

# A natural pharma standard supplement formulation to control treatment-related toxicity and oxidative stress in genitourinary cancer: a preliminary study

A. LEDDA<sup>1</sup>, G. BELCARO<sup>1</sup>, M. DUGALL<sup>1</sup>, R. LUZZI<sup>1</sup>, M. HOSOI<sup>1</sup>, B. FERAGALLI<sup>1</sup>, R. COTELLESE<sup>1</sup>, V. COSENTINO<sup>2</sup>, M. COSENTINO<sup>3</sup>, R. EGGENHOFFNER<sup>4</sup>, M. PELLIZZATO<sup>5</sup>, A. FRATTER<sup>5</sup>, L. GIACOMELLI<sup>4</sup>

<sup>1</sup>Department of Biomedical Sciences, Irvine 3 Labs, Chieti-Pescara University, Italy

<sup>2</sup>Idroflu S.r.L., Conegliano, Italy

<sup>3</sup>Casa di Cura Villa Maria, Padova, Italy

<sup>4</sup>Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy

<sup>5</sup>Labomar s.r.l., Istrana, Italy

**Abstract.** – **OBJECTIVE:** Oncological treatments are associated with toxicities that may decrease compliance to treatment in most genitourinary cancer patients. Supplementation with pharmaceutical-standardized supplement may be a supplementary method to control the side effects after chemo- and radiotherapy and the increased oxidative stress associated to treatments. This registry study evaluated a natural combination of supplements containing curcumin, cordyceps, and astaxanthin (Oncotris™) used as supplementary management in genitourinary cancer patients who had undergone oncological therapy.

**PATIENTS AND METHODS:** Patients with genitourinary cancers (prostate or bladder malignancies) who had undergone and completed cancer treatments (radiotherapy, chemotherapy or intravesical immunotherapy with increased oxidative stress and residual symptoms) were recruited in this registry, supplement study. Registry subjects (n = 61) freely decided to follow either a standard management (SM) (control group = 35) or SM plus oral daily supplementation (supplement group = 26). Evaluation of severity of treatment-related residual side effects, blood count test, prostate-specific antigen (PSA) test and plasma free radicals (oxidative stress) were performed at inclusion and at the end of the observational period (6 weeks).

**RESULTS:** Two patients dropped out during the registry. Therefore, the analysis included 59 participants: 26 individuals in the supplementation group and 33 in the control group. In the supplement group, the intensity of signs and symptoms (treatment-related) and residual side effects significantly decreased at 6 weeks: minimal changes were observed in controls. Supplementation with Oncotris™ was associated with a significant improvement in blood cell count and with a decreased level of plasmatic PSA and oxidative stress.

**CONCLUSIONS:** Naturally-derived supplements, specifically Oncotris™ (patent pending), could support the body to overcome the treatment-related toxicities – and the relative oxidative stress in cancer patients.

Key Words

Genitourinary cancer, Prostate cancer, Bladder cancer, Treatment-related toxicities, Curcumin, Astaxanthin, Cordyceps.

## Introduction

Cancer is the second leading cause of death worldwide, following cardiovascular diseases; it was globally responsible for 8.8 million deaths in 2015<sup>1</sup>. Between 2005 and 2015 cancer cases increased by 33%<sup>1</sup>. However, the cancer incidence is expected to increase further in the next decade due to population ageing. In the last years, significant advances have been achieved in early detection, diagnosis and treatment of cancer, leading to a prolonged survival rate an increasing number of cancer survivors<sup>2</sup>. Nowadays, some types of cancer may be managed as a chronic illness<sup>3</sup>. In this light, the goals for management of cancer patients should also include the improvement of their quality of life (QoL), by choosing personalized therapies and taking into account physical and psychological effects of long-term treatments<sup>4</sup>. In addition to symptoms related to the disease, treatment-related toxicities also affect patients' QoL and physical and psychological functioning.

The majority of cancer patients experience one or more side effects correlated with therapy, with pain, depression and fatigue being the most frequently reported<sup>5</sup>. In particular, in genitourinary cancers, such as prostate and bladder malignancies, patients who have been treated with surgery and radiation therapy commonly experience painful urination, hematuria, incontinence, infections, erectile dysfunction, and bowel complications<sup>6</sup>. Chemotherapeutic agents induce alteration of blood parameters leading to increased risk of infections, easy bruising or bleeding and fatigue<sup>7</sup>. Usually, a combination of radiation and chemotherapy can also be used to treat invasive disease. In this complex scenario supplements with pharmaceutical standards (PS) may be both useful and safe, when prescribed on an individual basis, to control treatment-related side effects. Around one-third of prostate cancer patients use supplementary management to improve symptoms and alleviate treatment-related toxicities<sup>8,9</sup> very often associated to an increase in oxidative stress. The pharmacological properties of PS supplements (including an anti-oxidant and anti-inflammatory activity) make their use justifiable as supplementary management – planned on an individual basis – particularly in cancer patients, as PS supplements do not interfere with other treatments. Previous studies showed that curcumin alleviates most side effects of cancer chemo- and radiotherapy possibly through the curcumin ability to upregulate anti-oxidative responses and downregulate inflammatory pathways<sup>10-12</sup>. More studies are showing the effects of PS supplements and particularly curcumin in improving residual symptoms after cancer treatment. This registry study evaluates a naturally-derived, formulation (containing curcumin, cordyceps and astaxanthin) used as a supplement in genitourinary cancer patients who had undergone oncological treatments.

## Patients and Methods

This was a registry, supplement study conducted in patients with genitourinary cancers (prostate or bladder malignancies) who had undergone and completed cancer treatments (radiotherapy, chemotherapy or intravesical immunotherapy), at least one week before inclusion.

The following patients were eligible:

- Adult subjects affected by prostate (T1/T2) or bladder cancer;

- Subjects who completed cancer treatments (radiotherapy, chemotherapy or intravesical immunotherapy), at least 1 week before inclusion.

The following patients were excluded:

- Subjects who had thrombosis or infections;
- Subjects who are being treated or taking medications due to other chronic or major diseases;
- Subjects who are allergic to food related to the investigational product or pharmaceuticals.

Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, pre-therapeutic applications. “Supplement human studies” produce supplementary data to be compared with those from the best available management plans. These types of studies are performed with products with high level of safety and pharmaceutical standards and as non-interventional trials involving a food supplement, they do not strictly require the Ethics Committee approval<sup>13-15</sup>. Informed participants (n=61) freely decided to follow either a validated standard management (SM) to control the treatment-related side effects (control group = 35) or SM plus oral daily supplementation (supplement group = 26). Daily supplementation dosage consisted of 2 tablets of a multi-component formulation (Oncotris™: Idroflu s.r.l., Conegliano, TV, Italy), for 6 weeks. The multi-component product includes: a delivery form of curcumin Enterosoma® [a delivery form of curcuma containing *Curcuma Longa L.* extract standardized to 95% curcuminoids, N-acetylcysteine, grapefruit (*Citrus paradisi* Macfad) seeds, chitosan derived from shellfish, resveratrol derived from *Polygonum cuspidatum* Sieb. et Zucc rizoma, black pepper (*Piper nigrum L.*) fruit, emulsifier (polysorbate 80)]; astaxanthin (derived from *Haematococcus pluvialis*); cordyceps (*Cordyceps sinensis*). Clinical assessments and laboratory exams were performed at inclusion and at the end of the observational period (6 weeks) and included:

- Evaluation of severity of treatment-related side effects by using an arbitrary analogue scale ranging from 0 (absence of side effects) to 5 (very severe side effects requiring medical attention);
- Blood count test;
- Prostate-Specific Antigen (PSA) test;
- Plasma free radical test: oxidative stress was evaluated by diacron-reactive oxygen metabolites (d-ROMs) test, through free radical analytical system (FRAS).

**Table I.** Genitourinary cancer and treatment distribution in the study group.

Genitourinary cancer and treatments	Standard management	Standard management + Oncotris™
<b>Prostate cancer</b>		
Chemotherapy	8	6
Radiotherapy	7	4
<b>Bladder cancer</b>		
Chemotherapy	8	6
Radiotherapy	5	5
Intravesical immunotherapy	6	5
<b>TOTAL</b>	<b>33</b>	<b>26</b>

**Statistical Analysis**

Intragroup comparisons were performed by using Student *t*-test. *p*-value <0.05 was considered statistically significant.

**Results**

Overall 61 patients with genitourinary cancers who were previously treated with standard

therapy were recruited in this study. As two participants dropped out during the study period, the final analysis set included 59 participants: 26 individuals in the supplementation group and 33 in the control group. The age of patients ranged from 58 to 74 years. The distributions of type of cancer and related treatment in the study group are shown in Table I. Table II summarizes the treatment-related side effects severity assessed by an arbitrary analogue scale. In supplemented patients, the intensity of signs and symptoms evaluated significantly decreased after the observational period. On the other side, no significant changes were observed in the control group. In addition, supplementation with Oncotris™ was associated with a significant improvement in hematological parameters, particularly in hemoglobin level (13.9±1.0 vs. 13.8±1.1 g/dL), number of red blood cells (4.8±0.6 vs. 4.6±0.7, expressed as 10<sup>6</sup>/mm<sup>3</sup>) and white blood cells (4.8±0.5 vs. 4.3±0.8 expressed as 10<sup>6</sup>/mm<sup>3</sup>) (Table III). A significant increase in number of red blood cells was also recorded in patients who received standard management only. Blood exam also revealed a decreased level of PSA and free radicals in supplemented patients at the end

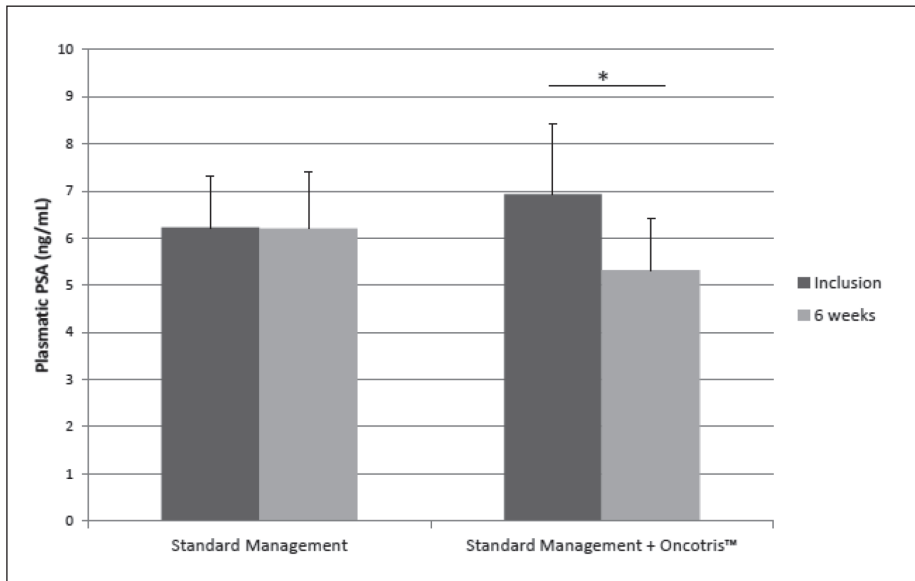
**Table II.** Evaluation of the severity of treatment-related side effects in patients with genitourinary cancers.

	Standard Management		Standard Management + Oncotris™	
	Inclusion	6 weeks	Inclusion	6 weeks
<b>Symptoms</b>				
Pain	4.3±0.7	3.3±1.1	4.6±0.2	3.1±1.0*
Dysuria	3.2±1.2	3.0±1.1	3.8±1.1	2.1±0.7*
Urgency	3.4±0.4	3.1±0.6	3.7±1.2	2.0±1.0*
Infections	3.4±0.3	2.5±0.7	3.3±0.5	1.2±0.3*
Nausea/vomiting	2.3±0.5	2.0±0.2	2.2±0.4	1.0±0.5*
Fatigue	3.4±0.8	3.0±0.9	3.5±1.0	2.1±0.7*
<b>Signs</b>				
Hematuria	3.0±0.3	2.4±0.6	3.1±0.4	2.0±0.5*
Retention	3.7±0.8	2.8±0.7	3.6±1.0	1.8±0.4*

Range of arbitrary analogue scale: 0 (no side effects) – 5 (severe side effects requiring medical attention). Data are expressed as mean±standard deviation. \**p*<0.05 vs. inclusion.

**Table III.** Blood count test in in patients pre-treated for genitourinary cancers. Data are expressed as mean±standard deviation. \**p*<0.05 vs. inclusion.

	Standard Management		Standard Management + Oncotris™	
	Inclusion	6 weeks	Inclusion	6 weeks
Hemoglobin (g/dL)	13.8±1.0	13.8±1.1	13.8±1.1	13.9±1.0*
Red blood cells (10 <sup>6</sup> /mm <sup>3</sup> )	4.4±0.4	4.5±0.7*	4.6±0.7	4.8±0.6*
White blood cells (10 <sup>3</sup> /mm <sup>3</sup> )	4.3±1.0	4.3±0.5	4.3±0.8	4.8±0.5*



**Figure 1.** The level of plasmatic prostate specific antigen (PSA) in our study population. \* $p < 0.05$ .

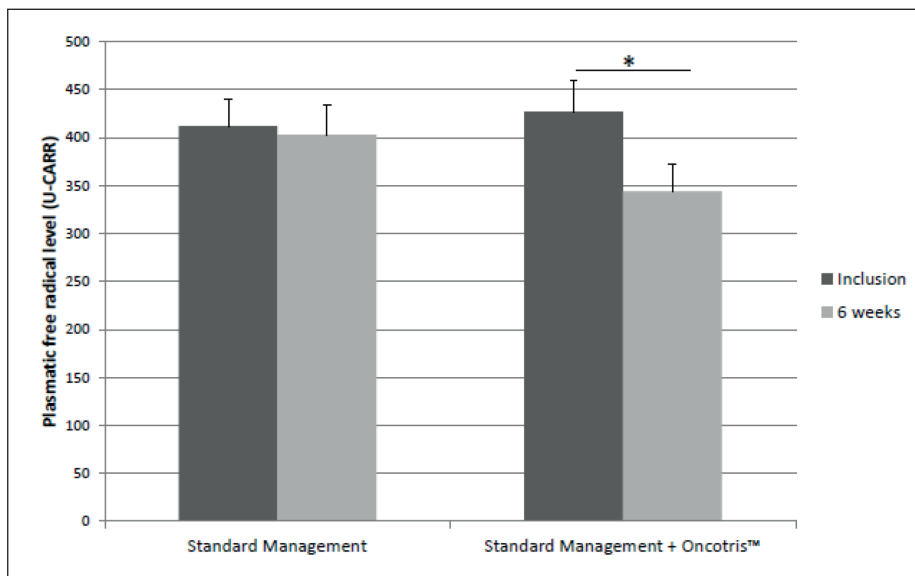
of the study period ( $5.3 \pm 1.1$  ng/mL and  $344 \pm 28$  U-CARR, respectively), compared with baseline values ( $6.9 \pm 1.5$  ng/mL and  $427 \pm 33$  U-CARR, respectively) (Figures 1 and 2).

### Safety

All subjects correctly took the supplementation showing a complete adherence to treatment (100%) and complete compliance (100%) to the proposed protocol. No adverse effects, neither toxicities, were reported.

### Discussion

Treatment-related toxicities decrease tolerance and compliance in all (including) genitourinary cancer patients. A prompt diagnosis and adequate management of these treatment-related toxicities could help to prevent or alleviate fatigue, nausea, vomiting, malaise, diarrhea, rashes, infections, headaches, and other problems and improve the patients' quality of life. One of the most promising approaches to effectively manage side effects in cancer therapies (especially chemo- and radio-



**Figure 2.** Plasmatic free radical level in our study population. \* $p < 0.05$ .

therapy) is non-pharmacologic intervention based on dietary supplementation<sup>16,17</sup>. In our registry, a remarkable improvement in the side-effect profile was observed in genitourinary cancer patients (prostate or bladder tumors) supplemented with a naturally-based multi-component formulation (Oncotris™). This clinical benefit could be ascribed to the biological properties of each supplementation components. Curcumin is an active compound isolated from *Curcuma longa* which has gained considerable interest over the last decades due to its beneficial effects for human health<sup>18</sup>. Its well-known and documented anti-oxidant and anti-inflammatory actions<sup>10,19</sup> could explain the reduction of pain, infections, dysuria observed in supplemented patients. Moreover, previous studies reported the efficacy of curcumin-based supplementation in alleviating urinary signs and symptoms of benign prostatic hyperplasia, including urgency, infections and retention<sup>20-22</sup>. Although curcumin is also functional against inflammation, rheumatism, and joint pain<sup>23-25</sup>, it has a low bioavailability; therefore, Oncotris™ includes *Curcuma Enterosoma*®, a patented technology that increases the absorption of substances that are scarcely bioavailable. This new oral delivery system has been projected aiming to improve BC (Berberina Chloride) absorption along enteric tract. The main concept surrounding this new technological system is the evidence described in many papers about the ability of Chitosan (CH) to interact with both enteric TJ (Tight Junctions)<sup>26,27</sup> and P-gP (P-gP protein)<sup>28,29</sup>. These phenomena are thought to be directly connected to the capability of CH and particularly cationized and quaternized chemical derivatives of CH, to improve absorption of poorly absorbable molecules. Particularly, the acidic molecule selected to project this technology is N-Acetylcysteine (NAC) that is a sulphureted N-Acetylated amino acid very notorious as mucolytic agent. The tablet nucleus is coated with a gastro-resistant film to avoid premature cationization of CH occurring in the stomach by the side of gastric chloride acid that would compromise the enteric absorption enhancing effect. In the present study, curcumin-based supplementation was also related to improvement in blood cell count, particularly white blood cells ( $4.8 \pm 0.5$  vs.  $4.3 \pm 0.8$ , expressed as  $10^3/\text{mm}^3$ ), as already observed in previous *in vitro* investigations where curcumin showed radioprotective effects on human peripheral blood lymphocytes<sup>30</sup>. In our work, the Oncotris™ multi-component formula-

tion seemed to act also as anti-oxidant, reducing the level of free radical in genitourinary cancer patients ( $344 \pm 28$  vs.  $427 \pm 33$  U-CARR). Besides curcumin, also astaxanthin and cordyceps have been recognized as active agents associated with oxidative stress protection<sup>31,32</sup>. Astaxanthin is a xanthophyll carotenoid found in microalgae, yeast and seafood that was approved as dietary supplement in 1999 by the Food and Drug Administration<sup>33</sup>. Cordyceps are specific macrofungi distributed worldwide, particularly in tropical forests and humid temperate, whose main chemical constituents are cordycepin, an adenosine analogue, and polysaccharides<sup>34</sup>. Recently, some very preliminary studies are investigating the anti-proliferative and anti-metastatic action of some constituents of Oncotris<sup>35-43</sup>. However, these effects have null clinical value at present.

## Conclusions

Although with some limitations, such as heterogeneity of the study population and limited sample size, this work showed that a nutritional approach based on naturally-derived ingredients could support the body to overcome the treatment-related side effects in the supportive management of genitourinary cancer.

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## Conflict of Interest

VC is a partner of Idroflu. LG is a consultant of Idroflu s.r.l., Conegliano, TV, Italy.

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