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Suppression of Alkaline Phosphatase in Prostate Cancer Patients by High Dose Intravenous Vitamin C Treatment: Three Cases

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Abstract

Background: Intravenous vitamin C (IVC) may have anti-cancer and anti-inflammatory properties. Many studies have demonstrated that IVC has a good safety profile, and can improve the quality of life of cancer patients. IVC has been proposed as an adjuvant treatment for cancer in conjunction with other therapies.

Design: A retrospective study was conducted using clinical data from the Riordan Clinic (Wichita, KS) database. We collected data, when available, on the following patient characteristics at diagnosis and during the courses of IVC therapy: age, tumor stage, Gleason score, serum prostate specific antigen (PSA) and alkaline phosphatase (ALP) levels, and location of metastases. The study was conducted under the Institutional Review Board Approval of the Riordan Clinic. Demographics were limited to ensure patient confidentiality.

Results: Tracking the changes in PSA and ALP in patients for whom data was available indicated that the level of ALP correlated with the presence of metastasis in our patient group. In the few cases where we found both PSA and ALP measurements, these variables tended to track each other and decrease during IVC therapy. The reductions in PSA and/or ALP concentrations (or their stabilization) were reversed once treatment stopped.

Conclusion: Further research into the use of IVC in prostate cancer patients is warranted.

Introduction

Like most other solid malignancies, prostate cancer can metastasize to distant organs such as the liver, lungs and brain, but has much stronger affinity for the bones. In prostate cancer metastasis to bone is the main cause of death. In autopsy studies, more than 80% of the men who had died from prostate cancer possessed bone metastases (Jin, Dayyani & Gallick, 2011; Bubendorf, Schopfer,

Wagner, et al., 2000). In patients with localized prostate cancer, the 5-year survival approximates 100%; however, in patients in whom distant metastases have occurred, the 5-year survival drops to 31% (Jemal, Siegel, Xu, & Ward, 2010).

Bone metastases from prostate cancer are characterized by both excessive bone formation and resorption due to the increased number and activity of osteoblasts and osteoclasts (Cook, Coleman, Brown, et al., 2006). When metastatic cancer cells grow in the bone, they also produce many of the growth factors, resulting in stimulation of proliferation and maturation of osteoblasts and osteoclasts that, in turn, produce or release growth factors that further stimulate metastatic growth.

One of the markers that partly reflects the osteoblastic activity is total serum alkaline phosphatase (ALP), which is most often used for indicating bone formation (Brown, Cook, Major, et al., 2005). Although serum ALP is a relatively nonspecific biomarker, patients with bone metastasis and an elevated baseline ALP are likely to have bone as the dominant source of ALP (Sonpavde, Pond, Berry, et al., 2012).

ALP measurements can be used alongside bone scintigraphy in the diagnosis and follow-up of bone metastases in patients with prostate cancer (Morote, Lorente & Encabo, 1996; Wymenga, Boomsma, Groenier, et al., 2001). Moreover, as was shown in large multivariate analyses of patients with metastatic androgen-independent prostate cancer, elevated levels of serum total ALP, were independently associated with shorter survival and were predictors of early death (Smaletz, Scher, Small, et al., 2002; Halabi, Lin, Kelly, et al., 2014; Ramankulov, Lein, Kristiansen, et al., 2007; Johansen, Brasso, Iversen, et al., 2007; Robinson, Sandblom, Johansson, et al., 2008).

Assessment of ALP levels before and during prostate cancer treatment might provide useful prognostic information and indicate the efficacy of treatment on the suppression of bone metastasis.

Most current treatments for individuals with bone metastases have only palliative effects, with little effect on long-term survival (Costa, & Major, 2009; Lee, Saylor, & Smith, 2011). The main treatment at this stage is castration, either surgical or medical, ending the patients' testosterone production and causing a temporary regression in disease activity. Eventually, the cancer will progress, usually within two years.

In our study, we investigated the effect of high dose intravenous vitamin C (IVC) on the marker of the osteoclast activity, i.e., ALP, in several patients treated at the Riordan Clinic for whom the detailed data was available. We found that IVC provided a benefit to patients with metastatic prostate cancer by suppression of ALP levels.

Method

We analyzed data of prostate cancer patients from the Riordan Clinic database who were treated with IVC and who had ALP and PSA levels measured at some point before and after treatment. The study was conducted under the Institutional Review Board Approval of Riordan Clinic (Wichita, KS). Demographics were limited to ensure patient confidentiality.

The parameter we investigated in detail was ALP, a marker of bone formation that can be used to some degree to track bone metastases in prostate cancer patients. ALP is one of the older biochemical tools for investigating and monitoring prostate cancer, and a reliable indicator of osteoblastic activity and bone metastases (Lieberherr, Vrevan, & Vaes, 1973). Using the LabNet laboratory management program (Henry Schein, Melville, NJ), we collected data, when available, on the following patient characteristics at diagnosis and during the courses of IVC therapy: age, tumor stage and grade at diagnosis, Gleason score, serum PSA and ALP levels, and location of metastases (if present). Note that not all of these parameters were available in the database for all patients.

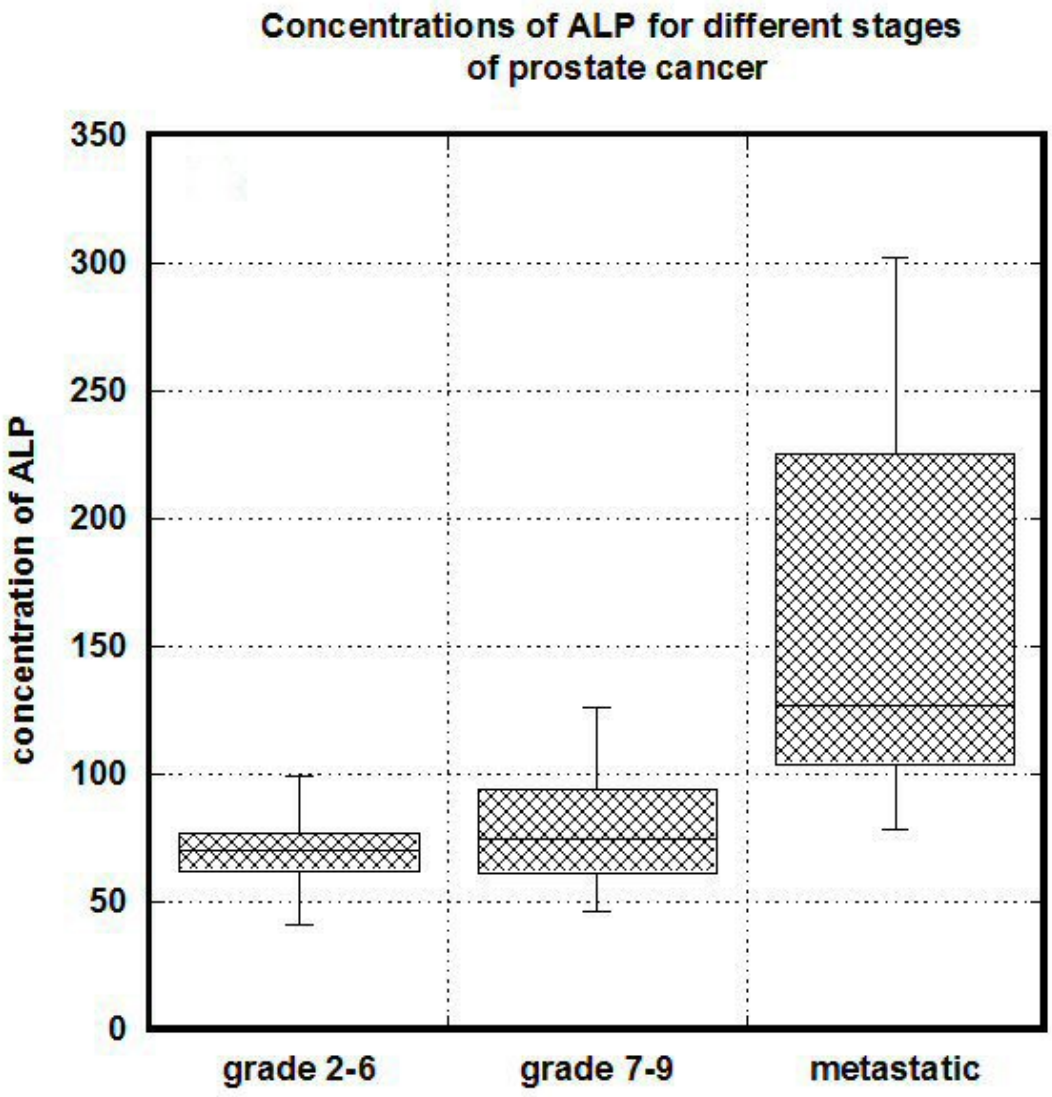
All laboratory tests were conducted by the Riordan Clinic Bio-Center Laboratory (Wichita, KS), a licensed and certified medical laboratory working in full compliance with HIPPA regulations and using standard methodologies. Serum PSA concentrations were determined using an equimolar immunoassay (PSA kit, Abbott Laboratories, UK). According to this protocol, the normal range for PSA is 0.0 to 4.0 ng/mL. Serum ALP was measured using a standard commercially available assay, with the normal range in our laboratory being 30U/L- 90 U/L.

Statistical analyses were carried out using the Excel spreadsheet program (Microsoft, Redmond WA) while graphs were constructed using the Kalaidagraph program (Synergy Software, Reading PA).

Results

Our database contained more than 100 prostate cancer patients; though complete information on tumor stage, presence or absence of metastases, and history concerning the use of conventional therapies was not available for some of these subjects. The effect of tumor stage on values of ALP marker is shown in Figure 1. Distributions of ALP were constructed for different Gleason scores and for localized or metastatic disease. The stages of prostate cancer were divided by Gleason scores of 6 or less, without metastases; Gleason scores of 7 or more, without metastases; Gleason Scores of 7 or more, with metastases. Box plots indicate quartile ranges (1st quartile to 3rd quartile in box, with line inside box representing a median value). According to our data a significant increase in ALP was measured for metastatic state of the cancer (ALP averages 70 ±14 U/L for grades 2-7, 79±24 U/L for grades 7-9, and 196±127 U/l for metastatic stage of disease). Increases in these markers with metastatic stage shown here are as expected based on prior reports.

Figure 1. Relationships between tumor stage and serum concentrations of ALP. The stages of prostate cancer were divided by Gleason scores of 6 or less without metastases; Gleason scores of 7 or more without metastases; Gleason Scores of 7 or more with metastases.



Since ALP was not measured very often, we were confined to examining three subjects who had detailed ALP vs. time data. The data for these subjects are shown in Figure 2 (a-c), with descriptions of each patient given below. The patients had the levels of ALP at the beginning of IVC treatment 500 U/L (patient 1), 110 U/L (patient 2) and 600U/L (patient 3). According to the studies [17] ALP levels of >90 U/L indicated a 60% chance for the presence of bone metastases.

Data in Figure 2 presented concentrations of PSA shown by open circles on right Y-axis and concentrations of ALP are shown by dark squares on the left Y-axis. Open squares indicate times when IVC treatments were given.

Figure 2. ALP concentration (IU/L) and the PSA concentration (ng/mL) for Patients 1, 2, and 3. Concentrations of PSA are shown by open circles on right Y-axis and concentrations of ALP are shown by dark squares on the left Y-axis. Open squares indicate times when IVC treatments were given.

Figure 2(a)

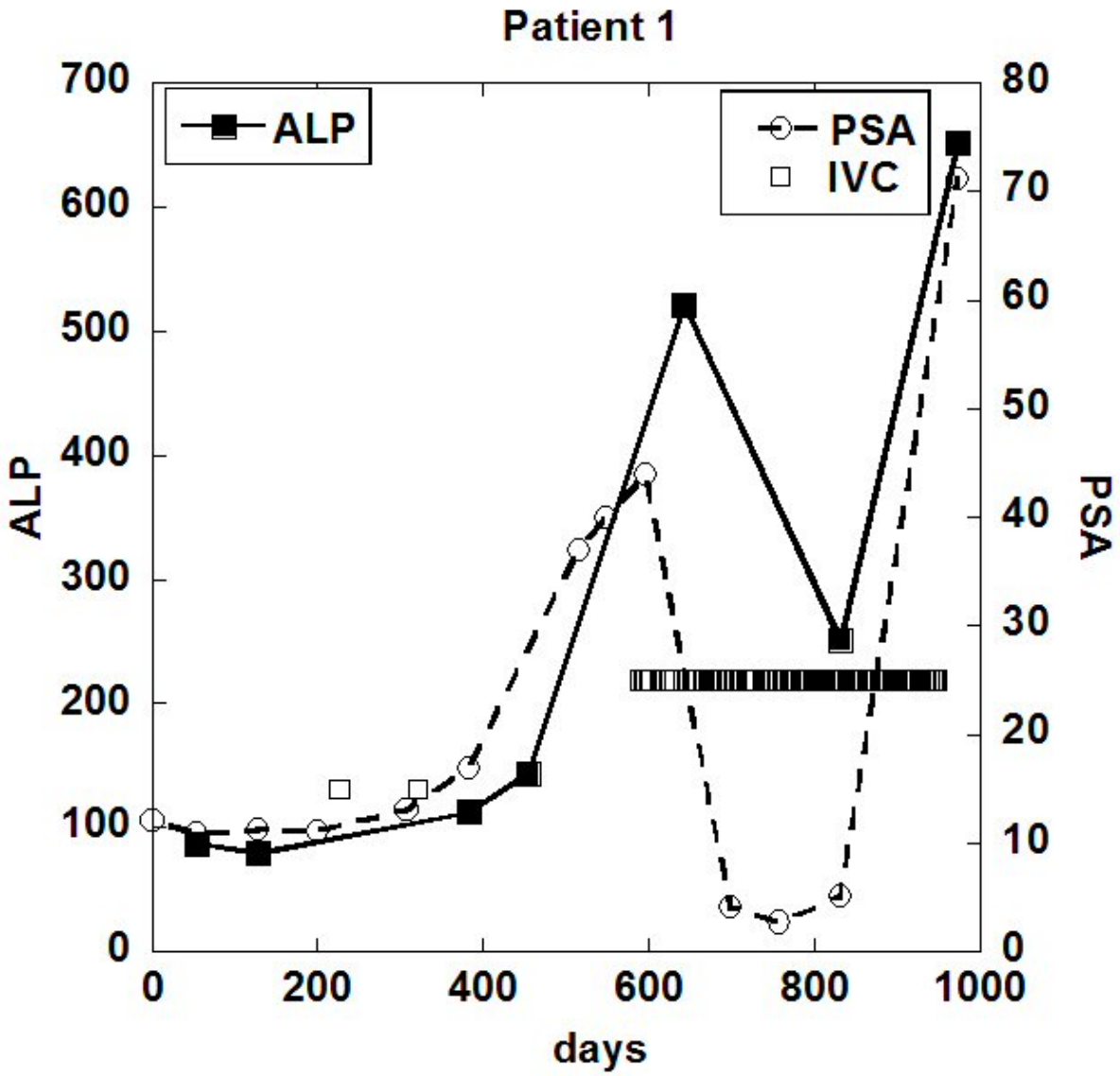


Figure 2(b)

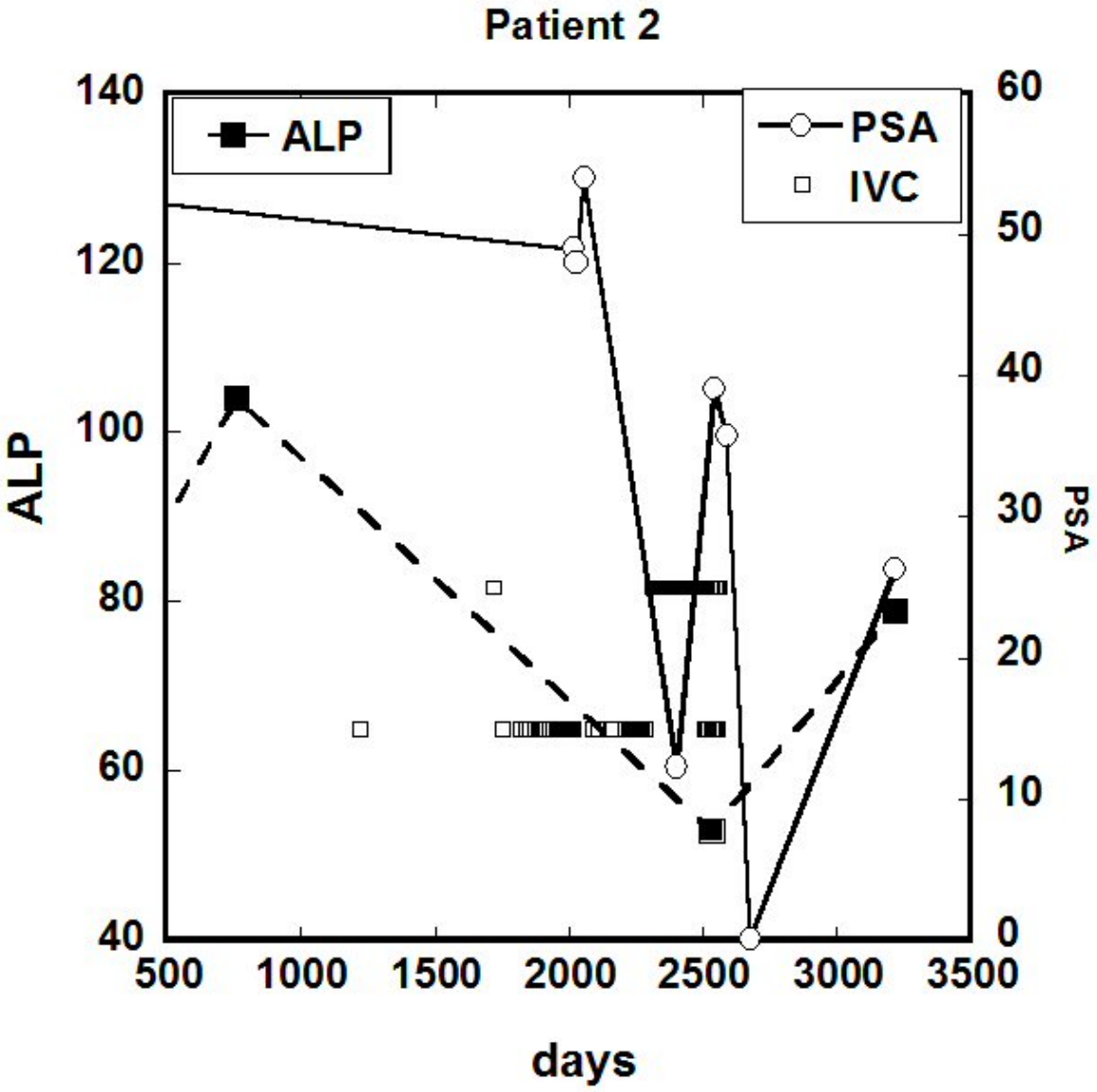
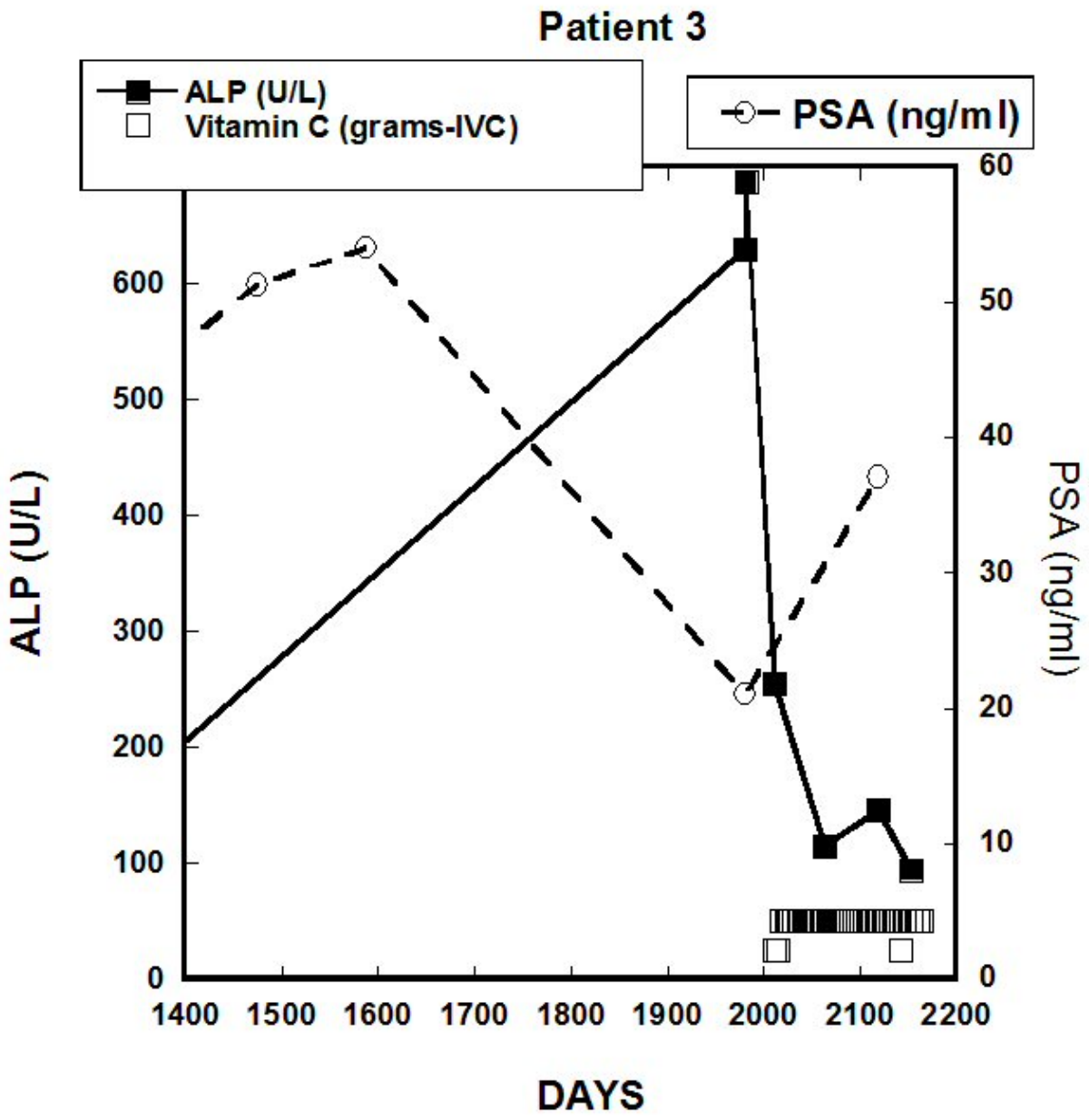

Patient 2
ALP
PSA
IVC
ALP
PSA
days
140
120
100
80
60
40
60
50
40
30
20
10
0
500
1000
1500
2000
2500
3000
3500

Figure 2(c)



In these patients, the onset of IVC therapy, and the increasing of its frequency, led to reductions in ALP values. PSA levels also tended to track with APL levels for these subjects.

- Patient 1 (Figure 2a): Had transurethral resection of prostate (TURP) five years before he came to the clinic for IVC treatment. He had a Gleason score at diagnosis of 4 and elected nutritional therapies, refusing surgery and radiation. During next half year he had 42 IVC treatments (25 grams IVC each), an average of one treatment every five days. PSA concentration was reduced from 41 ng/ml to 5 ng/ml. During treatment patient said that he had best sleep in many years. Patient continued treatment for additional three months and then stopped treatment.

One month after discontinuation of the treatment he complained of the increased pain, and his serum PSA increased to 71ng/ml. Patient 1 also showed ALP increases from 149 U/L to 512 U/L in the six months prior to treatment. After 76 IVC treatments at 15 g each, ALP concentration decreased to 251 U/L. This also correlated with a decrease in PSA. One month after the discontinuation of IVC therapy, the concentrations of PSA and ALP showed sharp increases.

- Patient 2 (Figure 2b): Came to the clinic with diagnosis of prostate cancer. He refused a biopsy, bone scan, and conventional therapy. The patient was treated with 15 grams IVC at a frequency of roughly once per week. During the first year of treatment, his PSA concentration decreased from 54 ng/mL to 12 ng/mL, and eventually was reduced to normal levels after another year of treatment. One year without treatment, his PSA levels increased to 26 ng/mL. ALP levels over time decreased from an initial level of 105 U/L to 53 U/L after 80 IVC treatments, and increased to 73 U/L one year after discontinuation of treatment.

- Patient 3 (Figure 3c): First came to the Riordan Clinic having a “hard and nodular” prostate. He did not have a biopsy and refused chemotherapy. Seven years later, metastases were diagnosed in the liver and bone. At this time, the patient’s ALP concentration was 687 U/L. The patient had surgery (cholecystojejunostomy and gastrojejunostomy) prior to starting IVC therapy. Two weeks post surgery ALP concentration was reduced to 255 U/L. At this point the patient started 50 g IVC treatments two times per week. Two months later the level of ALP decreased to 155 U/L. After 3 months and 24 IVCs ALP decreased further to 94 U/L. During treatment with IVC the patient recorded that he was feeling a lot better. PSA concentrations ranged from 37 to 20 ng/ml during the period of IVC treatment.

These three cases show dynamic changes in ALP during IVC therapy. Since ALP suppression is thought to indicate suppression of osteoblastic bone formation in prostate cancer patients, the ALP decreases with IVC treatment are encouraging, albeit preliminary.

Discussion

In an effort to develop effective alternative strategies that increase the therapeutic efficacy and minimize the systemic toxicity of chemotherapeutic agents, many efforts are being directed towards the investigation of nutraceutical agents and in particular high dose vitamin C as a therapeutic agent. The purpose of this study was to determine if IVC therapy could suppress ALP levels in prostate cancer patients. Our detailed analysis of three cancer patients from the Riordan Clinic indicates that this may well be the case, and suggests that further systematic clinical studies into this phenomenon are warranted. Our conclusions can be summarized as follows:

1. Consistent with earlier studies, we found that the increase in the level of ALP correlated with the presence of metastasis in our patient group;

2. In the few cases where we found both PSA and ALP measurements recorded, these variables tended to track each other, and they tended to both decrease during IVC therapy; and

3. In several cases, the reductions in PSA and/or ALP concentrations (or their stabilization) were reversed once treatment stopped.

Our preliminary observations concerning IVC therapy and ALP levels are encouraging. According to a large multivariate analysis of patients with metastatic androgen-independent prostate cancer, elevated serum ALP levels were independently associated with shorter survival (Halabi, Lin, Kelly, et al., 2014); moreover, ALP levels have been associated with progression of skeletal metastases in patients with prostate cancer (Lorente, Morote, Raventos, et al., 1996; Lein, Wirth, Miller, et al., 2007), and have also been shown to be significant predictors of early death (Ramankulov, Lein, Kristiansen, et al. 2007).

While osteoclastic processes are seen as a potential target for prostate cancer therapy, chemotherapeutic drugs aimed at inhibition of these processes offer only a few months advantage over placebo in prolonging survival time (Orwoll et al., 2012), and often produce side effects such as osteonecrosis of the jaw, hypocalcemia, and deterioration of renal function (Gartrell et al., 2014). IVC therapy is unlikely to produce such severe side effects, and may act as an adjuvant to reduce the side effects of other agents. Also, ascorbic acid induces formation of the collagen matrix and enhances osteoblast differentiation (Urban, Höhling, Lüttenberg, et al., 2012; Takamizawa et al., 2004; Hausmann, 1967). Since cancer patients are often ascorbate deficient, and have an abnormal demand for ascorbate due to oxidative stress, using IVC to support these processes may help prevent metastasis in prostate cancer patients. In summary, our study is the first to address dynamic changes in ALP during high dose IVC. The data demonstrates the putative clinical benefits when high dose IVC is administered to prostate cancer patients with metastasis.

The study was limited by the small number of patients in our database who had sufficiently detailed PSA and ALP measurements, and consistently participated in the high dose IVC protocol. A controlled clinical study using a larger population of prostate cancer patients would allow for a more rigorous assessment of the promising trends reported in this study.

Competing Interests

The authors declare that they have no competing interests.

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