considered for this study but deemed impractical and unlikely to complete for the following reasons; Firstly, a no intervention arm would have significantly impaired trial accrual in a cohort of men who had been told they had progressive cancer. Secondly, two further arms would have significantly increased the total patient numbers to maintain statistical power and even if they could be recruited would take several years to complete. Thirdly**,** over a third of elderly men entering this study were taking low dose aspirin for cardio-protective reasons. These men would have had to be excluded as if aspirin continued in the salicylate group there would have been an increase risk of gastro-intestinal side effects and in the placebo group this would have resulted in increased risk thrombolytic events. Likewise, excluding lifestyle advice within a surveillance study would have been unacceptable to most patients because although the association between diet and prostate cancer was not so widely accepted during the initial stages of this trial, it is now familiar conversation amoung patients and their families, via patient advocacy groups or just in the waiting room.

A complete review of the underlying mechanisms and other available evidence for the benefits of lifestyle after prostate cancer has been reviewed elsewhere {Thomas, Thomas etc].

In terms of cancer progression the basic premise for the benefits of lifestyle is that although patients with established cancer have already sustained the DNA damage in order to mutate from benign to malignant cells, avoiding further DNA insult may avoid further mutation of indolent malignant or pre-malignant cells into more aggressive phenotypes{Chan JM, 2005 #91; Sonn GA, 2005 #90; Wilkinson S, 2003 #64, thomas}. A healthy diverse diet ensures adequate intake of vitamins, antioxidants and mineral to ensure efficient function of the enzymatic defences against carcinogens. A healthy lifestyle reduces total carcinogenic exposure and has numerous other general wellbeing benefits. The same cannot be said for taking additional dietary supplements. This study confirms previous studies that a one tablet fits all dietary supplement is unlikely to be helpful and may even be harmful [ref-thomas lifestyle]. For example, in the health professionals study in which 3348 of 50,000 people observed developed prostate cancer, dietary analysis showed that men who took normal amounts of zinc had the normal incidence of prostate cancer but those who took supplemental zinc at levels of more than 100mg/day or for long durations were more than twice as likely to develop advanced prostate cancer{Giovannucci E, 2002 #186}. Another dietary prevention study combined beta-carotene with retinol. People who started the trial with naturally low blood levels of beta-carotene had lower levels of prostate cancer but those people who had adequate blood levels at the start of the study ended up with a higher risk of cancer, including prostate {Omenn GS, 1996 #182}. If supplements are therefore, to be included in future dietary studies, the design should include bespoke analysis of individual's baseline status to detect sub-clinical dietary deficiencies in trace elements and vitamins and avoid over supplementation of adequate levels {Li H, 2005 #162}. Simple serum vitamin, mineral and essential fatty acid levels may not be enough however as this has not always been found to reflect the true status of individual requirements {Joosten E, 1992 #189}. More complex tests may be required in addition to detailed dietary questionnaires. including measurement of serum metabolites that accumulate in vitamin deficiencies{Slater TF, 1987 #190}; serum lipid peroxide levels as an indicator of oxidative free radical damage{Slater TF, 1987 #190}; or markers relating too the function of the primary defence enzymes, catalase, glutathione S-tranferase glutathione and manganese, copper, zinc Super Oxide Dimutase (SOD) {Marklund SL, 1982 #84}. { #192}.

The rational for including a sodium salicylate in this study arises from the knowledge that the enzyme cycloxidase 2 is over expressed in over three quarters of cases of prostate cancers Chaudry AA, 1994 #121; Gupta S, 2000 #40}{Madaan S, 2000 #118. Higher expression correlates with a higher histological grade and molecular markers of reduced apoptosis, loss of adhesion, invasion, angiogenesis and metastasis {Warner TD, 1999 #89; Hirsch FR, 2005 #63; Lim H, 1999 #31; Mestre JR, 2001 #32; Parrett ML, 1997 #39}. In vitro, non steroidal anti-inflammatory drugs (NSAID's) have been shown to induce apoptosis and inhibit proliferation of prostate cancer cell lines {Hsu AL, 2000 #122; Liu XH, 1998 #123}. Although anti-inflammatory drugs, classified as pure COX-2 inhibitors, may avoid the unwanted COX-1 effects whilst at the same time amplifying the COX-2 effects, the benefits over salicylates have not yet been established. Firstly, the reduction in gastrointestinal side effects of pure COX-2 inhibitors has not been as strong as expected when tested clinically {Mims, 2003 #131}. Secondly, significant safety issues remain a concern with some NSAIDs {Dieppe P, 2004 #52; Hippisley-Cox J, 2005 #130; Hudson M, 2005 #129}. Third, a number of retrospective analyses of a reduction in cancer risk have found an association with aspirin rather than other NSAID {Greenberg ER, 1993 #4; Harris RE, 1996 #21; Logan RF, 1993 #5; Reeves MJ, 1996 #7; Suh O, 1993 #6; Thun MJ, 1991 #3}. Fourth, prospective studies including a Cochrane meta-analysis again showing a reduced incidence of malignancy have mainly used salicylates rather than other more selective NSAIDs {Egan KM, 1996 #20; Fuchs

C, 2005 #132; Schreinemachers DM, 1994 #17}{Mahmud S, 2003 #129}. Fifth, the only prospective randomised clinical study in oncology published to date showing a protective benefit against recurrent cancer used salicylates {Baron JA, 2003 #81; Sandler RS, 2003 #78}. Sodium salicylate has a further advantage over acetyl salicylate (aspirin) in that it has 100% bioavailability to its active form, salicylic acid, after oral administration in man so that a lower dose has the same effect. Studies in man have found that an oral dose of 250mg SS gives plasma salicylic acid levels similar to those obtained with 320mg oral acetyl salicylate (Cerletti, 1984). This was substantiated by early observations in both the rat and man found that sodium salicylate (SS) produced less gastrointestinal irritation than aspirin (Leonards, 1973).

In conclusion, this study has probably generated as many questions as answers and further studies are necessary to confirm these preliminary findings. Nevertheless, this was the first prospective study of salicylate and lifestyle conducted in patients with progressive prostate cancer. It confirmed the finding of other studies, that patients with prostate cancer are motivated and willing to consider dietary change as a part of their therapy {Kristal AR, 2002 #76, Thomas-cv247}. It highlighted that non bespoke dietary supplements are unlikely to be helpful. The data suggested that an element of this intervention could slow the rate of progression in over a third of patients with progressive disease and in a group with an indolent natural history, this could substantially delay or even avoid the need for more radical therapy and this percentage may be even improved by careful patient selection.

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Summary of lifestyle advice

Unhealthy Fats; reduce saturated fats such as those in crisps, deep fried snacks, batter, pastries and cheap processed meats. Remove excess fat from meat, grill or stew rather than fry. If extra oil is needed, use olive oil.

Additives; Foods containing artificial colours, flavourings and preservatives should be avoided. This essentially means the majority of processed foods, and ready meals.

Cancer forming chemical (carcinogens); Avoid heavily processed foods. Wash salads and vegetables thoroughly to avoid pesticides and airborne chemicals, which may have settled on them. Organic foods reduce the pesticide exposure further. Avoid excessive amounts of foods containing high levels of aromatic hydrocarbons and acrylamides such as smoked food, or those associated with high temperature cooking processes such as dried snacks, deep fried foods, crisps, chips barbecued and heavily fried meats.

Meat; Avoid cheap processed meat such as burgers, sausages, pies. Buy organic meat if possible, to avoid associated chemicals. The total quantity should generally be reduced and therefore it should be used as a garnish rather than as the constituent of the main meal.

Sugar; Try and avoid all processed sugar and do not add it to tea or coffee or other meals. Avoid soft drinks and snacks which contain sugar. If you need to sweeten things, try apple juice or honey.

Salt; Avoiding processed foods will reduce your salt intake but also avoid adding salt when cooking such as when cooking vegetables. Reducing the amount of time that vegetables are cooked should maintain the flavour.

Vegetable intake should be increased, ideally organically grown as this avoids the associated pesticides. Fresh green leafy and calciferous vegetables are particularly healthy such as lettuce, cabbage, spinach, broccoli, cauliflower as well as onions, celery, leaks, mushrooms and foods used as natural flavours including pepper, herbs, coriander, parsley, cunamin, chilli Take vegetables them raw were possible.

Legumes; Soybeans, peas, lentils, pinto (baked beans) and other beans

Fruit; Unless you have diarrhoea try to increase your daily intake fruit, ideally by eating the whole fruit such as apples, bananas, plums, kiwis, grapes. Fruit juices are highly recommended but not those bought from shops in cartons but made freshly and preferably unpasteurised. Berries such as blackcurrant, blackberries, strawberries, blueberries, goji berries and cranberries are ideal, as are pomegranates, dried prunes, fresh or cooked tomatoes.

Fibre: Increasing fruit and vegetables will naturally increase fibre intake but seeds such as linseeds sprinkled on foods or soaked over night and eaten with natural yogurt is ideal

Fish; Increase all fresh fish but particularly the oily varieties mackerel and sardines. Fresh water fish such as trout have the advantage of avoiding potential heavy metal contamination of tuna & sword fish which some suggest should not be eaten more than twice / week

Nuts; A good source of protein, health oils such as omega 3 and trace elements such as selenium particularly in Brazil nuts.

Healthy oils; Increasing nuts and vegetable intake will naturally increase the health unsaturated oil intake. Use extra virgin olive oils (or other natural oils). Avocados and oily fish will also increase the particularly healthy unsaturated oil, omega -3

Liquids; Up to two litres of water a day are recommended. However, these should not be in the form of alcoholic drinks traditional teas or coffee, as these act as diuretics that make your body loose water. Herbal teas can be drunk liberally.

Smoking; Stopping smoking is the greatest single step smokers can do for their health. If you smoke give up – if this is difficult your GP has the details of smoking cessation programmes.

Alcohol; Although red wine contains some antioxidants this does not make up for the other the harmful effects so avoid alcohol if possible or limit to small amounts 2-3 times a week

Exercise: Try to take the more strenuous everyday options such as taking the stairs rather than the lift, talking rather than taking the car. Consider joining a gym, exercise or dance class and exercise until you get breathless and sweaty at least 3 times a week.

Sunlight; burning in the sun is dangerous and can cause skin cancer but regular light exposure is encouraged and is the best way to boost your vitamin D levels

Table.1 Baseline demographics

	CV247 (n = 54)	Salicylate (n = 56)	Total (n = 110)
Mean age	73 yrs (range 61-81)	76 yrs (64-87)	75 (61-87)
Previous treatment	29	31	70 (64%)
Gleason ≤6	28	33	61 (55%)
Gleason ≥7	26	23	49 (45%)
Mean entry PSA (range) ng/ml	12.4 (6.5 - 23)	10.6 (5.5 - 21)	11 (5.5 - 23)
Mean baseline PSAdt (range)months	9.7 (1.1- 48)	12.5 (2.3 - 48)	10.2 (1.1-48)
Previous aspirin	11	21	32 (29%)

* Radiotherapy (63), Surgery (7). There was no statistical demographic difference between the two randomised groups (Chi squared test)

Table.2 Results of primary and secondary end points

	CV247	Sodium salicylate	Difference (significance)
Number (percentage) stabilised at 12 months	19 (45%)	21(55%)	2 (p=0.92)

Table.3 Profile of men still taking trial medication at one year

Category (number)	Continuing after 1 year (n= 40, 36.6%)	Withdrawn before 1 year (n=70, 63.4%)	Statistical Difference
Previous Rxt (63)	14 (22%)	49 (78%)	56% (p = 0.02)
Previous aspirin (32)	10 (31%)	22 (69%)	38% (p = 0.04)
Entry PSA>20 (14)	5 (36%)	9 (64%)	28% (p = 0.23)
Entry PSA10-20 (39)	13 (33%)	26 (67%)	34% (p = 0.12)
Entry PSA<10 (57)	22 (39%)	35 (61%)	22% (p = 0.12)
Gleason $\geq$7 (38)	9 (24%)	29 (76%)	52 % (p = 0.04)
Gleason $\leq$6 (72)	31 (43%)	41 (57%)	14% (p = 0.2)