Polyamine-reduced diet in metastatic hormone-refractory prostate cancer (HRPC) patients

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Abstract
Polyamine (PA) deprivation is effective in prostate carcinoma models. We have assessed the observance by patients, tolerance and side effects of a PA-reduced diet (PRD) and intestinal decontamination (ID), in order to reduce PA dietary and intestinal bacterial pools, in metastatic, hormone-refractory prostate cancer (HRPC) patients. A total of 13 volunteers (mean age, 67 ± 10 years) with metastatic HRPC were proposed for PRD and ID (0.75 g/day of oral neomycin every other week). The mean time from HRPC diagnosis to the start of the diet was 12 ± 8 months. Of the total 13, seven patients had received prior chemotherapy or Estramustine phosphate. PRD was obtained after HPLC assessment of PA contents in current foods and given 5 days a week. Toxicity, performance and pain status were assessed according to the World Health Organisation and EORTC scales. Prostatic specific antigen (PSA), blood counts, ionograms, transaminases and erythrocyte PA spermidine (Spd) and spermine (Spm; assessed by HPLC) were evaluated regularly. Mean observance was 8 ± 7 months (range, 2–26 months). One case of grade II toxicity to neomycin was observed. Cancer-specific survival (after the diet) was 14 ± 7 months, and two patients are still alive. All the other patients have died of their cancer at 12 ± 6 months (range, 4–20 months). Cancer-specific survival after hormonal escape was 27 ± 11 months (range, 9–45 months). Performance status was improved during the regimen and deteriorated 3 months after stopping. Pain score was improved (1.3 versus 0.6; \(P = 0.04\)) during the diet and increased (2.1 versus 0.3) 3 months after stopping. Erythrocyte Spd (11.6 ± 7 versus 7.7 ± 2 nmol/8 \(\times 10^9\) erythrocytes; \(P = 0.036\)) and Spm (7 ± 6 versus 3.9 ± 1.6 nmol/8 \(\times 10^9\) erythrocytes; \(P = 0.036\)) levels were significantly reduced at 3 months. One patient had a >50% reduction in PSA, three patients had PSA stabilization for 6 months. PSA progression was observed in all other patients. No significant modification of other studied biological parameters was noted. Reducing PA dietary intake and ID is a well-observed and tolerated regimen and seems to be beneficial for patient quality of life and pain control. Patients with low initial PSA can experience durable stabilization. These encouraging results in such an aggressive disease certainly warrant further investigation.

Introduction
Prostate cancer has become the second leading cause of cancer death in the industrialized world. Early detection can diagnose more men with early-stage, potentially curable disease but patients with more advanced disease or relapsing after local treatment require hormonal therapy. Sooner or later, inevitably, for most of these patients, hormonal therapy will fail. Mean survival time for hormone-refractory prostate cancer (HRPC) patients is 12 months, as chemotherapy regimens have not yet prolonged survival [1].

Polyamine (PA) metabolism is important in the prostate gland [2–4] and a potential target in cancer [5]. More than 95% of circulating spermidine (Spd) and spermine (Spm) is transported by red blood cells and originate from extra-erythrocytic cell metabolism [6,7]. In 3LL Lewis lung carcinoma tumour-bearing mice, the tumoral origin of erythrocyte Spd has been determined [8,9]. In the same tumour model [10] and in partially hepatectomized rats [11] erythrocyte Spd levels and the Spd/Spm ratio were correlated to cell proliferation and appeared to be a reliable index of tissue hyperplasia.

We demonstrated that erythrocyte PA Spd and Spm levels are enhanced in prostatic carcinoma patients compared with controls with levels correlated to tumour stage. Spm levels are significantly higher in HRPC patients compared with others [12,13]. Furthermore, in metastatic patients, pre-hormonal treatment Spm levels significantly predict prognosis and hormonal escape [14,15].

PAs are available for tumour growth from cellular metabolism, intestinal bacterial pools and food. It has been demonstrated that PA deprivation, incorporating a PA-free diet, neomycin intestinal decontamination (ID) and ornithine decarboxylase and polyamine oxidase inhibitors, significantly

Key words: diet, polyamines, prostate cancer.
Abbreviations used: HRPC, hormone-refractory prostate cancer; PA, polyamine; PRD, PA-reduced diet; PSA, prostatic specific antigen; Spd, spermidine; Spm, spermine; ID, intestinal decontamination.

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Table 1 | Polyamine contents in regular food

<table>
<thead>
<tr>
<th>Permitted every day (&lt;100 nmol/g)</th>
<th>Permitted once in a while (101–200 nmol/g)</th>
<th>Forbidden (&gt;201 nmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td>Yoghurt</td>
<td>Carrots (young)</td>
</tr>
<tr>
<td>Meats, beef, veal, pork, poultry</td>
<td>Pasteurized cheese</td>
<td>Radishes</td>
</tr>
<tr>
<td>Eggs</td>
<td>Jams</td>
<td>Celery</td>
</tr>
<tr>
<td>Fish (fresh)</td>
<td></td>
<td>Green beans</td>
</tr>
<tr>
<td>Milk and white cheese</td>
<td></td>
<td>Oranges and juice</td>
</tr>
<tr>
<td>Pasta and rice</td>
<td></td>
<td>Bananas</td>
</tr>
<tr>
<td>Tomatoes, onions, mushrooms,</td>
<td></td>
<td>Prunes</td>
</tr>
<tr>
<td>lettuce, spinach, potatoes, beetroot</td>
<td></td>
<td>Grapefruit</td>
</tr>
<tr>
<td>Apples, pears, peaches, strawberries, grapes</td>
<td></td>
<td>Melon</td>
</tr>
<tr>
<td>Flour, margarine, butter, oil</td>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td>Salt and pepper</td>
<td></td>
<td>Fermented cheese: stilton, roquefort, gorgonzola, camembert</td>
</tr>
<tr>
<td>Biscuits</td>
<td></td>
<td></td>
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<tr>
<td>Water, coffee, tea</td>
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</tbody>
</table>

reduces tumour growth in the rat HRPC Dunning Mat LyLu tumour model [16] and enhances the potential of low-dose chemotherapy by cyclophosphamide [17].

In spite of the inavailability of the widely known ornithine decarboxylase inhibitor 2-difluoromethylornithine for our human trials, we have decided to start proposing a reduced-PA programme to our HRPC patients combining a PA-reduced diet (PRD) with ID (to reduce bacterial intestinal PA pools), and to assess its observance by patients, tolerance and effects.

Patients and methods

After written informed consent, 13 volunteers (mean age, 67 ± 10 years) with metastatic HRPC were proposed a PRD and ID (0.75 g/day of oral neomycin every other week). Mean time from HRPC diagnosis to the diet was 12 ± 8 months. A total of seven patients had received prior chemotherapy or Estramustine (a combination of high-dose oestrogens and a nitrous mustard). Previous therapy was continued but no other treatment, i.e. oestrogens, corticoids or chemotherapy, was introduced during the study.

PRD was obtained after HPLC assessment of PA contents in current foods and given 5 days a week. Three groups of foods were established according to their PA contents. Group I foods (containing <100 nmol/g PA) could be eaten freely, group II foods (101–200 nmol/g PA) could be eaten three or four times a week and group III foods (>201 nmol/g PA) were forbidden (see Table 1). Toxicity was noted. Performance and pain status were assessed according to the World Health Organization (grade 0, able to carry out all normal activity without restriction; grade 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; grade 2, ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours; grade 3, capable of only limited self-care; confined to bed or chair more than 50% of waking hours; grade 4, completely disabled; cannot carry on any self-care, totally confined to bed or chair) and European Organization for Research and Treatment of Cancer scales (grade 0, no antalgics; grade 1, occasional non-morphinic antalgics; grade 2, regular non-morphinic antalgics; grade 3, occasional morphinic antalgics; grade 4, regular morphinic antalgics). Prostatic specific antigen (PSA), blood counts, ionograms, hepatic transaminases and erythrocyte PA Spd and Spm (assessed by HPLC and expressed in nmol/8 × 10^9 erythrocytes) were regularly evaluated. The regimen was proposed for 6 months but patients could stop when they wished or continue after 6 months. The trial was approved by the local ethics committee. Results are expressed as means ± S.D. Statistics were performed with the non-parametric Wilcoxon test.

Results

Observance: mean regimen observance by patients was 8 ± 7 months (range, 2–26 months). Tolerance: only one case of mild toxicity to neomycin was observed (diarrhoea). Survival: cancer-specific survival (after the diet) was 14 ± 7 months. Only two patients are still alive; all the other patients died of their cancer after 12 ± 6 months (range, 4–20 months). Cancer-specific survival after hormonal escape was 27 ± 11 months (range, 9–45 months).

Performance status: six patients had improved performance status and four maintained a good status during the regimen. Performance deteriorated 3 months after stopping the regimen (Table 2).

Pain: use of antalgics was reduced as far as the therapeutic class was concerned and stopped altogether for two patients. The pain score was improved (1.3 versus 0.6; P = 0.04) during the diet. Some 3 months after stopping the diet the pain score was higher (2.1 versus 0.3; Table 2).

Biological responses were as follows. PSA: one patient had a >50% reduction in PSA (concomitant with diethylstilbestrol), one patient had PSA increases and decreases correlated with bad or good diet observance, and two...
patients had PSA stabilization for 6 months and are still alive. Progression of PSA was observed in all other nine patients. Erythrocyte PA: levels of Spd (11.6 ± 7 versus 7.7 ± 2 nmol/8 × 10^11 erythrocytes; P = 0.036) and Spm (7 ± 6 versus 3.9 ± 1.6 nmol/8 × 10^11 erythrocytes; P = 0.036) were significantly reduced at 3 months. Other parameters: no significant modification of other studied biological parameters was noted.

Discussion

The outcome for the metastatic HRPC patients is grim. At this stage of hormonal escape, only palliative treatment can be proposed, focused on quality of life and pain control. Chemotherapy regimens have not yet enhanced survival time and may significantly alter quality of life due to adverse side effects.

Proposing a therapeutic dietary regimen in cancer is a novel approach. Up to now, dietary complements (i.e. vitamins and hypercaloric supplements) were given to patients with an altered general status to accompany other treatments. Accepting such a dietary protocol, when many other treatments have failed, is not obvious for patients, especially in France, when culinary pleasures are entirely part of quality of life and culture and when life expectancy is short. That is probably why three out of our first four patients asked to stop being part of the study because they had experienced PSA progression. Although PSA progression (translating into tumour growth for the patient) was of prime concern throughout the study, significant improvement of performance status and pain control progressively enhanced patient observance to the regimen and no drop-outs occurred later in the study. Remarkably, four patients recovered enough well-being and strength to be able to once again undertake major work at home, such as cementing and paving a terrace, working in the fields stacking hay, and dancing.

Improved performance status is probably linked to pain control, which is remarkably improved or maintained by the regimen in patients, who all had bone metastases. Pain control in patients with rising PSA cannot be explained by a reduced tumour burden. One explanation might be due to PA deprivation itself, which has indeed been shown to provoke analgesic effects in animals submitted to painful stimuli [18,19]. Furthermore, the impact of the regimen on quality of life is outlined by a progressive degradation of performance status and pain after the regimen is stopped.

Improved performance status and better pain control by the regimen leads to a much better quality of life during survival. The standard actual chemotherapy regimen combining mitoxantrone and prednisolone yields a 29% palliative response rate without prolonging survival time (median, 12 months) and with patients experiencing nausea and vomiting (29%), alopecia (24%), and to a lesser extent haematological and cardiac toxicity [20].

The impact of this regimen on the course of the disease is difficult to assess. Using PSA as an endpoint, patients with high initial PSA levels did not respond favourably. The only patient that had a major decline in PSA took concomitant oestrogens shortly before the regimen without telling us. It would have been usual not to retain this patient in the study but we should point out that such durable responses to oestrogens are not so frequent. Two patients had stabilized PSA levels for 6 months and then their PSA values rose slowly to respond (under the regimen) to a third line of treatment. These two patients are still alive and well. One patient had an anecdotal response and the rise of his PSA correlated with his lack of observance of the diet. These three patients initially had low PSA levels, which could lead us to speculate that the regimen is more effective on the PSA response if given early after hormone escape. Overall survival is noteworthy, with five patients (38%) surviving 20 months compared with only a 20% survival rate when chemotherapy is proposed [20], but the small number of patients in our study cannot allow any firm conclusions.

These encouraging results with only a PRD and neomycin treatment show that interfering with PA metabolism may be of importance in the treatment of prostate cancer. PA Spd and Spm erythrocyte levels can be reduced by this regimen. This suggests that refining the content of PAs in food for culinary diversification and effect optimization and also the development of PA-free dietary complements would be beneficial. The next step would then be to combine the regimen with low-dose non-toxic oral chemotherapy.

Conclusions

Reducing PA dietary intake and ID is a well-observed and tolerated regimen and seems to be beneficial for patient quality of life and pain control. Patients with low initial PSA values can experience enduring stabilization. These encouraging results in such an aggressive disease certainly warrant further investigation.

Table 2  Mean pain scores and performance status during and after the regimen

<table>
<thead>
<tr>
<th></th>
<th>During regimen</th>
<th>After stopping the regimen</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1 day</td>
<td>3 months</td>
</tr>
<tr>
<td>Pain score</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Performance status</td>
<td>0.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>
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References


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