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Original article

Polyamine reduced diet (PRD) nutrition therapy in hormone refractory prostate cancer patients

Bernard G. Cipolla [a,b,*], René Havouis [b], Jacques-Philippe Moulinoux [b]

[a] Department of Urology, centre hospitalier privé Saint-Grégoire, 6, boulevard de la Boutière, 35760 Saint-Grégoire, France
[b] UPRES EA 3891, groupe de recherche en thérapeutique anticancéreuse, faculté de médecine, CHU de Rennes, 2, avenue Pr-Léon-Bernard, CS 34317, 35043 Rennes cedex, France

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ABSTRACT

Background. – Reducing polyamine uptake by selecting low polyamine-containing foodstuffs and reducing bacterial gut production can improve performance status and pain control in hormone refractory prostate cancer (HRPC) patients. Long term PRD observance and tolerance were assessed. Cancer specific survival was studied in function of PRD and time of PRD initiation.

Methods. – Twenty-six volunteers, age: 68 ± 10 years with metastatic HRPC accepted a polyamine reduced diet and partial gut decontamination with oral neomycin or nifuroxazide (750 mg daily, one week out of two). Time from HRPC to PRD initiation was 10 ± 8 months. WHO performance status, EORTC pain scale, body weight, blood counts and serum proteins were regularly assessed. Sixteen other HRPC patients eating a normal diet served as "controls".

Results. – Mean diet observance is 25 ± 24 months. Tolerance is good. WHO performance status and EORTC pain scales were significantly improved respectively at 3 months (0.5 ± 0.7 vs 0.7 ± 0.9: $p = 0.03$) and 6 months (0.5 ± 0.8 vs 1 ± 1.3, $p = 0.02$) compared to initial values. Median cancer specific survival times after HRPC and PRD initiation are respectively 36 and 21 months. Eleven PRD patients started the diet before a 9 months cut-off period (after HRPC) and 15 patients after. Median cancer specific survival times for these two groups of patients are respectively 44 and 34 months, $p = 0.014$. Median cancer specific survival times (after HRPC) for PRD patients compared to controls are 36 vs 17 months ($p = 0.004$).

Conclusions. – Polyamine-reduced diet is well observed and tolerated. It seems to improve and/or maintain quality of life for HRPC patients. Early PRD initiation in HRPC is promising and may impact favorably cancer specific survival. These results open a rationale for PRD in HRPC management and warrant further investigation.

1. Introduction

The incidence of prostate cancer is increasing and is now the most common male cancer in the Western world. Cure is possible if the disease is radically treated in its early stages, but no curative therapy exists in advanced stages when hormonal escape inevitably occurs and the best palliation possible is the most we can offer.

The polyamines (PA) belong to a very wide range of biogenic amines that are involved in many physiological functions [1]. These ubiquitous chemical entities are believed to participate in cellular proliferation and differentiation. In mammals, cellular PAs (i.e., putrescine, spermidine [Sd], spermine [Sm]) derive from endogenous biosynthesis, as well as from the diet and from intestinal microorganisms. Putrescine (Pt) is synthesised from ornithine by a reaction catalysed by ornithine-decarboxylase (ODC), the limiting enzyme in PA synthesis. The other two mammalian PAs derive from putrescine by successive attachment of two propylamine groups by the action of aminopropyl-transferases, namely Sd and Sm synthase. The propylamine group donor is S-adenosyl-S-methyl-homocysteamine derived from S-adenosyl-methionine by the action of SAM-decarboxylase. Abnormalities in the homeostatic control of PAs metabolism are implicated in several pathological processes, including cancer.

The metabolic requirement for PAs is particularly high in rapidly growing tissues, during normal growth and development, and in tumors [2].

In vitro, difluoro-methylornithine (DFMO), an inhibitor of ODC, is an effective inhibitor of malignant cell proliferation, but *in vivo* the effectiveness of DFMO is reduced by tumour cell uptake of PAs released into the circulation by normal and cancer cells and from gut flora or dietary sources. Tumour-bearing animals fed with a PA deficient diet (PDD) and treated by DFMO and neomycin (partial decontamination of the gastro-intestinal tract), exhibit a very

* Corresponding author. Tel.: +33 2 99 23 33 24; fax: +33 2 99 23 33 39.
E-mail address: bcipolla@cpa-sante.com (B.G. Cipolla).

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Table 1
Group I foodstuffs and drinks containing < 100 nmol/g/ml PA can be eaten at will.

Langoustine, scampi, crayfish, hake, cod, whiting, smoked and tinned salmon, tinned tuna
Bacon, sausages, chipolata, pork, turkey
Chorizo, minced pork, saveloy, salami
Salsify, onions, celery, carrots, green cabbage, beetroot, skinned potatoes, sorrel
String beans, small tomatoes, peppers
Tinned vegetable soup
Raisins, apples, prunes, pears, avocado, peach, dates, pineapple, grapes, kiwi, lemon, strawberries, fruit salad
Butter, cream, milk, yoghurt, soft cheese, Emmental, goat cheese without rind, pasteurized brie, grated cheese, camembert
Eggs
Rice, semolina, pasta
White bread
Sugar, pancakes, chocolate éclair, honey, cookies, pound cake, chocolate, lemon pie, strawberry pie, apricot, strawberry, prune and raspberry jams
Salt, pepper, oils, vinegar
Coffee, tea, cider, cola, whisky, cognac, Indian tonic, pastis, port, wine, apple, grape and apricot juices, beer, tropical fruit cocktail, tomato juice

significant inhibition of tumour progression and of metastasis spreading [2,3], as well as an anticancer immunity stimulation [4], without inducing deleterious secondary effects. Furthermore, we have demonstrated that PA deprivation and low dose cyclophosphamide chemotherapy have synergistic effects [5].

In tumour-grafted animals only fed with PDD and receiving neomycin in the drinking water (i.e., without DFMO), we have observed a 40% inhibition in tumour progression [2]. Given alone, neither neomycin nor DFMO was able to positively modify the malignant evolution.

As previously shown by Bardocz et al. [6], some food ingredients contain large quantities of PAs. As 80% of exogenous PAs are of dietary origin [2,6], this led us to analyse the PA content of common foodstuffs in an attempt to reduce the PA intake in cancer patients.

A preliminary clinical trial performed in 13 metastatic hormone-refractory prostate cancer (HRPC) patients revealed the feasibility of this nutrition therapy based upon a 6 months PA reduced diet combined with oral neomycin treatment [7]. Reducing PA dietary intake and partial intestinal decontamination is well observed and tolerated. It also seemed to be beneficial for the patient's quality of life: performance status and pain scores were improved during the regimen and deteriorated 3 months after stopping it. No significant modification of other studied biological parameters was noted.

We have recently published the PA contents of 233 foodstuffs and drinks, which can serve as a basis for PRD. Furthermore, PRD tolerance and observance is very good in prostate cancer patients [8].

In this prospective observational study, 26 HRPC patients accepted and continued PRD for as long as they wanted. We present the results relating to its observance, safety and effect on quality of life (performance status and pain control). Cancer specific survival has been assessed for the study population but also in function of early, compared to later PRD initiation. In a non randomized manner, PRD patient survival was compared to "control" patients (HRPC patients eating a normal diet).

2. Methods

2.1. Foodstuff and erythrocyte polyamine extraction and determination

Foodstuff and erythrocyte PA extraction and determination were performed as previously described [8–10].

2.2. Food lists

A list of these different foods, drinks and their PA contents was given to each patient who could thus prepare his meals freely.

Table 2
Group II foodstuffs and drinks containing 101–200 nmol/g/ml PA, can be eaten 3 or 4 times a week.

Red mullet, fresh salmon
Beef and ox tongue, chicken, rabbit, veal, lamb, beef
Ham, garlic sausage
Paella
Red beans, radish, chicory, leek, endives, potatoes with skin, spring potatoes, Brussels sprouts, lettuce, cucumber
Melon
Goat cheese with rind, sweet Cantal cheese without rind
Oat, rye and whole breads
Ketchup
Grapefruit and orange juices

Patients were instructed to follow the diet 5 days a week but could eat what they wanted any other two days. Three groups of foods were established according to their PA contents. Group I (containing < 100 nmol/g/ml PA) could be eaten at will (Table 1), Group II (101–200 nmol/g/ml PA) 3 or 4 times a week only (Table 2), and Group III (> 201 nmol/g/ml PA) foods or beverages were forbidden (Table 3). Food/beverage quantities were equally free of choice [8].

2.3. Patients

From 1996 to 2004, of 42 consecutive metastatic HRPC patients (T1-4NxM1), 26, mean age 68 ± 10, median 71, (range: 48–82) years, after informed consent and extensive explanation of the trial rationale, accepted a PA reduced diet (PRD) in association with conventional HRPC management. The 16 other patients, mean age: 74 ± 8 years, did not follow a PRD, either because they refused either because regular observance was not predictably possible (patients living in an institution where special diets are not possible). They had conventional HRPC management as the PRD patients. For survival study, they retrospectively served as "controls".All 26 PRD patients with HRPC had prior PSA relapse following secondary hormonal manipulations (anti-androgen addition or withdrawal and then diethylstilbestrol), thus defining HRPC. Mean PSA at PRD entry is

Table 3
Group III foodstuffs and drinks > 201 nmol/g/ml PA, are forbidden except two out of every seven days.

Calamari, squid, oysters, muscles, crab, scallops
Liver mousse, chitterlings, duck-liver pâté, pork liver pâté
Garlic, chervil, tarragon, cabbage, broccoli, parsley, mushrooms, green peas, egg plants, ripe tomatoes, courgette (marrow), oranges
Hazelnuts, almonds, pistachios, peanuts, bananas
Sweet Cantal cheese with rind, Roquefort, Comté and Saint-Nectaire cheese.
Wheat
Mustard, tinned gherkins, tomato concentrate
Instant mashed potatoes, minced spinach, lentils, chickpeas, ratatouille, sauerkraut