Does Perioperative Oxandrolone Improve Nutritional Status in Patients With Cachexia Related to Head and Neck Carcinoma?

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**Background:** Cancer cachexia affects up to over 50% of advanced head and neck cancer (HNC) patients. To date, the potential utility of anabolic steroids in perioperative cachectic HNC patients has not been determined.

**Methods:** Retrospective review of pre- and post-oxandrolone administration prealbumin levels in 18 perioperative HNC patients between October 2007 and October 2014 at a tertiary academic medical center.

**Results:** The median pretreatment prealbumin was 88.5 mg/L. The median post-treatment prealbumin was 227 mg/L. The median interval improvement of the prealbumin level was 131.5 mg/L. The median differences between the pretreatment and post-treatment prealbumin levels were found to be statistically significant ($P < .001$). Subjective improvement in wound healing was also observed.

**Conclusions:** Perioperative administration of oxandrolone resulted in objective improvements in prealbumin levels and subjective improvements in surgical wounds. Oxandrolone administered 10 mg twice daily (BID) for 10 days may be a useful adjunct in the perioperative care of nutritionally deficient HNC patients who are at risk for or have demonstrated impaired wound healing.

**Key Words:** Head and neck cancer, cancer cachexia, anabolic steroids, oxandrolone, prealbumin.

**Level of Evidence:** 3

A Special Visual Abstract has been developed for this paper
INTRODUCTION

Cancer cachexia is a paraneoplastic syndrome characterized by progressive weight loss, anorexia, metabolic alterations, depletion of lipid stores, and severe muscle wasting which leads to a constant state of catabolism. Although multiple international consensus groups have proposed different frameworks of diagnostic criteria for cancer cachexia incorporating these various factors, there is not one set standard. In general, weight loss is caused by decreased intake or increased energy expenditure. However, in cachectic patients, the body tissue wasting is multifactorial, with anorexia, early satiety, blunted muscle protein synthesis, increased muscle protein breakdown, enhanced lipolysis, and increased systemic inflammatory mediators (interleukin 6, interleukin 8, tumor necrosis factor alpha) all playing roles. From these disturbances, patients experience nausea, vomiting, and gastrointestinal symptoms. Psychiatric disturbances, such as depression, only further exacerbate their poor nutritional intake. As a result, cachexic patients experience a poorer quality of life and survival and are at increased risk for infection and perioperative complications such as wound dehiscence and fistula formation.

Anabolic steroids have long been studied as an aid in the reversal of cachexia in burn victims, postoperative patients, and HIV/AIDS wasting myopathy patients. Their use has led to significant improvements in nitrogen balance, weight, and quality of life measures. The literature on the use of anabolic steroids in cancer cachexia, however, is much less robust. Many studies look at their use alongside multiple other agents such as corticosteroids, appetite stimulants, ghrelin mimetics, anti-IL-6 antibodies, and nonsteroidal selective androgen receptor modulators as agents with the potential to have significant impact for patients with cancer cachexia. Others postulate their potential to inhibit the catabolic process. Trials specifically looking at the use of oxandrolone, a synthetic testosterone analogue, in the cachectic population, are even sparser. The most relevant study has compared the use of oxandrolone to megestrol acetate, a synthetic derivative of progesterone, in cachectic patients with solid tumors undergoing chemotherapy. Interestingly, the effects of the two medications were found to be complimentary, leading to the proposal that they be used as adjuncts, which may result in the most effective treatment for this patient population. This conclusion is actually reflective of prior reviews which have suggested that a multimodal approach to treating cancer cachexia may be necessary given it is a multifactorial process. To date, the potential utility of anabolic steroids in perioperative cachectic HNC patients has not been determined.

Oxandrolone is an orally administered, anabolic-androgenic steroid approved by the Food and Drug Administration (FDA) for weight gain following disease-related weight loss. It is an agonist of the androgen receptor and increases protein synthesis thereby increasing muscle growth and lean body mass. It has been shown to significantly improve weight, performance status, and quality of life in cancer patients. Studies have revealed promising results with an oral dose of 10 mg BID. Oxandrolone is ideal for populations at high risk for comorbid liver disease as it is primarily excreted in the urine and has minimal hepatic metabolism. It also has the benefit of fewer androgenic effects with a more favorable ratio of anabolic : androgenic potency compared to other anabolic androgenic steroids. It does, however, come with a black box warning for peliosis hepatitis, hepatic tumors, and lipid changes.

The objective of this study was to investigate the impact of oxandrolone on cancer cachexia in HNC patients with impaired wound healing during the perioperative period as measured by prealbumin levels.

MATERIALS AND METHODS

Beginning in 2007, malnourished HNC patients who were felt to be at high risk for (ie, history of wound healing issues or recent progressive weight loss, anorexia, muscle wasting, or lipid depletion) or had demonstrated impaired wound healing (either known outpatient wound healing failure or inpatient wound healing/nonhealing during the postoperative period which had already required repeat surgical procedures to address fistulas, dehiscences, etc) were selectively treated with oxandrolone. Patients were otherwise treated with the postoperative standard of care. After obtaining approval from the Institutional Review Board at the University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma, a retrospective chart review was performed to analyze the effectiveness of this practice. The pharmaceutical database was utilized to identify all HNC patients diagnosed with squamous cell carcinoma and treated with oxandrolone during the perioperative period between October 2007 and October 2014. A total of 53 patients were identified. Those without documented pretreatment and post-treatment prealbumin levels were excluded, leaving 18 in the study group.

The patient charts were reviewed and data collected included demographics, duration of inpatient drug administration, and pretreatment and post-treatment prealbumin levels (Table I). The change in prealbumin level over the course of therapy for each patient was calculated along with the median pretreatment and post-treatment prealbumin levels for the group. The median change in prealbumin level was then analyzed using a paired sample Wilcoxon signed-rank test. The data were then further analyzed to determine the duration of treatment necessary to demonstrate a measurable response in prealbumin levels. The clinical course of each patient was also reviewed to determine if subjective improvement in surgical wounds was identified during the course of therapy.

RESULTS

Eighteen patients were identified who met inclusion criteria. The patients ranged in age from 44 to 75 years with an average age of 63.4 years; 11 (61%) were men and seven (39%) were women. Patients received oxandrolone for an average of 22.8 days (range: 7–45 days). Table II outlines oxandrolone dosing for each patient. The majority of patients (15/18) received

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TABLE I. Patient Demographics.

| Patient | Age  | Cancer Type       | Prior Therapy | Initiation POD | Additional Procedures* | Feeding Tube | Antibiotics |
|---------|------|-------------------|---------------|----------------|------------------------|--------------|-------------|
| Male 1  | 71   | Hypopharynx       | No            | 12             | 2                      | Yes          | Inpatient   |
| Male 2  | 62   | Glottic larynx    | **RT**        | 15             | 2                      | Yes          | Inpatient   |
| Male 3  | 75   | Glottic larynx    | No            | 1              | 0                      | Yes          | None        |
| Male 4  | 67   | Oral cavity       | No            | 8              | 1                      | Yes          | Both        |
| Male 5  | 63   | Oral cavity       | No            | 22             | 2                      | Yes          | Inpatient   |
| Male 6  | 71   | Oral Cavity       | No            | 12             | 1                      | Yes          | Inpatient   |
| Male 7  | 54   | Supraglottic larynx| **CRT, HBO**| 17             | 5                      | Yes          | Inpatient   |
| Male 8  | 55   | Glottic larynx    | **RT**        | 7 mo           | 1                      | Yes          | Inpatient   |
| Male 9  | 50   | Oral cavity       | No            | 2              | 1                      | Yes          | Inpatient   |
| Male 10 | 63   | Supraglottic larynx| **CRT**      | 16 mo          | 2                      | Yes          | Inpatient   |
| Male 11 | 64   | Oral cavity       | No            | 10             | 3                      | Yes          | Inpatient   |
| Female 1| 63   | Supraglottic Larynx| No            | 6              | 1                      | Yes          | Both        |
| Female 2| 72   | Oral cavity       | No            | 2              | 0                      | Yes          | Inpatient   |
| Female 3| 51   | Supraglottic larynx| **RT**        | 6              | 2                      | Yes          | Both        |
| Female 4| 64   | Oral cavity       | **CRT**       | 14             | 3                      | Yes          | Inpatient   |
| Female 5| 62   | Oropharynx        | **CRT**       | 16             | 5                      | Yes          | Inpatient   |
| Female 6| 44   | Supraglottic larynx| No            | Preop          | 0                      | Yes          | Inpatient   |
| Female 7| 62   | Hypopharynx       | **CRT**       | 2 mo           | 1                      | Yes          | Both        |

Eight patients received prior therapy (bold). Four patients had feeding tubes placed preoperatively (italic).

*Additional Procedures: number of surgical procedures performed in addition to the admission operation to address wound healing issues (ie, fistulas, dehiscences, feeding tube placement, etc) during the hospitalization during which oxandrolone was administered. Both: received inpatient and also outpatient antibiotics after hospital discharge.

CRT = chemotherapy and radiation; HBO = hyperbaric oxygen therapy; POD = postoperative day; RT = radiation therapy.

TABLE II. Oxandrolone Dosing Schedule.

| Patient | Dose (mg) | Interval | Days of Treatment |
|---------|-----------|----------|-------------------|
| Male 1  | 10        | BID      | 27                |
| Male 2  | 5         | BID      | 11                |
| Male 3  | 10        | BID      | 7                 |
| Male 4  | 10        | BID      | 11                |
| Male 5  | 10        | BID      | 15                |
| Male 6  | 10        | BID      | 29                |
| Male 7  | 10        | BID      | 19                |
| Male 8  | 10        | BID      | 28                |
| Male 9  | 10        | BID      | 28                |
| Male 10 | 10        | BID      | 44                |
| Male 11 | 10        | BID      | 18                |
| Female 1| 10        | BID      | 17                |
| Female 2| 10        | BID      | 34                |
| Female 3| 10        | QD, BID  | 16                |
| Female 4| 10        | BID      | 30                |
| Female 5| 10        | BID      | 45                |
| Female 6| 10        | TID      | 18                |
| Female 7| 2.5       | QID      | 14                |

Patients received oxandrolone for an average of 22.8 days (range: 7–45 days). The majority of patients (15/18) received 10 mg PO BID, with one patient receiving 5 mg PO BID, another 2.5 mg PO QID, and the third 10 mg PO TID.

BID = twice daily; PO = per os; QD = daily; QID = four times daily; TID = three times daily.

10 mg per os (PO) BID, with one patient receiving 5 mg PO BID, another 2.5 mg PO four times daily (QID), and the third 10 mg PO three times a day. The decision on when to start treatment (ie, preoperatively or postoperatively/which postoperative day), the dose administered, how often prealbumin was checked (ie, every 4, 8, or 14 days), and the length of therapy (ie, total days administered inpatient as no patients was discharged on oxandrolone therapy) were all nonstandardized decisions made by the treating surgeon, which accounts for the variability seen in these numbers.

Table III shows the pretreatment and post-treatment prealbumin levels for each patient. The normal range in our laboratory was 180–360 mg/L. The median pretreatment prealbumin was 88.5 mg/L (range: 75–160 mg/L), with every patient demonstrating a pretreatment prealbumin level below the lower limit of normal. The median post-treatment prealbumin was 227 mg/L (range: 148–370 mg/L). The median interval improvement of prealbumin was 131.5 mg/L (range: 61–252 mg/L). Utilizing the Wilcoxon signed-rank test, the median differences/improvement between the pretreatment and post-treatment prealbumin levels were found to be statistically significant ($P < .001$).

All 18 patients demonstrated an overall improvement in prealbumin levels during the course of their treatment. The degree of improvement and the time over which this occurred, however, varied by patient. The earliest response to therapy was seen after 4 days; 50% showed improvement by day 8, 70% by day 10, and 100%
by day 18. Concurrent subjective improvement in wound healing was also observed, as documented by the evaluating surgeon.

Given the risk for drug-related hepatotoxicity, combined with the high percentage of HNC patients who abuse alcohol, liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were checked periodically on each patient during the course of treatment. Of the 18 patients, only two (male 1, female 7) demonstrated mild increases above the upper limit of normal in both AST and ALT during the course of treatment. Male 1 demonstrated this increase on day 7 of treatment, while female 7 demonstrated this increase on day 13. Oxandrolone was not stopped in male 1, and he demonstrated stability at this mild elevation in all subsequent AST values and a steady decline in ALT over the subsequent 2 weeks of treatment. Oxandrolone was stopped in female 7, and labs checked 2 days later demonstrated return of her AST to normal with stable elevation of her ALT. No other medication intolerances were documented or caused discontinuation of therapy in the study group.

**DISCUSSION**

The purpose of this study was to evaluate the effect of oxandrolone administration on cancer cachexia in HNC patients with impaired wound healing during the perioperative period as measured by prealbumin level. Nearly all of the patients studied suffered from dysphagia, odynophagia, anorexia, and overall deconditioning prior to the commencement of their surgical therapy. After administration of oxandrolone 10 mg PO BID over the course of 7–14 days, an objective improvement in prealbumin levels was identified in the majority (14/18) of patients. All patients ultimately achieved an improvement in prealbumin after 18 days of treatment (Fig. 1). Subjective clinical improvement, as assessed by daily physical exam, was found to correlate with these increases in prealbumin. The patients treated with oxandrolone demonstrated reversal of complications including wound dehiscence, fistula formation, and infection. None of the patients experienced side effects such as nausea, emesis, acne, headache, mood change, or trouble sleeping. An increase in AST and ALT was identified in only two patients, and in both cases, the rise was minimal over the upper limit of normal. Overall, oxandrolone was shown to be a relatively safe medication and was well tolerated by these HNC patients.

**TABLE III. Interval Improvement in Prealbumin.**

| Patient | Pretreatment | Post-Treatment | Interval Improvement |
|---------|--------------|----------------|---------------------|
| Male 1  | 75           | 202            | 127                 |
| Male 2  | 124          | 260            | 136                 |
| Male 3  | 81           | 148            | 67                  |
| Male 4  | 75           | 221            | 146                 |
| Male 5  | 138          | 231            | 93                  |
| Male 6  | 92           | 235            | 143                 |
| Male 7  | 94           | 155            | 61                  |
| Male 8  | 102          | 217            | 115                 |
| Male 9  | 85           | 230            | 145                 |
| Male 10 | 83           | 335            | 252                 |
| Male 11 | 81           | 218            | 137                 |
| Female 1| 75           | 174            | 99                  |
| Female 2| 75           | 299            | 224                 |
| Female 3| 106          | 206            | 100                 |
| Female 4| 143          | 224            | 81                  |
| Female 5| 75           | 315            | 240                 |
| Female 6| 135          | 232            | 97                  |
| Female 7| 160          | 370            | 210                 |

The median pretreatment prealbumin was 88.5 mg/L (range: 75–160 mg/L). The median post-treatment prealbumin was 227 mg/L (range: 148–370 mg/L). The median interval improvement of prealbumin was 131.5 mg/L (range: 61–252 mg/L). Utilizing the Wilcoxon signed-rank test, the median differences between the pretreatment and post-treatment prealbumin levels were found to be statistically significant ($P < .001$).

Fig. 1. Prealbumin improvement based on days of treatment with oxandrolone. This figure demonstrates the percentage of patients with improved prealbumin over the course of time. The first patient to demonstrate improved prealbumin was identified after 4 days of treatment. Over 60% of patients demonstrated increased prealbumin after 10 days of treatment. All patients’ prealbumin levels improved by day 18.

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HNC patients are a population at high risk for perioperative complications given up to over half of them present in a catabolic state at the time of initial diagnosis. Neoadjuvant chemotherapy and/or radiation therapy often further contribute to this malnutrition. By the time these patients undergo surgery, they are resultant more prone to infections, wound breakdown, and fistula formation. This is a major concern, as wound healing is an important issue for HNC patients, given the vast majority of them require adjuvant treatment (chemotherapy, radiation, or both).

Delays in initiation of adjuvant treatment because of poor wound healing are not uncommon and the repercussions can be significant. Recent research suggests that the postoperative window for starting adjuvant treatment, as recommended by the NCCN, may be narrower than within 6 weeks. Graboyes et al demonstrated that delay beyond 7 weeks was associated with a small, yet
progressive survival decrement. Improved wound healing by the addition of oxandrolone to the perioperative management of nutritionally deficient HNC patients could help to prevent such delays in adjunctive treatment and ultimately affect long-term survival.

There are several limitations to this study. First, this is a small, retrospective study with only 18 patients. Second, although the majority of patients were treated with oxandrolone 10 mg PO BID, there was not a standardized protocol followed for administration initiation or administration dosage and prealbumin levels were not measured at regular intervals before, during, or at the end of each treatment course (ie, some after 4 days and others after 8 or 14 days). Therefore, the true minimum number of days needed to demonstrate an improvement in prealbumin level is not known nor can an exact percentage improvement in prealbumin level based on the number of days treated be estimated. Additionally, prealbumin levels were not checked after discharge from the hospital and therefore the length of time prealbumin levels remained elevated after discontinuation of the medication is not known. Third, prealbumin is a negative acute-phase reactant and therefore not the most adequate way to measure/reflect nutritional deprivation. It is because of this that a trend in prealbumin level improvement was measured in conjunction with daily wound assessment to determine if a decrease in inflammation and an improvement in wound healing were actually occurring. Finally, there was not a standard protocol for objectively assessing wound improvement; therefore, documentation for each clinical exam varied as did the person performing each exam. If a prospective study was conducted, these limitations could be addressed in the study design.

Although this pilot study only represents a small subset of patients examined retrospectively, a larger prospective study would more appropriately examine the impact of oxandrolone on the nutritional status of perioperative HNC patients. By utilizing a protocol for initiation of oxandrolone in patients with a prealbumin level <100 mg/L who are at risk for or have demonstrated impaired wound healing, which also takes into account other factors tightly linked with wound healing such as thyroid function and the perioperative enteral nutritional regimen, these patients could be evaluated objectively in a more precise and standardized manner.

CONCLUSION

The administration of oxandrolone statistically improved nutritional status, as measured by prealbumin, during the perioperative period in this group of HNC patients and was well tolerated with acceptable toxicity. Subjective clinical improvement in the healing of surgical wounds was identified in all patients and correlated with objectively improved prealbumin levels. Although a larger clinical trial would better define a regimen, we propose that oxandrolone administered orally 10 mg BID for 10 days may be a useful adjunct in the perioperative care of nutritionally deficient HNC patients who are at risk for or have demonstrated impaired wound healing.

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