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ORIGINAL ARTICLE

# Prevention of Acute Radiation-associated Toxicity by Traditional Chinese Medicine *Tianwang Buxin Mini-Pills* in Patients with Head and Neck Cancer

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**Background:** Anemia and oral mucositis are main side effects of radiotherapy (RT) and are important factors affecting the quality of life (QOL) in head and neck cancer (HNC) patients treated with RT. This study aimed to explore the safety and therapeutic efficacy of *Tianwang Buxin Mini-pills* (*TWBXM*) for the prevention of acute RT toxicity in HNC patients by using a randomized, double-blind and placebo-controlled study design. **Patients and Methods:** Seventy-three HNC patients participated the study. They were randomized into a treatment group ($n$ = 38) and a control group ($n$ = 35). All patients received daily either *TWBXM* treatment or placebo starting from the initiation of RT until 1-month follow-up after RT completion. All patients were evaluated for QOL, acute RT toxicities and laboratory data (hemoglobin [Hgb], white blood cell and platelet) at 3 time points: Pre-RT, upon RT completion and at *TWBXM* completion. **Results:** The *TWBXM* group maintained normal levels of Hgb during the duration of the study while the placebo group showed a decrease in Hgb ($P$ = 0.035). **Conclusions:** This study demonstrated the safety and efficacy of *TWBXM* applied in the HNC patients receiving RT. It prevented the decrease of Hgb in HNC patients undergoing RT treatment as well 1-month-post-RT treatment. Further studies are needed to assess the effects of *TWBXM* for the prevention of other RT toxicities.

Key words: Head and neck cancer, traditional Chinese medicine, *Tianwang Buxin Mini-pills*, radiotherapy, toxicities

## INTRODUCTION

Head and neck cancer (HNC) is a broad term that encompasses epithelial malignancies that includes paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx. Radiotherapy (RT) is an effective treatment for HNC, but side-effects such as anemia and oral mucositis are common in patients undergoing RT.[1,2]

Anemia may conduct to tumor hypoxia by decreasing the oxygen-carrying capacity of the blood, resulting in RT and in some instances, chemotherapy resistance. It may constitute an obstacle to achieving maximal loco-regional tumor control and survival with chemotherapy and RT for HNC.[3,4] In addition, anemia negatively affects the quality of life (QOL) of cancer patients, as evidenced by worsening fatigue.[2] Correction of anemia has been associated with QOL improvements in anemic cancer patients.[5] Erythropoietin has been shown to correct anemia and improve QOL,[6] however, erythropoiesis-stimulating agents may increase the risk of thrombovascular events and result in decreased survival and poorer tumor control.[7,8] Therefore, safer alternative strategies are needed to correct anemia in patients undergoing RT.

Radiation fields from RT for HNC cover not only salivary glands but also all or part of the oral mucosa, thereby increasing the risks of oral mucositis.[9] Xerostomia, pain, burning sensation, dysphagia, slurred speech, and related symptoms can cause discomfort, while accelerated dental caries may contribute to more serious complications such as osteoradionecrosis.[10,11] During the last decade there has been increasing interest in the prevention of RT-induced severe mucositis.[12-15] However, effective and safe intervention for the prevention of oral mucositis in RT has yet to be identified to date.[16,17]

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*Tianwang Buxin Mini-pills* (TWBXM) has been used for centuries for the treatment of anemia, oral mucositis, xerositis and oral ulcers in traditional Chinese medicine (TCM). Several studies have revealed the potential effectiveness of TCM on the treatment of RT-associated toxicity in HNC patients.[18,19] However, all these studies had poor randomization techniques or lack of blind testing. In order to clarify the safety and efficacy of *TWBXM* in preventing RT-associated acute toxicity in HNC patients, we conducted a randomized, double-blind and placebo-controlled clinical trial to evaluate the effectiveness of *TWBXM* in preventing RT associated acute side-effects.

## PATIENTS AND METHODS

### Patient evaluation

From January 2003 to November 2004, 103 patients with histological evidence of carcinoma at the head and neck were identified by the otolaryngologist from Tri-Service General Hospital, Taipei, Taiwan. Every patient was classified according to the tumor node metastasis (TNM) (1997 AJCC TNM edition) classification system (*T* describes the size of the tumor and whether it has invaded nearby tissue, *N* describes any lymph nodes that are involved, and *M* describes distant metastasis). All the patients included for the study received treatment with RT, with life expectancy ≥3 months, showed no evidence of brain metastasis, and had Eastern Cooperative Oncology Group status of ≤2. The patients also had white blood cell (WBC) count ≥ 2500/uL, platelets (PLT) ≥75,000/uL, hemoglobin (Hgb) ≥8 g/dL, serum creatinine (Cr) ≤3.0 mg/dL, total bilirubin ≤ 3.0 mg/dL, and serum glutamic oxaloacetic transaminase (GOT), glutamate pyruvate transaminase (GPT) ≤ 3 times the upper limit of normal. Patients with prior RT, presence of oral lesions, and severe organ failure were excluded from the study.

Seventy-three patients who fulfilled the inclusion criteria and met none of the exclusion criteria signed the informed consent to join the study. All patients were required to sign an informed consent before study entry. The study was approved by the Institutional Review Board of Tri-Service General Hospital.

### Study medication

The herbal formulation used in this study was modified from *TWBXM* first described in the Ming Dynasty, which is aimed at strengthening the qi, blood and yin functions to improve fatigue, anemia, oral mucositis, xerositis and oral ulcers.[20] Hence, we chose *TWBXM* to determine whether it can improve the side effects of RT in HNC patients.

The herbal preparation (*TWBXM*) used in this study contained 13 herbs, which were listed in Table 1. All herbs were obtained from Sun Ten pharmaceutical Co. Limited, (Taipei, Taiwan). After extraction of mixed herbs, decoction was separated, concentrated, and spray-dried into powder form. The powder was then packed in sealed opaque aluminum foil bags. The placebo was made of starch and designed to taste, smell, and look similar to the Chinese herbal formula and was packed in an identical package. All packages were stored reserved in a refrigerator at the hospital by the chief investigator.

### Study design

This study was a double-blind, randomized, and placebo-controlled trial. The enrolled patients were randomized to the study medication according to a computer-generated randomization schedule. Seventy-three patients who fulfilled the recruitment criteria were randomized to receive *TWBXM* (study group) or placebo (control group) [Figure 1].

All patients, the study nurse, and doctors were blinded to the group of the treatment group. All the patients took 3 g of *TWBXM* or placebo orally 3 times a day starting from the initiation of RT, and the treatment was not finished until 1-month after RT completion. All patients were monitored at pre-RT, upon RT completion, and at *TWBXM*/placebo completion for receiving a complete set of the QOL questionnaires, radiation and hematologic evaluation.

The QOL questionnaires included the cancer specific questionnaire "European Organization for Research and Treatment of Cancer into QOL-Cancer 30" (EORTC QLQ-C30) and the head and neck specific QLQ-H & N35 (Head & Neck 35).[21-23] The questionnaires were filled by a trained study nurse. Radiation toxicities were graded according to the Radiation Therapy Oncology Group (RTOG)

Table 1: The Compositions of *Tianwang Buxin Mini-pills (TWBXM)*

| Mandarin pronunciation | Latin botanical name | Gram |
|---|---|---|
| Ren Shen (人參) | *Radix Ginseng* | 9 |
| Shengdihuang (生地黃) | *Rehmanniae Radix* | 30 |
| Danshen (丹參) | *Salvia Miltrorrhiza* | 9 |
| Xuanshen (玄參) | *Radix Scrophulariae* | 9 |
| Fu Ling (茯苓) | *Poria cocos (Schw.) Wolf* | 9 |
| Nanwuweizi (南五味子) | *Schisandra sphenanthera* | 18 |
| Yuan zhi (遠志) | *Radix Polygalae* | 9 |
| Jie geng (桔梗) | *Radix Platycodonis* | 9 |
| Danggui (當歸) | *Radix Angelica Sinensis* | 18 |
| Tian men dong (天門冬) | *Asparagus cochinchinensis* | 18 |
| Maimendong (麥門冬) | *Ophiopogonis Radix* | 18 |
| Baiziren (柏子仁) | *Platycladus orientalis* | 18 |
| Suanzaoren (酸棗仁) | *Ziziphus jujuba Mill. Var. spinosa* | 18 |

Every 9.0 gram of *TWBXM* powder is prepared from the above raw herbs.
*TWBXM = Tianwang Buxin Mini-pills*

acute radiation morbidity scoring criteria[24,25] by the evaluating physician. The hematologic side effect included neutropenia, thrombocytopenia, and anemia. Liver and renal functions such as GOT, GPT, blood urea nitrogen (BUN), Cr, were evaluated at pre-RT and at *TWBXM*/placebo completion.

### Statistical methods and analysis

All the analysis was performed using the SAS statistical software (version 9.1.3, SAS Institute, Cary, NC). First, the narrating statistics express with percentage the patient's basic analysis. Next, we analyzed with Fisher's exact that assays the baseline assessment, characteristics of tumor and RTOG Acute Morbidity Scoring Criteria. Finally, Independent *t*-test were used to detect the difference between the two different treatment groups in body mass index (BMI), age, EORTC QLQ-C30 scores, EORTC QLQ-H & N35 scores, the radiation dose, body weight loss and the laboratory blood test.

All tests were performed two-tailed and conducted at 5% significance level. To simplify the presentation, we chose only some items of the questionnaires listed in the text.

## RESULTS

### Patient demographics

Of the 73 patients with HNC and treated with RT, over 76% were male with an average age >50 years old. Thirty-eight patients were assigned to the *TXBXM* group and 35 to the placebo group. Age, BMI, lymph node metastasis, tumor localization, TNM classification, and tumor stage of the patients were similar between the two groups [Table 2].

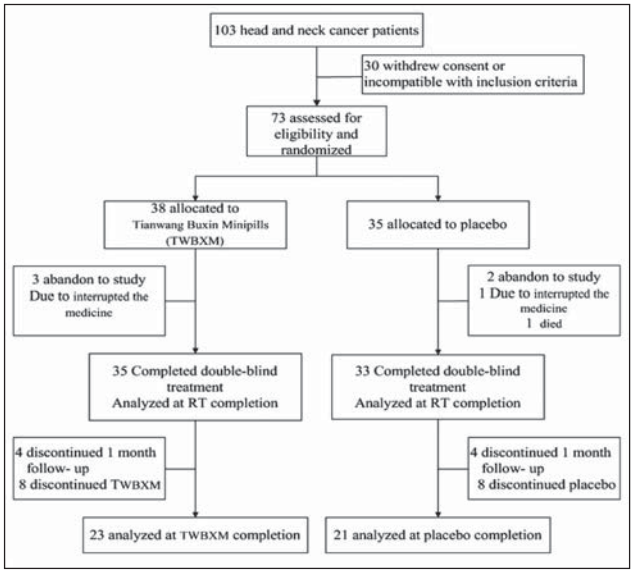


**Figure 1: Study flow chart**

Table 2: Baseline characteristics of patients

| Characteristics | *TWBXM* ($n$ = 38) | | Placebo ($n$ = 35) | | $P$ value |
|---|---|---|---|---|---|
| | $n$ (%) | Mean ± SD | $n$ (%) | Mean ± SD | |
| Sex | | | | | |
| Female | 9 (23.7) | | 3 (8.6) | | 0.116 |
| Male | 29 (76.3) | | 32 (91.4) | | |
| Inclusion age | | 50.87±14.56 | | 54.03±16.10 | 0.381 |
| <18 | 0 (0.0) | | 0 (0.0) | | 0.589 |
| 18-44 | 14 (36.8) | | 11 (31.4) | | |
| 45-64 | 17 (44.7) | | 14 (40.0) | | |
| ≥65 | 7 (18.4) | | 10 (28.6) | | |
| Disease | | | | | |
| NPC | 19 (50.0) | | 18 (51.4) | | >0.999 |
| Non-NPC | 19 (50.0) | | 17 (48.6) | | |
| Therapy | | | | | |
| RT | 21 (28.8) | | 16 (21.9) | | |
| CCRT | 17 (23.3) | | 19 (26.0) | | |
| BMI (kg/m$^2$) | | 24.00±4.12 | | 24.67±3.90 | 0.475 |
| <24 | 15 (39.5) | | 16 (45.7) | | 0.320 |
| 24-27 | 17 (44.7) | | 10 (28.6) | | |
| ≥27 | 6 (15.8) | | 9 (25.7) | | |
| Stage groupings | | | | | |
| 0 | 4 (10.5) | | 3 (8.6) | | 0.990 |
| I | 4 (10.5) | | 5 (14.3) | | |
| II | 10 (26.3) | | 8 (22.9) | | |
| III | 4 (10.5) | | 4 (11.4) | | |
| IVA | 12 (31.6) | | 10 (28.6) | | |
| IVB | 4 (10.5) | | 5 (14.3) | | |
| TNM classification-T | | | | | |
| T0 | 2 (5.3) | | 2 (5.7) | | 0.487 |
| Tis | 0 (0.0) | | 1 (2.9) | | |
| T1 | 7 (18.4) | | 12 (34.3) | | |
| T2 | 11 (28.9) | | 6 (17.1) | | |
| T3 | 4 (10.5) | | 2 (5.7) | | |
| T4 | 14 (36.8) | | 12 (34.3) | | |
| TNM classification-N | | | | | |
| N0 | 25 (65.8) | | 19 (54.3) | | 0.738 |
| N1 | 7 (18.4) | | 10 (28.6) | | |
| N2 | 2 (5.3) | | 1 (2.9) | | |
| N2a | 1 (2.6) | | 1 (2.9) | | |
| N2c | 1 (2.6) | | 0 (0.0) | | |
| N3 | 2 (5.3) | | 4 (11.4) | | |
| TNM classification-M | | | | | |
| M0 | 34 (89.5) | | 32 (91.4) | | >0.999 |
| M1 | 4 (10.5) | | 3 (8.6) | | |

SD = standard deviation; *TWBXM* = *tianwang Buxin Mini-pills*; RT = radiotherapy; CCRT = concurrent chemoradiotherapy; BMI = body mass index; TNM = tumor-node metastasis. Analyzed using the Fisher's exact test and independent *t*-test. T describes the size of the tumor; N describes any locoregional lymph node; M describes distant metastasis

Five patients withdrew from the study during RT completion (three patients in the *TWBXM* group and two in the placebo group). During the follow-up phase after RT completion, eight patients failed to return for follow-up and 16 patients refused to take *TWBXM*/placebo after completion of RT. There was no significant difference in patient pulling out between the two groups (12 patients in the *TWBXM* group and 12 in the placebo group).

There were also no differences in the mean radiation dose between the *TWBXM* group (6944.9 cGy) and the control group (7098.4 cGy, $P = 0.476$) [Table 3].

### Laboratory data (complete blood count/renal and liver function)

Hematological abnormalities were frequently observed in cancer patients with RT. In our study, complete blood counts were normal during the pre-RT in both groups [Table 4]. Hgb remained the level >12 g/dL from the pre-RT to the *TWBXM* completion in the *TWBXM* group, but the placebo group showed a significant drop (10.88 g/dL) at the placebo completion. At the completion of the study, A significant decrease ($P = 0.035$) in Hgb was found in the placebo group [Table 4]. The mean of WBC and PLT count were at normal range during the study period in both groups.

Renal and liver function tests (BUN, Cr, GOT, and GPT) obtained after *TWBXM* treatment showed no abnormal values [Table 4].

### Results of the European Organization for Research and Treatment of Cancer QLQ-C30 and European Organization for Research and Treatment of Cancer QLQ-H and N35

For evaluating the QOL of HNC patients treated with RT, we used the EORTCQLQ-C30 and QLQ-H & N 35 to compare the QOL at all points and the changes in QOL from baseline for subgroups of patients with and without *TWBXM* treatment. Patients treated with RT showed a clinically significant deterioration in both functions and symptoms. The *TWBXM* group showed more pain score, while RT completion ($P = 0.022$), but less pain score at *TWBXM* completion (*TWBXM* group: 31.61; placebo group: 37.84) in QLQ-H & N 35, however, these improvements were not statistically significant. Other functions and symptoms analyzed in both QOL questionnaires also did not show any significant difference between the two groups [Tables 5 and 6].

### Acute morbidity scoring criteria of radiation toxicities

At the pre-RT and RT completion, the patient's acute radiation toxicities were independently evaluated by radiation oncologists. At each evaluation, the patients were weighed, and the degrees of acute radiation toxicities for the following items were evaluated: Skin, oral mucosa, mucositis, nausea, vomiting, leukopenia, dry mouth, and loss of taste. In our study, the severity of skin, oral mucosa, mucositis, dry mouth and loss of taste increased from the pre-RT to RT completion both two groups. However, *TWBXM* treatment did not significantly improve the radiation toxicity [Table 3].

## DISCUSSION

To our best knowledge, this is the first clinical trial using TCM in the prevention of radiation-induced toxicity of HNC patients with randomization, double-blinding, and a placebo-controlled group. *TWBXM* was aimed to improve acute side effects of RT in HNC patients such as anemia, oral mucositis, xerositis and fatigue. Liver and renal functions were monitored for all the study participants as a safety precaution, because liver and renal dysfunction has been reported to associate with the use of Chinese herbs.[26-28] In our study, liver and renal function were assessed at the end of *TWBXM* administration and the results showed that the use of *TWBXM* did not cause liver and renal dysfunction in all the patients [Table 4].

Birgegard *et al.* had noted that the correlation between a low Hgb level and poorer performance status revealed in European Cancer Anemia Survey is consistent with clinical evidence supporting a relationship between Hgb levels and relevant QOL parameters.[29] McCloskey *et al.* retrospectively reviewed outcomes among 78 patients at Roswell Park Cancer Institute, who were treated definitively with RT and concurrent chemotherapy for Stage III-IV squamous cell carcinoma of the head and neck. Patients with pretreatment Hgb levels <12 g/dL was found to have significantly inferior overall survival and local control.[30] The mean of pre-RT Hgb levels in our study were >12 g/dL in both groups (*TWBXM* group: 12.9; placebo group: 12.6). Hence, this study did not indicated that the loco-regional tumor control and patient survival of our patients. However, at the end of *TWBXM*/placebo treatment, the Hgb levels for patients in the placebo group dropped to 10.88 g/dL. Our study demonstrated that *TWBXM* could effectively prevent the decrease of Hgb in HNC patients have undergone RT. The result showed that the effects of *TWBXM* conformed to the theory of TCM on anemia-related hemogram parameters for "nourishing blood" and might provide HNC patients having undergone RT with better QOL.

Crawford's *et al*. has noted that a direct relationship exists between Hgb increases during epoetin alfa therapy and corresponding QOL improvements in cancer patients receiving chemotherapy across the clinically relevant Hgb range of 8-14 g/dL.[6] Our results revealed the *TWBXM* group

Table 3: Acute morbidity scoring criteria of radiation toxicities assessment of the two patient groups on the effects of *TWBXM*/placebo therapy

| Side effects | Pre-RT | | | RT completion | | |
|---|---|---|---|---|---|---|
| | A ($n$ = 38) | B ($n$ = 35) | $P$ value | A ($n$ = 35) | B ($n$ = 33) | $P$ value |
| Radiation dose[a,c] | 1097.21 | 1148.26 | 0.856 | 6944.93 | 7098.35 | 0.476 |
| Skin[b] | | | | | | |
| No change | 38 (100) | 30 (88.2) | 0.045* | 3 (7.9) | 3 (9.1) | 0.815 |
| Dry desquamation | 0 (0) | 4 (11.8) | | 27 (71.1) | 20 (60.6) | |
| Tender or bright erythema | 0 (0) | 0 (0) | | 7 (18.4) | 9 (27.3) | |
| Moist desquamation | 0 (0) | 0 (0) | | 1 (2.6) | 1 (3.0) | |
| Mucositis[b] | | | | | | |
| No change | 29 (76.3) | 26 (76.5) | 0.578 | 3 (7.9) | 4 (12.1) | 0.672 |
| Mild pain not requiring analgesics management | 8 (21.1) | 5 (14.7) | | 9 (23.7) | 8 (24.2) | |
| Moderate pain requiring analgesics management | 1 (2.6) | 2 (5.9) | | 12 (31.6) | 6 (18.2) | |
| Scattered mucositis or pain requiring narcotics | 0 (0) | 1 (2.9) | | 12 (31.6) | 14 (42.4) | |
| Confluent mucositis | 0 (0) | 0 (0) | | 2 (5.3) | 1 (3.0) | |
| Nausea/vomiting[b] | | | | | | |
| None | 24 (63.2) | 25 (73.5) | 0.460 | 26 (68.4) | 29 (87.9) | 0.183 |
| Nausea | 6 (15.8) | 6 (17.6) | | 6 (15.8) | 2 (6.1) | |
| N and V manageable with medication | 7 (18.4) | 2 (5.9) | | 6 (15.8) | 2 (6.1) | |
| Intractable vomiting | 1 (2.6) | 1 (2.9) | | 0 (0) | 0 (0) | |
| Leukopenia[b] | | | | | | |
| WBC >4000 | 35 (92.1) | 31 (93.9) | >0.999 | 25 (67.6) | 22 (81.5) | 0.376 |
| 3000< WBC <4000 | 3 (7.9) | 2 (6.1) | | 7 (18.9) | 4 (14.8) | |
| 2000< WBC <3000 | 0 (0) | 0 (0) | | 5 (13.5) | 1 (3.7) | |
| Dry mouth[b] | | | | | | |
| None | 15 (39.5) | 14 (41.2) | 0.967 | 5 (13.2) | 1 (3.0) | 0.349 |
| Slight | 19 (50.0) | 17 (50.0) | | 15 (39.5) | 14 (42.4) | |
| Moderate dryness, poor response on stimulation | 4 (10.5) | 3 (8.8) | | 18 (47.4) | 18 (54.5) | |
| Loss of taste(−, ±, +)[b] | | | | | | |
| − | 33 (86.8) | 30 (88.2) | 0.490 | 6 (15.8) | 4 (12.1) | 0.125 |
| ± | 5 (13.2) | 3 (8.8) | | 7 (18.4) | 3 (9.1) | |
| + | 0 (0) | 1 (2.9) | | 25 (65.8) | 22 (66.7) | |
| ++ | 0 (0) | 0 (0) | | 0 (0) | 4 (12.1) | |
| Hoarseness[b] | | | | | | |
| 0: None | 36 (94.7) | 31 (91.2) | 0.662 | 37 (97.4) | 30 (90.9) | 0.255 |
| 1: Yes | 2 (5.3) | 3 (8.8) | | 1 (2.6) | 3 (9.1) | |
| Nasal obstruct[b] | | | | | | |
| None | 37 (97.4) | 31 (91.2) | 0.338 | 36 (94.7) | 32 (97.0) | 0.553 |
| Yes | 1 (2.6) | 3 (8.8) | | 2 (5.3) | 1 (3.0) | |
| BW loss (kg)[a] | 64.32 | 67.12 | 0.346 | 60.13 | 61.86 | 0.556 |

RT = radiotherapy; WBC = white blood cell; A = the *TWBXM* group; B = the placebo group. [a]Statistics amount is mean; [b]analyzed using the Fisher's exact test; [c]analyzed using the independent-$t$-test; *$P$ < 0.05. B.W. loss (kg) = median (25%,75%) of change weight (RT completion minus pre-RT). Data are shown as $n$ (%)

Table 4: Laboratory data assessment of the two patient groups on the effects of *TWBXM*/placebo therapy

| Category | Pre-RT | | | RT completion | | | TWBXM completion | | | Post-Rre change[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | *P* value[b] | A | B | *P* value[b] | A | B | *P* value[b] | A | B | *P* value[b] |
| WBC ($10^3$/uL) | 7.57±2.99 | 8.55±2.83 | 0.153 | 47.72±260.29 | 6.00±2.77 | 0.361 | 5.96±2.63 | 6.94±4.62 | 0.388 | −1.91±3.75 | −1.75±5.05 | 0.904 |
| RBC ($10^6$/uL) | 4.42±0.76 | 4.33±0.67 | 0.584 | 4.04±0.63 | 4.15±0.98 | 0.574 | 3.93±0.69 | 3.56±0.6 | 0.063 | 0.47±0.9 | −0.73±0.68 | 0.290 |
| Hgb (g/dL) | 13.16±1.69 | 13.13±2.05 | 0.952 | 12.12±1.8 | 14.83±15.56 | 0.289 | 12.14±1.9 | 10.88±1.92 | 0.035* | −1.19±2.15 | −1.98±1.92 | 0.208 |
| Platelet count ($10^3$/uL) | 281.51±97.69 | 259.21±66.51 | 0.273 | 242.87±72.25 | 238.85±151.31 | 0.900 | 272.95±97.52 | 223.37±110.16 | 0.146 | −19.28±123.2 | −58.62±88.58 | 0.270 |
| BUN (mg/dL) | 15.09±6.56 | 14.38±4.66 | 0.611 | | | | 12.86±5.6 | 14.48±7.2 | 0.412 | −1.15±5.1 | 0.41±7.39 | 0.435 |
| Cr (mg/dL) | 0.92±0.29 | 0.96±0.25 | 0.529 | | | | 0.86±0.21 | 1.8±3.11 | 0.162 | −0.03±0.17 | 0.82±3.14 | 0.220 |
| GOT (U/L) | 21.43±6.95 | 27.53±14.2 | 0.029* | | | | 20.80±7.32 | 19.95±5.17 | 0.300 | 30.6±142.34 | −5.24±10.73 | 0.256 |
| GPT (U/L) | 24.86±12.58 | 27.53±14.29 | 0.412 | | | | 19.45±8.22 | 18.73±6.7 | 0.031* | 43±221.96 | −5.32±15.14 | 0.314 |

SD = standard deviation; *TWBXM* = *tianwang Buxin Mini-pills*; RT = radiotherapy; WBC = white blood cell; RBC = red blood cell; Hgb = hemoglobin; BUN = blood urea nitrogen; Cr = creatinine; GOT = glutamic oxaloacetic transaminase; GPT = glutamate pyruvate transaminase; A = the *TWBXM* group; B = the placebo group. [a]Post-Rre change = the changes in score between *TWBXM* completion minus pre-RT; [b]analyzed using the independent *t*-test; *$P < 0.05$. Data are shown as mean ± SD

Table 5: "EORTC-C30" assessment of the two patient groups on the effects of *TWBXM*/placebo therapy

| Category | Pre-RT | | | RT completion | | | TWBXM completion | | | Post-Rre change[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A ($n$ = 38) | B ($n$ = 35) | *P* value[b] | A ($n$ = 35) | B ($n$ = 33) | *P* value[b] | A ($n$ = 23) | B ($n$ = 21) | *P* value[b] | A ($n$ = 23) | B ($n$ = 21) | *P* value[b] |
| Global health status/QOL | 64.26±27.05 | 57.85±26.96 | 0.315 | 51.35±22.53 | 48.96±24.2 | 0.673 | 60.26±24.98 | 58.33±25.6 | 0.793 | 1.92±32.27 | −0.75±26.97 | 0.759 |
| Functional scales | | | | | | | | | | | | |
| Physical functioning | 88.42±18.26 | 83.42±21.23 | 0.283 | 75.14±25.85 | 74.17±25.15 | 0.876 | 78.72±26.13 | 77.88±24.29 | 0.909 | −8.45±16.94 | −6.96±19.78 | 0.779 |
| Role functioning | 82.89±26.98 | 78.57±30.67 | 0.524 | 64.87±31.37 | 61.99±25.84 | 0.682 | 71.80±30.83 | 75±28.99 | 0.714 | −7.69±23.19 | −9.85±27.04 | 0.767 |
| Emotional functioning | 79.83±17.28 | 77.15±18.23 | 0.521 | 74.11±21.94 | 71.88±24.3 | 0.690 | 77.88±20.68 | 82.58±21.96 | 0.450 | −0.97±20.6 | 5.67±21.88 | 0.284 |
| Social functioning | 73.69±25.59 | 70.49±23.59 | 0.580 | 59.46±33.23 | 66.68±24.69 | 0.306 | 69.24±26.54 | 75.01±26.6 | 0.457 | −0.64±33.16 | 6.06±33.93 | 0.493 |
| Symptom scales/items | | | | | | | | | | | | |
| Fatigue | 25.43±22.22 | 29.19±23.2 | 0.481 | 43.23±26.17 | 42.35±23.02 | 0.883 | 31.18±28.29 | 36.35±25.02 | 0.510 | 1.7±23.02 | 4.05±38.43 | 0.808 |
| Pain | 22.36±26.92 | 23.33±21.07 | 0.865 | 46.84±23.19 | 41.67±27.44 | 0.399 | 35.90±26.96 | 40.91±29.87 | 0.544 | 8.98±30.28 | 15.91±39.32 | 0.493 |
| Dyspnea | 12.28±21.11 | 13.33±20.13 | 0.829 | 17.11±23.07 | 16.66±20.73 | 0.932 | 20.50±21.24 | 13.63±22.2 | 0.280 | 6.4±24.98 | 3.04±20.33 | 0.615 |
| Insomnia | 24.55±27.6 | 25.7±25.68 | 0.854 | 40.53±25.03 | 31.24±25.32 | 0.131 | 30.75±24.81 | 31.81±28.14 | 0.891 | 1.28±27.46 | 3.03±33.97 | 0.843 |
| Appetite loss | 14.91±25.35 | 21.56±27.07 | 0.285 | 45.04±30.66 | 45.83±29.04 | 0.914 | 28.18±26.14 | 34.85±29.96 | 0.415 | 8.96±32.05 | 12.7±38.7 | 0.718 |
| Constipation | 16.66±22.93 | 13.32±18.43 | 0.498 | 37.82±27.41 | 29.15±20.31 | 0.145 | 29.48±30.3 | 25.74±20.4 | 0.626 | 10.25±26.28 | 7.57±30.73 | 0.746 |
| Diarrhea | 6.13±13.08 | 10.47±19.42 | 0.272 | 9.00±14.99 | 6.24±13.21 | 0.424 | 8.97±15.06 | 6.06±16.7 | 0.529 | 1.28±17.57 | −3.02±17.54 | 0.401 |
| Financial difficulties | 21.04±26.19 | 24.75±26 | 0.546 | 24.32±31.08 | 30.2±28.54 | 0.418 | 23.07±29.47 | 15.15±22.37 | 0.307 | −2.56±22.95 | −3.03±28.92 | 0.950 |

SD = standard deviation; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer into QOL-Cancer 30"; *TWBXM* = *Tianwang Buxin Mini-pills*; RT = radiotherapy; QOL = quality of life; A = the *TWBXM* group; B = the placebo group. [a]Post-Rre change = The changes in score between *TWBXM* completion minus pre-RT; [b]analyzed using the Independent *t*-test. Higher scores in "global health status" and "functional scales" correlated to improved functions; higher scores in "symptom scales/items" correlated to greater symptoms. Data are shown as Mean ± SD

Table 6: "EORTC-H and N35" assessment of the two patient groups on the effects of *TWBXM*/placebo therapy

| Category | Pre-RT | | | RT completion | | | *TWBXM* completion | | | Post-Rre change[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A ($n$ = 37) | B ($n$ = 35) | $P$ value[b] | A ($n$ = 35) | B ($n$ = 33) | $P$ value[b] | A ($n$ = 23) | B ($n$ = 21) | $P$ value[b] | A ($n$ = 23) | B ($n$ = 21) | $P$ value[b] |
| Symptom scales/items | | | | | | | | | | | | |
| Pain | 18.69±23.60 | 16.19±16.9 | 0.609 | 55.39±25.10 | 42.43±20.46 | 0.022* | 31.61±24.23 | 37.84±23.31 | 0.348 | 12.81±27.07 | 22.92±22.83 | 0.1556 |
| Swallowing | 22.74±28.78 | 16.43±19.55 | 0.283 | 50.23±26.32 | 38.89±25.91 | 0.074 | 30.17±29.75 | 26.73±24.83 | 0.654 | 7.45±30.88 | 9.38±25.23 | 0.8083 |
| Senses problems | 12.61±16.85 | 10.95±19.36 | 0.699 | 40.54±20.99 | 44.94±21.04 | 0.384 | 36.91±26.59 | 35.42±25.20 | 0.837 | 24.70±28.99 | 21.53±33.86 | 0.7201 |
| Speech problems | 21.92±28.39 | 18.72±21.69 | 0.595 | 36.33±26.68 | 28.61±26.22 | 0.227 | 27.37±28.61 | 22.68±19.52 | 0.500 | 4.93±24.72 | 0.00±25.18 | 0.4843 |
| Trouble with social eating | 14.19±22.47 | 12.38±15.18 | 0.692 | 48.19±29.99 | 39.65±28.65 | 0.229 | 26.49±32.00 | 20.49±25.54 | 0.464 | 11.73±31.46 | 8.69±26.52 | 0.7124 |
| Trouble with social contact | 13.33±20.67 | 9.52±11.23 | 0.332 | 27.56±27.49 | 24.65±27.76 | 0.660 | 22.62±29.55 | 15.00±22.00 | 0.303 | 9.38±22.88 | 3.89±22.74 | 0.3949 |
| Less sexuality | 31.53±39.04 | 38.72±36.4 | 0.426 | 48.57±36.47 | 52.08±35.11 | 0.691 | 42.25±37.81 | 49.30±34.58 | 0.490 | 11.10±42.12 | 4.16±19.81 | 0.4480 |
| Teeth | 35.13±30.38 | 33.33±35.24 | 0.817 | 37.83±26.26 | 40.39±28.58 | 0.697 | 33.32±29.55 | 34.72±25.03 | 0.855 | −2.39±42.49 | 5.55±34.98 | 0.4699 |
| Opening mouth | 19.81±30.89 | 18.09±23.35 | 0.791 | 39.63±28.16 | 41.41±27.69 | 0.791 | 32.17±31.48 | 33.33±24.09 | 0.884 | 8.33±30.93 | 12.50±27.48 | 0.6126 |
| Dry mouth | 27.92±27.8 | 26.65±25.31 | 0.841 | 53.15±31.89 | 55.56±25.93 | 0.732 | 47.12±30.25 | 47.22±27.67 | 0.990 | 16.66±33.34 | 18.07±36.76 | 0.8859 |
| Sticky saliva | 25.21±29.82 | 19.99±28.24 | 0.449 | 50.45±32.04 | 45.45±27.42 | 0.488 | 33.33±32.72 | 33.33±31.09 | >0.999 | 4.94±31.62 | 8.33±37.11 | 0.7260 |
| Felt ill | 26.12±30.57 | 27.61±23.56 | 0.818 | 52.25±32.92 | 44.44±25.93 | 0.278 | 32.13±33.31 | 30.54±29.35 | 0.857 | 4.93±32.95 | 2.78±33.93 | 0.8189 |
| Pain killers | 43.24±50.22 | 45.71±56.06 | 0.844 | 67.57±47.46 | 66.67±47.87 | 0.937 | 46.43±50.79 | 37.50±49.45 | 0.525 | 11.11±64.05 | 0.00±58.98 | 0.5241 |
| Nutritional supplements | 43.24±50.22 | 40.00±49.71 | 0.784 | 62.16±49.17 | 54.55±50.56 | 0.525 | 53.57±50.79 | 54.17±50.90 | 0.967 | 22.22±50.64 | 16.67±56.47 | 0.7126 |
| Feeding tube | 16.22±37.37 | 5.71±23.55 | 0.161 | 18.92±39.71 | 9.09±29.19 | 0.239 | 10.71±31.5 | 12.50±33.78 | 0.845 | −3.7±33.76 | 12.50±33.78 | 0.0936 |
| Weight loss | 51.35±50.67 | 48.57±50.71 | 0.817 | 72.97±45.02 | 78.79±41.51 | 0.578 | 42.86±50.4 | 41.67±50.36 | 0.933 | −3.7±70.61 | −8.33±71.73 | 0.8175 |

SD = standard deviation; EORTC = European Organization for Research and Treatment of Cancer; *TWBXM* = *Tianwang Buxin Mini-pills*; RT = radiotherapy; A = the *TWBXM* group; B = the placebo group. [a]Post-Rre change = the changes in score between *TWBXM* completion minus pre-RT; [b]analyzed using independent $t$-test; *$P < 0.05$. Higher scores in "symptom scales/items" correlated to greater symptoms. Data are shown as mean ± SD

showed more pain score while RT completion ($P = 0.022$), but less pain score at *TWBXM* completion. However, it failed to achieve statistical significance. This may be explained by the fact that two of RT's main toxicities, oral mucositis and dry mouth, which caused great discomfort to the patients showed no significant improvement in both groups [Table 3], and thus, this would significantly reduce the QOL scores examined on these patients.

One of the main reasons why *TWBXM* was chosen for this study because it has been used to treat oral mucositis. RT induced oral mucositis are initially thought to be damage to epithelial cells caused by radiation during RT. However, recent evidence suggests that RT induced oral mucositis is more biologically complex than originally suspected, involving a sequential interaction of all cell and tissue types that comprise the oral mucosa and various physiological elements (e.g., tissue factors, cytokines).[1] It can be speculated that the mechanism of action for mucositis in *TWBXM* does not target directly of the pathways of RT-induced oral mucositis, since our results did not support it. It is also likely that the dose used in this study was insufficient to treat RT induced mucositis.

The major limitation associated with this study was the high dropping rate. Most patients suffered from oral pain and mucositits after RT, so they refused to take oral medicine. In order to increase the compliance of patients, the next study we could use the liquid form of *TWBXM*. In addition, this study only monitored patients for 1-month after the completion of RT, and thus, it could not determine whether the use of *TWBXM* could improve mucositis of RT for more than 1-month. A study with longer follow-up is required to examine this.

It concluded that *TWBXM* may prevent the decrease of Hgb in HNC patients until *TWBXM* completion (1-month after the completion of RT). In this randomized, double-blinded and placebo-controlled trial, *TWBXM* was shown to be safe. Although not all radiation-associated toxicities responded to this therapy, our positive finding supports the consideration of further investigation of *TWBXM*. Additional research would be necessary to an extensive clinical trial with the liquid form of *TWBXM* and long-time follow-up study for understanding of the prevention of other acute RT toxicities, dose — response relationship.

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## DISCLOSER

All authors declare that there are no conflicts of interest.

## REFERENCES

1. Scully C, Sonis S, Diz PD. Oral mucositis. Oral Dis 2006;12:229-41.
2. Harrison LB, Shasha D, Homel P. Prevalence of anemia in cancer patients undergoing radiotherapy: Prognostic significance and treatment. Oncology 2002;63 Suppl 2:11-8.
3. Fortin A, Wang CS, Vigneault E. Effect of pretreatment anemia on treatment outcome of concurrent radiochemotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2008;72:255-60.
4. Daly T, Poulsen MG, Denham JW, Peters LJ, Lamb DS, Krawitz H, *et al.* The effect of anaemia on efficacy and normal tissue toxicity following radiotherapy for locally advanced squamous cell carcinoma of the head and neck. Radiother Oncol 2003;68:113-22.
5. Lloyd A, van Hanswijck de Jonge P, Doyle S, Cornes P. Health state utility scores for cancer-related anemia through societal and patient valuations. Value Health 2008;11:1178-85.
6. Crawford J, Cella D, Cleeland CS, Cremieux PY, Demetri GD, Sarokhan BJ, *et al.* Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer 2002;95:888-95.
7. Juneja V, Keegan P, Gootenberg JE, Rothmann MD, Shen YL, Lee KY, *et al.* Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. Clin Cancer Res 2008;14:3242-7.
8. Badzek S, Curić Z, Krajina Z, Plestina S, Golubić-Cepulić B, Radman I. Treatment of cancer-related anemia. Coll Antropol 2008;32:615-22.
9. Fischer DJ, Epstein JB. Management of patients who have undergone head and neck cancer therapy. Dent Clin North Am 2008;52:39.
10. Nguyen NP, Vos P, Moltz CC, Frank C, Millar C, Smith HJ, *et al.* Analysis of the factors influencing dysphagia severity upon diagnosis of head and neck cancer. Br J Radiol 2008;81:706-10.
11. Ringash J, Warde P, Lockwood G, O'Sullivan B, Waldron J, Cummings B. Postradiotherapy quality of life for head-and-neck cancer patients is independent of xerostomia. Int J Radiat Oncol Biol Phys 2005;61:1403-7.
12. Andreassen CN, Grau C, Lindegaard JC. Chemical radioprotection: A critical review of amifostine as a cytoprotector in radiotherapy. Semin Radiat Oncol 2003;13:62-72.
13. de Castro G Jr, Federico MH. Evaluation, prevention and management of radiotherapy-induced xerostomia in head and neck cancer patients. Curr Opin Oncol 2006;18:266-70.

14. Blijlevens N, Sonis S. Palifermin (recombinant keratinocyte growth factor-1): A pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis. Ann Oncol 2007;18:817-26.
15. Brizel DM, Murphy BA, Rosenthal DI, Pandya KJ, Glück S, Brizel HE, *et al.* Phase II study of palifermin and concurrent chemoradiation in head and neck squamous cell carcinoma. J Clin Oncol 2008;26:2489-96.
16. Stokman MA, Spijkervet FK, Boezen HM, Schouten JP, Roodenburg JL, de Vries EG. Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: Results of meta-analyses. J Dent Res 2006;85:690-700.
17. Russo G, Haddad R, Posner M, Machtay M. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. Oncologist 2008;13:886-98.
18. Xu GZ, Cai WM, Qin DX, Yan JH, Wu XL, Zhang HX, *et al.* Chinese herb "destagnation" series I: Combination of radiation with destagnation in the treatment of nasopharyngeal carcinoma (NPC): A prospective randomized trial on 188 cases. Int J Radiat Oncol Biol Phys 1989;16:297-300.
19. Yan R. Combination of chemo-radiotherapy with Chinese medicine in the treatment of nasopharyngeal carcinoma (NPC). J New Chin Med 2008;40:98-9.
20. Young WC. Formula Of Traditional Chinese Medicine. 4th ed. Taipei: Le Que KE LAI CO., Ltd.; 1992. p. 420-1.
21. Bozec A, Poissonnet G, Chamorey E, Casanova C, Laout C, Vallicioni J, *et al.* Quality of life after oral and oropharyngeal reconstruction with a radial forearm free flap: Prospective study. J Otolaryngol Head Neck Surg 2009;38:401-8.
22. Meyer F, Fortin A, Gélinas M, Nabid A, Brochet F, Têtu B, *et al.* Health-related quality of life as a survival predictor for patients with localized head and neck cancer treated with radiation therapy. J Clin Oncol 2009;27:2970-6.
23. Epstein JB, Robertson M, Emerton S, Phillips N, Stevenson-Moore P. Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. Head Neck 2001;23:389-98.
24. Wu HG, Song SY, Kim YS, Oh YT, Lee CG, Keum KC, *et al.* Therapeutic effect of recombinant human epidermal growth factor (RhEGF) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer: A double-blind placebo-controlled prospective phase 2 multi-institutional clinical trial. Cancer 2009;115:3699-708.
25. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol 2008;26:3770-6.
26. Kane JA, Kane SP, Jain S. Hepatitis induced by traditional Chinese herbs; possible toxic components. Gut 1995;36:146-7.
27. Dasgupta A, Bernard DW. Herbal remedies: Effects on clinical laboratory tests. Arch Pathol Lab Med 2006;130:521-8.
28. Lee S, Lee T, Lee B, Choi H, Yang M, Ihm CG, *et al.* Fanconi's syndrome and subsequent progressive renal failure caused by a Chinese herb containing aristolochic acid. Nephrology (Carlton) 2004;9:126-9.
29. Birgegard G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, *et al.* Cancer-related anemia: Pathogenesis, prevalence and treatment. Oncology 2005;68 Suppl 1:3-11.
30. McCloskey SA, Jaggernauth W, Rigual NR, Hicks WL Jr, Popat SR, Sullivan M, *et al.* Radiation treatment interruptions greater than one week and low hemoglobin levels (12 g/dL) are predictors of local regional failure after definitive concurrent chemotherapy and intensity-modulated radiation therapy for squamous cell carcinoma of the head and neck. Am J Clin Oncol 2009;32:587-91.