



## Phase III randomised trial

## A prospective, randomized, multi-center trial to investigate Actovegin in prevention and treatment of acute oral mucositis caused by chemoradiotherapy for nasopharyngeal carcinoma

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## ARTICLE INFO

## Article history:

Received 18 October 2009

Received in revised form 25 March 2010

Accepted 13 August 2010

Available online 7 September 2010

## Keywords:

Actovegin

Mucositis

Radiotherapy

Chemotherapy

Nasopharyngeal carcinoma

## ABSTRACT

**Purpose:** A multi-center prospective randomized trial was conducted to evaluate the efficacy and safety of Actovegin in the prevention and treatment of chemoradiotherapy-induced acute oral mucositis.

**Methods and materials:** Between February 2006 and May 2007, 156 evaluable patients with nasopharyngeal carcinoma were randomized to Group 1 ( $n = 53$ ) for prevention, Group 2 ( $n = 51$ ) for treatment, and Group 3 ( $n = 52$ ) for control. All patients received concomitant chemoradiotherapy  $\pm$  induction chemotherapy. Radiation technique and dose were similar among 3 groups. Intravenous Actovegin of 30 ml daily (5 days/week) was administered from day 1 of the radiotherapy for Group 1 and from the onset of grade 2 mucositis for Group 2, until the end of the radiotherapy.

**Results:** The incidence of grade 3 mucositis was lower in Group 1 compared with Group 3 (26.4% vs. 55.8%,  $P = 0.002$ ). Group 2 had a lower progression rate of mucositis from grade 2 to 3 compared with Group 3 (39.2% vs. 60.4%,  $P = 0.035$ ). There was no difference in the onset time of grade 3 mucositis among 3 groups. Actovegin was well tolerated and no treatment-related adverse events were observed.

**Conclusions:** Actovegin is effective in the prevention and treatment of chemoradiotherapy-induced oral mucositis.

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Oral mucositis is a common complication during chemoradiotherapy (CRT) for head and neck cancer. It is estimated that approximately 30–60% patients receiving standard radiotherapy alone and more than 90% patients receiving CRT will develop severe oral mucositis [1–7]. Oral mucositis often interferes with the patient's quality of life and nutrition as a result of pain and dysphagia. Mucositis also increases the risk of systemic infections due to disrupted mucosal barriers and treatment may need to be interrupted with negative impacts on tumor control [8–10].

Topical agents such as sucralfate, prostaglandins, benzydamin, granulocyte-macrophage or granulocyte colony-stimulating factor and treatment using laser and cryotherapy were studied in the past in the prevention and treatment of chemotherapy/radiotherapy-induced oral mucositis but no consistent benefits were observed and none can be accepted as a standard therapy for mucositis [11].

Actovegin is a deproteinized extract with a molecular weight less than 6000 Da and prepared from the blood of 6-month old calves. Actovegin has been demonstrated to have a good effect

on the treatment of various types of skin and mucosal ulcers [12]. Recently, a study demonstrated that Actovegin can postpone the development of radiation-induced oropharyngeal mucositis and decrease the incidence of grades 3–4 mucositis [13].

To further evaluate the efficacy of Actovegin in oral mucositis, we conducted a multi-center, prospective randomized trial on the use of Actovegin in the prevention and treatment of oral mucositis for patients with nasopharyngeal carcinoma (NPC) treated with CRT.

### Materials and methods

#### Eligibility criteria

Eligibility criteria for this study included the following: patients with newly diagnosed stage III–IVB (UICC 2002 staging criteria) NPC scheduled for CRT, age 18–70 years, a Karnofsky performance score  $\geq 70$ , no significant oral disease, and normal cardiac, hepatic, renal, and hematopoietic functions. Pretreatment evaluation included a complete history and physical examination, complete blood count, and blood chemistry analysis. Staging evaluations included a CT scan or MRI of the nasopharynx and neck, chest X-ray, bone scan, and liver sonography.

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Randomization was performed centrally at the Cancer Center of Sun Yat-Sen University using a computer-generated code after checking the eligibility criteria. Patients were randomized to prevention, (Group 1), treatment (Group 2) or control group (Group 3). The study protocol was approved by the ethics committee for drug clinical studies of the Cancer Center of Sun Yat-Sen University (Lead organization) and registered at the Chinese Anti-Cancer Association (CACA). All patients gave written informed consent prior to the enrollment.

### Radiotherapy

All patients underwent mask immobilization with CT simulation and CT-based planning. Conventional radiotherapy or intensity-modulated radiotherapy was administered according to the extension of primary tumor. Photons of 6-MV were used along with electrons, when indicated. The prescription doses of the nasopharynx and neck were 66–70 Gy and 60–66 Gy, respectively. The prophylactic doses of the neck were 50 Gy. A daily dose of 2 Gy per fraction, 5 fractions per week was given in this study.

### Chemotherapy

Concomitant chemoradiotherapy was employed for all the patients. The chemotherapy regimen consisted of cisplatin 80 mg/m<sup>2</sup> iv on day 1 and 22 of radiotherapy. Thirty-five patients also received induction chemotherapy of PF ( $n = 20$ ) or TP regimen ( $n = 15$ ), which was used based on every departmental protocol. The distributions of PF or TP regimen in Groups 1, 2, and 3 were not different significantly, being 9, 7, and 4 patients, or 4, 4, and 7 patients ( $P = 0.234$ ), respectively. The PF regimen consisted of two cycles of cisplatin 100 mg/m<sup>2</sup> iv on day 1 and 5-fluorouracil 750 mg/m<sup>2</sup> iv on day 1–5. The TP regimen consisted of two cycles of taxol 135 mg/m<sup>2</sup> iv on day 1 and carboplatin (dose calculated according to an AUC of 6 mg ml/min) iv on day 1. Cycles were given thrice weekly. The second cycle was followed by radiotherapy in 3 weeks. All the patients were treated using 5-HT<sub>3</sub> antagonists as antiemetic premedication as well as dexamethasone of 10 mg prior to chemotherapy.

### Study drug administration

Actovegin (Nycomed Corp.) was injected intravenously over 30 min at a dose 1200 mg added to 250 ml of 5% glucose solution or 0.9% normal saline 250 ml once daily, five times per week until the endpoint of radiotherapy. Group 1 received Actovegin from Day 1 of radiotherapy and Group 2 received Actovegin following the onset of grade 2 oral mucositis. No Actovegin was given to Group 3.

### Concomitant medication

All the patients were instructed to rinse their mouths daily using chlorhexidine gargle during radiotherapy. Steroids or antibiotics were not allowed for oral mucositis before the occurrence of grade 3 reaction. Topical anesthetics were allowed to be used only for grade 2 or 3 oral pain.

### Evaluation

Acute toxicity of oral mucosa and oral pain were carefully observed and evaluated daily during the treatment according to NCI Common Toxicity Criteria (NCI CTC) 2.0 criteria and verbal rating scales (VRS) criteria [14], respectively. The grading criteria of NCI CTC 2.0 were as follows: 0 = normal, 1 = erythema, 2 = patchy pseudomembrane, 3 = confluent pseudomembrane, and 4 = necro-

sis or deep ulceration. The grading criteria of VRS were as follows: 0 = no pain, 1 = mild pain, sleep unaffected, 2 = moderate pain, sleep affected, and 3 = severe pain, sleep severely affected. The time to the occurrence of grade 3 mucositis was recorded from day 1 of radiotherapy. The primary endpoints were the incidence and the time of occurrence of grade 3 mucositis during concomitant chemoradiotherapy. The time span of grade 3 mucositis was not listed as an endpoint because of the use of additional interventions after grade 3 mucositis occurred.

### Safety observations

Adverse events during Actovegin treatment were closely monitored and recorded. Blood routines, electrolytes and hepatic and renal functions were examined before, during and after the treatment. The responses of primary tumor and cervical nodes were evaluated using nasopharyngoscopy and CT/MRI at the end of the treatment.

### Statistical methods

The study was designed to detect a 30% difference in the incidence of grade 3 mucositis, assuming an incidence of 60% in the control group and a sample size of 156 (52 each group) was needed for a power of 80% and a significant level (alpha) of 0.05. All statistical analyses were performed using the commercial software package SPSS 12.0 (SPSS, Chicago, USA). One-way ANOVA and chi-square test were used for comparing measurement data and count data among the three groups, respectively.

### Results

A total of 160 patients at 4 participating treatment centers entered into the trial and were randomized into Group 1 ( $n = 53$ ), Group 2 ( $n = 55$ ) and Group 3 ( $n = 52$ ) between February 2006 and May 2007. Four patients in Group 2 were considered ineligible for an efficacy analysis. Of these 4 patients, 2 withdrew from study at their request after the first or the third dose of Actovegin, another 2 did not have oral mucositis  $\geq$  grade 2 during chemoradiotherapy and hence Actovegin was not administered. Clinical characteristics of all the patients in the three groups are summarized in Table 1. The distributions of the patients' main characteristics were comparable among these three groups.

### Severity of mucositis

All patients in the three groups developed acute oral mucosal reaction of varying degrees during CRT (Table 2). The incidences of grade 3 mucositis in Group 1, 2 and 3 were 26.4%, 39.2% and 55.8%, respectively. The difference between Group 1 and 3 was significant ( $P = 0.002$ ). No difference between Group 2 and 3 was noted ( $P = 0.093$ ).

Group 1 also had a lower incidence of grade 2 mucositis when compared with Group 3 (73.6% and 92.3%,  $P = 0.011$ ). The progression rate of mucositis from grade 2 to 3 in Group 1 (35.9%,  $P = 0.023$ ) and Group 2 (39.2%,  $P = 0.035$ ) were both lower than that in Group 3 (60.4%), respectively. The rates of mucositis from grade 2 to 1 in Group 1 (41.0%,  $P = 0.022$ ) and Group 2 (47.1%,  $P = 0.003$ ) were higher than Group 3 (18.8%), respectively. However, the rates of mucositis from grade 3 to 2 among the three groups were not different significantly ( $P = 0.444$ ).

### Onset time of mucositis

The cumulative incidences of grade 2 and 3 mucositis in all three groups increased gradually with the continuation of the

**Table 1**  
Clinical characteristics of patients.

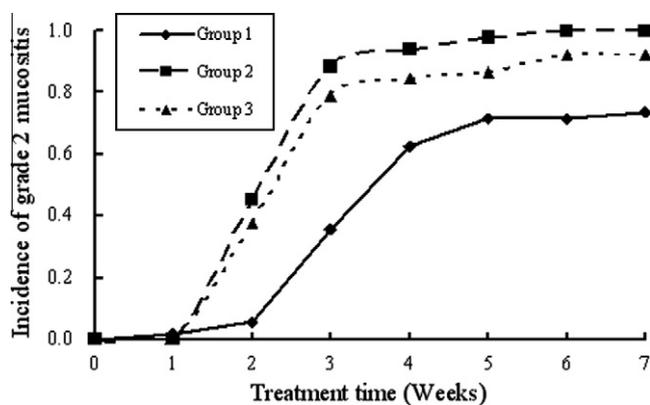
Items	Group 1 (n = 53)		Group 2 (n = 55)		Group 3 (n = 52)		P
	No.	%	No.	%	No.	%	
<i>Gender</i>							
Male	41	77.4	40	72.7	36	69.2	0.641
Female	12	22.6	15	27.3	16	30.8	
<i>Age</i>							
≤45 years	23	43.4	25	45.5	20	38.5	0.755
>45 years	30	56.6	30	54.5	32	61.5	
<i>Clinical staging</i>							
III	41	77.4	40	72.7	42	80.8	0.612
IV	12	22.6	15	27.3	10	19.2	
<i>RT techniques</i>							
Conventional RT	29	54.7	34	61.8	29	55.8	0.722
IMRT	24	45.3	21	38.2	23	44.2	
<i>RT dose (Gy)</i>							
Primary lesion <sup>a</sup>	70 (68–76)		70 (66–76)		70 (68–76)		0.265
Neck <sup>a</sup>	62 (50–72)		62 (50–70)		62 (50–78)		0.626
<i>CT methods</i>							
CCRT	40	75.5	44	80.0	41	78.8	0.841
ICT + CCRT	13	24.5	11	20.0	11	21.2	

Abbreviation: RT, radiotherapy; IMRT, intensity modulated radiotherapy; CT, chemotherapy; CCRT, concomitant chemoradiotherapy; ICT, induction chemotherapy.

<sup>a</sup> Median dose, values in parenthesis represent dose range.

**Table 2**  
Incidence of acute oral mucositis for 156 evaluable patients.

Groups	No. of patients	Grading of mucositis							
		1	(%)	2	(%)	3	(%)	4	(%)
Group 1	53	53	(100)	39	(73.6)	14	(26.4)	1	(1.9)
Group 2	51	51	(100)	51	(100)	20	(39.2)	1	(2.0)
Group 3	52	52	(100)	48	(92.3)	29	(55.8)	3	(5.8)

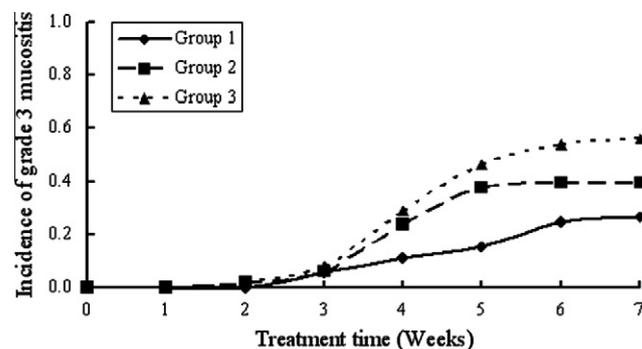


**Fig. 1.** Cumulative incidence of grade 2 mucositis during treatment in Group 1 (53 patients, at 7 weeks 39 at risk), Group 2 (51 patients, at 7 weeks 51 at risk) and Group 3 (52 patients, at 7 weeks 48 at risk).

treatment (Figs. 1 and 2). The mean onset times of grade 2 mucositis in Group 1, 2 and 3 were  $22 \pm 8$  days (5–49),  $17 \pm 6$  days (9–36) and  $18 \pm 7$  days (11–40), respectively. Group 1 had a significant longer onset time of grade 2 mucositis compared to Group 2 ( $P = 0.001$ ) and Group 3 ( $P = 0.01$ ). The mean onset times of grade 3 mucositis were  $30 \pm 8$  days (17–43),  $26 \pm 6$  days (12–37) and  $28 \pm 7$  days (12–46), respectively. The differences among the three groups were not significant ( $P = 0.382$ ).

#### Severity of oral pain

All three groups had oral pain of various severities during the treatment (Table 3). Group 1 had a lower incidence of grades 2–3



**Fig. 2.** Cumulative incidence of grade 3 mucositis during treatment in Group 1 (53 patients, at 7 weeks 14 at risk), Group 2 (51 patients, at 7 weeks 20 at risk) and Group 3 (52 patients, at 7 weeks 29 at risk).

**Table 3**  
Incidence of oral pain for 156 evaluable patients.

Groups	No. of patients	Grading of pain					
		1	(%)	2	(%)	3	(%)
Group 1	53	47	(88.7)	32	(60.4)	0	(0.0)
Group 2	51	49	(96.1)	37	(72.5)	3	(5.9)
Group 3	52	51	(98.1)	43	(82.7)	8	(15.4)

pain compared with Group 3, being 60.4% and 82.7% ( $P = 0.011$ ). No difference between Group 2 and 3 was noted (72.5% and 82.7%,  $P = 0.217$ ). Topical anesthetics were given in 61 patients (14 in Group 1, 19 in Group 2, and 28 in Group 3) due to grade 2 or 3 oral pain.

Four patients in Group 3 had only grade 1 mucositis and grade 0–1 pain during CRT. If the comparison was limited to those with grade 2 or above mucositis, Group 2 also had a lower incidence of grades 2–3 pain compared with Group 3, being 72.5% and 89.6% ( $P = 0.031$ ).

#### *Nutritional management and weight loss*

At the beginning of radiation, patients' feeding habits were not changed. After oral pain or xerostomia occurred, most patients (47 in Group 1, 54 in Group 2, and 51 in Group 3) had to have semiliquid or liquid meals, and 66 patients (14 in Group 1, 18 in Group 2, and 34 in Group 3) required partial parenteral nutrition by intravenous infusions. No patient received a feeding tube. The mean weight loss at the end of treatment in Group 1, 2 and 3 was  $3.6 \pm 3.2$  kg,  $3.3 \pm 3.4$  kg and  $3.6 \pm 3.2$  kg, respectively. There was no significant difference among the three groups ( $P = 0.832$ ).

#### *Acute toxicity of chemoradiotherapy*

Two patients in Group 1 and 2 developed grade 4 myelotoxicity during chemoradiotherapy and had to discontinue radiotherapy for 16 and 25 days, respectively. No significant differences among the three groups in the incidence and severity of acute toxicities other than mucositis, including skin reaction, myelosuppression, hepatic and renal functional impairment were noted.

#### *Adverse events*

There were two patients in Group 2 who withdrew due to fever and vomiting. Of these two patients, one patient developed a low fever after the first administration of Actovegin and subsequently returned to normal temperature after antipyretic treatment. This patient was treated using Actovegin again in two weeks after the discontinuation and no fever was observed. Therefore, the fever in this patient was not considered to be related to Actovegin treatment. The cause may be related to the common cold experienced before the first medication. Another patient developed vomiting after the third medication which was attributed to cisplatin. No adverse drug events, including fever, nausea, vomiting, allergic reaction, etc., in the other patients of Group 2 and all the patients of Group 1 were observed. Patient compliance to intravenous Actovegin was good. No patient refused to the drug administration during treatment except the two patients mentioned above. At the end of the treatment, the complete response rates of the primary tumor in Group 1, 2 and 3 were 83.0%, 78.2% and 86.5% ( $P = 0.520$ ), respectively. The corresponding figures of the cervical nodes were 88.7%, 87.3% and 75.0% ( $P = 0.112$ ), respectively.

## **Discussion**

Oral mucosa is composed of stratified squamous epithelia that are renewed quickly and are highly sensitive to irradiation. Radiotherapy often causes oral acute mucositis characterized by oral erythema, pseudomembrane, necrosis/ulceration, and pain. Acute mucositis is thought to be a complex biologic process, involving direct damage to the dividing cells of the oral epithelium with the depletion of the basal epithelium and inhibition of the proliferation of transit cells [15,16].

Similar to radiotherapy, chemotherapy can also produce oral acute mucositis that usually occurs 1–2 weeks after the initiation of drug therapy. Chemotherapy-induced mucositis is characterized by erythema of the mucosa. Pseudomembrane and ulceration are seen less [17–20]. In this study, only 14% (5/35) of patients receiving induction chemotherapy developed an oral erythema reaction 5–12 days after the start of anti-cancer drugs and the remainder were normal.

When chemotherapy was concomitantly combined with radiotherapy, the severity of mucositis will be aggravated significantly [4–7,19]. Recently, concomitant CRT with or without induction or adjuvant chemotherapy has widely been used for treating head and neck cancer, including NPC [21]. Management of oral mucositis induced by CRT has thus become an important issue since severe mucositis affects not only quality of life but may also affect treatment compliance and completion.

Actovegin is a deproteinized blood extract consisting of a series of physiologically active components, including oligosaccharides, nucleotides, low molecular polypeptides, glycolipids, metabolic intermediates of saccharides and lipids, amino acids, and trace elements [22]. It is often used to treat skin and mucosal ulcers, diabetic peripheral neuropathy and hypoxic ischemic encephalopathy [12,22–24]. However, reports on the treatment of radiation mucositis with Actovegin are relatively scanty. An early animal experiment on the treatment of lethal radiation damage indicated that Actovegin significantly increased the survival rate of mice after a total body irradiation [25]. Subsequently, several clinical studies showed that this drug could improve the symptoms of radiation-induced laryngopharyngeal mucositis, cystitis, dermatitis, and arm plexus pareses [26–29]. Recently, Zhang et al. [13] reported a small, randomized trial consisting of 35 patients with head and neck cancer treated by postoperative radiotherapy. The results showed that Actovegin was able to postpone the mean onset time of oral mucositis (18.2 days vs. 10.6 days,  $P = 0.0002$ ), decrease the incidence of grade 3–4 mucositis (23.5% vs. 61.1%,  $P = 0.0409$ ) and the severity of pain.

In this multicenter study, Actovegin as the preventive application (Group 1) had significant efficacy in the frequency of grade 3 oral mucositis and grade 2–3 oral pain during chemoradiotherapy. Actovegin as the therapeutic application (Group 2), similar to the preventive application, could produce inhibition of progression from grade 2 to 3 mucositis and hasten the regression from grade 2 to 1 mucositis. However, no significant differences in the overall incidence of grade 3 mucositis and grade 2–3 pain between Group 2 and 3 were observed. The cause should be related to four patients developing only grade 1 mucositis during the treatment in Group 3, which will affect the comparability of these two groups. Otherwise, although the difference in the onset time of grade 3 mucositis among the three groups was not significant, Group 1 had a longer onset time and a lower incidence of grade 2 mucositis. These results revealed that it may be better to administrate Actovegin at the initiation of radiotherapy for the prevention of mucositis than to give it at the onset of grade 2 mucositis for the treatment intention.

Grading score of oral pain is generally related to the severity of oral mucositis. In this trial, most patients with grades 2–3 oral pain occurred during the phase of grades 3–4 mucositis and Actovegin appears to decrease the incidence of serious pain through reducing the severity of oral mucositis rather than possessing any analgesic effect.

Actovegin could not hasten the regression from grade 3 to 2 mucositis. The cause may be related to secondary infections of the damaged mucosa during the phase of grade 3 mucositis in a portion of the patients. Superinfection induced by the oral bacterial flora can exacerbate the severity of oral mucositis [30,31], therefore, the treatment of infections is an important part of mucositis therapy and can be directed locally or systemically depending on the type and extent of infection [32–34]. Chlorhexidine, an oral antimicrobial mouthwash, conventionally used for all patients in our trial, has been demonstrated to reduce oral microbial burden and improve oral hygiene but with generally no effect on the development or severity of mucositis [35,36]. Intravenous antibiotics are necessary when patients have suspicious oral infective lesions or severe mucositis. In this study, a total of 61 (39.6%)

patients were treated with broad spectrum intravenous antibiotics covering anaerobes and gram-negative organisms after the onset of grade 3 mucositis. In addition, glucocorticosteroids also play a significant role in the treatment of severe mucositis due to the properties of anti-inflammation [37]. Forty-six (29.5%) patients in our trial had to be treated using intravenous dexamethasone to alleviate serious oral pain (VRS grades 2–3) during the phases of grades 3–4 mucositis, which did not influence the observation of grade 3 mucositis as an endpoint of evaluation.

The mechanism of the beneficial effect of Actovegin on oral mucositis is not well known. Based on the results of animal studies and clinical observations reported by some authors, it is generally believed that the underlying mechanism is related to the ability of Actovegin to improve oxygen supply of hypoxic cells and enhance the cell proliferation and repair [25,26,38].

It was reported that the toxicity of Actovegin was very mild and infrequent. Side effects of urticaria, papule and fever were seen occasionally [22–24]. Our trial showed that no adverse reaction associated with Actovegin administration was observed in all the patients.

Will Actovegin stimulate the growth of tumor cells? The animal and clinical studies until the present have not shown any evidence of tumor cell growth produced by this drug. On the contrary, some authors believed that Actovegin was able to enhance the radiosensitivity of tumor cells through improving oxygen supply to hypoxic cells and accelerating healing of cancerous ulcers [25,38]. From the results of the tumor response at the end of the treatment with no significant difference among the three groups in this trial, it was suggested that the addition of Actovegin is unlikely at least to affect the short-term efficacy of anti-cancer therapy. However, its influence on long-term efficacy needs to be further followed up.

The optimal time and dosage of Actovegin application are unclear. In animal experiments, Barth et al. [25] compared the survival rates of mice at different intervals of the injection of Actovegin after total body radiation during an observation time of 30 days. The optimal time of the medication was found to be about 3 h after the radiation. In clinical study, some authors gave the drug before irradiation and tried to increase the radiosensitivity of hypoxia tumor cell while exerting an effect on mucositis [13], some had no special requirement for it [26]. However, there was no comparison study of different intervals of giving the drug before or after the irradiation. The dosage of Actovegin generally ranged from 400 mg to 2000 mg per day in clinical study but no dose-escalating study was reported. Since the primary objective of this study was to observe the effect of Actovegin on mucositis, we used the drug without a special time definition for clinical convenience. The same dose (1200 mg) as used by Zhang [13] was employed in this study and demonstrated favorable efficacy against mucositis. The results suggest that the time and dosage of Actovegin used in this study are feasible. Of course, the optimal time and dosage of the drug require further study.

In addition, topical application (e.g., mouth rinse and aerosol inhalation) is frequently used for treating radiation-induced oral mucositis, but it is difficult to achieve effective drug concentration for treating mucositis developing at hypopharynx, larynx, and even at deeper sites, such as esophagus and gastrointestinal tract. Intravenous application will have better effects on mucositis at these deep sites due to reaching uniform and effective drug concentration. Hence, we believe that intravenous Actovegin in the intervention of mucositis at deep sites has more advantages than the topical application of other drugs.

## Conclusions

In summary, our results show that intravenous Actovegin is effective in the prevention and treatment of oral mucositis induced

by CRT. Actovegin reduces the severity of oral mucositis and decreases the incidence of severe pain. The efficacy of preventive application appears to be better than therapeutic application.

## Conflict of interest statement

The authors claimed no conflict of interest in relation to this manuscript.

## Acknowledgements

We thank Nycomed China Limited to provide the study drug Actovegin, and Daniel T.T. Chua, F.R.C.R., Departments of Clinical Oncology, University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China, for his assistance in English editing and recommendations.

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