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The protective effects of *Bacillus licheniformis* preparation on gastrointestinal disorders and inflammation induced by radiotherapy in pediatric patients with central nervous system tumor

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ABSTRACT

Purpose: we studied the effect of *Bacillus licheniformis* preparation (ZCS) on CNST (central nervous system tumor) patients undergoing the gastrointestinal symptoms and inflammation induced by radiotherapy.
Materials and Methods: 160 CNST patients with craniospinal irradiation (CSI) treatment were divided into experiment and control group. The experiment group patients took one capsule per time of ZCS and three times a day until the end of radiotherapy, starting one day before radiotherapy. While the patients in control group were administrated placebo without any probiotics. Serum from one day before radiotherapy and the first day after radiotherapy were collected to measure the ET, CRP, TNF-α, IL-1β and IL-6.
Results: More than 70% CNST pediatric patients suffered from different degrees of gastrointestinal symptoms after radiotherapy, including mouth ulcer, nausea, vomiting, abdominal pain and diarrhea. And there was an obviously increased of serum ET, TNF-α, IL-1β, IL-6 and CRP after RT. Importantly, a markedly decreased of ET, CRP and inflammatory cytokines were detected in the experiment group comparing to the control group after radiotherapy, as well as the relief of the gastrointestinal symptoms. However, improvement of probiotics (or ZCS) of the survival rate of CNST children and the recurrence of tumor are not observed in this study.
Conclusions: Prophylactically administrated ZCS during radiotherapy for CNST patients can relieve RT-related gastrointestinal symptoms and inflammatory reaction.

1. Introduction

Central nervous system tumor (CNST) is the most common solid tumors in pediatric population especially in children aged under 5 years, which is accounting for about 24% of all malignant tumors in children, and just behind leukemia [1–3]. Currently, surgical resection is still the optimal choice for pediatric CNST, and CSI after operation is necessary in most of pediatric patients [4,5]. Although radiation therapy (RT) could improve the survival rate for patients with CNST, almost all children showed gastrointestinal symptoms, immune suppression, and even inflammatory response which decreased the efficacy of radiotherapy and even affected the growth of children [6–8]. Therefore, it is necessary to take measures to reduce the gastrointestinal toxicity and inflammation induced by radiotherapy, and improve the radiation therapy tolerance of CNST patients.

Probiotics are beneficial living microorganisms that can survive in the gastrointestinal tract, which play important roles in maintaining or restoring the intestinal flora balance, barrier defense and mucosal immunity [9]. It has been reported that probiotics might provide a favorable role to relieve diarrhea or intestinal inflammation caused by radiotherapy in people with cancer [10–12]. Bacillus licheniformis preparation (ZCS) is a viable probiotics *in vitro* and widely used in clinical treatment. It can balance the gastrointestinal flora, as well as acute and chronic enteritis, diarrhea and intestinal endotoxemia therapy without any

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evident adverse reaction [13]. Recently, there are still few data about the effect of ZCS on gastrointestinal disorders caused by CSI in CNST children.

Here, we reported the results of protective effective of *bacillus licheniformis preparation* on gastrointestinal disorders induced by RT in CNST children, who accepted RT from March 2013 to October 2014. The trial was designed to conform the favorable effects of ZCS on the quality life of children with RT.

2. Materials and methods

2.1. Eligibility

Criteria for inclusion were diagnosis of a primary intracarnial tumor, histologically confirmed diagnosis of glioblastoma, medulloblastoma, ependymocytoma and astrocytoma, age > 3 years at time of diagnosis, no medical contraindication to therapy, and no history of previous radiotherapy or chemotherapy. Patients were to have no evidence of disseminated diseases conformed by brain and spine magnetic resonance images and cerebrospinal fluid cytology at diagnosis. All legal representatives of patients approved and provided informed consent.

2.2. Patients, surgery, and pathological analysis

One hundred sixty children with newly diagnosed nondisseminated CNST, who were aged > 3 years at time of initial tumor surgery, and who had received a diagnosis during the period March 2013 through October 2014 at Beijing Shijitan Hospital in China. The maximum possible safe surgical removal of the primary tumor was recommended. All patients with CNST were performed by an experienced neuropathologist, and findings were classified according to the World Hearth Organization classification of brain tumors as glioblastoma (n = 48), medulloblastoma (n = 60), ependymocytoma (n = 34) and astrocytoma (n = 18).

2.3. Treatment

After surgery, craniospinal irradiation (CSI) was initiated within 2–4 weeks. Patients received CSI as 36 Gy (range from 21 to 54 Gy), and posterior fossa boost as 1.5 Gy (range from 1.5 to 1.8 Gy). No evidence of dissemination was found based on brain and spine magnetic resonance images and cerebrospinal fluid cytology; gross total resection or near total (> 90% resection) resection on postoperative neuroimaging; residual tumor (if present) diameter < 1.5 cm and Chang Stage T1-T3b; no previous RT or chemotherapy; without antibiotics and probiotics preparation in two weeks (see Table 1). Parents and caregivers or patients provided informed written consent, and data electronic medical records were reviewed and clinical information was abstracted for these patients in four weeks of follow-up.

According to age, sex, signs and symptoms, location of tumor, extent of surgical resection, histopathology, radiotherapy dose, and etc., all pediatric patients were divided into two groups: experiment group and control group. The experiment group patients took one capsule per time of ZCS (Northeast Pharmaceutical Group, Shenyang No. 1 Pharmaceutical Co. Ltd. Lot S10950019) and three times a day until the end of radiotherapy, starting one day before radiotherapy. While the patients in control group were administrated placebo without any probiotics.

This study was conducted in the pediatric oncology department of Beijing Shijitan hospital, Capital Medical University, in North China. The Research Ethics Committee of the hospital approved the study protocol and waived the need for informed consent because this analysis used the currently existing data collected during the course of routine treatment and care. The data were reported in aggregate.

Peripheral blood was taken on one day before and the first day after radiotherapy, and serum ET, TNF-α, IL-1β, IL-6 and CRP contents were measured by Enzyme-linked immunosorbent assay (ELISA) detection kit provided by BioSource (Nivelles, Belgiun)

Table 1
Patient characteristics and response to therapy.

Characteristic	Experiment group (n = 80)	Control group (n = 80)	Total (n = 160)
Sex			
Male (%)	50 (62.5%)	58 (72.5%)	108 (67.5%)
Female (%)	30 (37.5%)	22 (27.5%)	52 (32.5%)
Age at diagnosis (y)			
Median (range)	7.0 (1.3–14.1)	7.5 (1.5–15.5)	7.1 (1.3–15.5)
Brain tumor classification			
Medulloblastoma	30 (37.5%)	30 (37.5%)	60 (37.5%)
Glioblastoma	24 (30.0%)	24 (30.0%)	48 (30.0%)
Ependymoma	17 (21.2%)	17 (21.2%)	34 (21.2%)
Astrocytoma	9 (11.3%)	9 (11.3%)	18 (11.3%)
Postoperative residual tumor			
Yes (%)	16 (20.0%)	11 (13.7%)	27 (16.9%)
No (%)	50 (62.5%)	52 (65.0%)	102 (63.8%)
Indistinct (%)	14 (17.5%)	17 (21.3%)	31 (19.3%)
Best response to radiation therapy			
CCR	36 (45.0%)	37 (46.3%)	73 (45.6%)
CR	20 (25.0%)	15 (18.8%)	35 (21.9%)
PR	13 (16.3%)	14 (17.5%)	27 (16.9%)
IMP	7 (8.7%)	9 (11.2%)	16 (10.0%)
SD	4 (5.0%)	5 (6.2%)	9 (5.6%)
Progression/relapse			
No (%)	56 (70.0%)	49 (61.3%)	105 (65.7%)
Yes (%)	24 (30.0%)	31 (38.7%)	55 (34.3%)
Follow-up time of surviving patients			
median years (range)	2.4 (0.3–6.9)	3.3 (0.2–5.9)	2.8 (0.2–6.9)
Rate (%) of 3-year OS (±SE)	77.4 ± 5.6%	82.1 ± 4.6%	80.0 ± 3.6%
Rate (%) of 5-year OS (±SE)	63.5 ± 10.1%	68.3 ± 7.8%	66.6 ± 6.1%
Rate (%) of 3-year PFS (±SE)	71.7 ± 5.4%	70.8 ± 5.1%	71.4 ± 3.7%
Rate (%) of 5-year PFS (±SE)	55.0 ± 9.5%	48.3 ± 7.9%	50.7 ± 6.1%

Table 2
Cumulative number of patients with at least one episode of gastrointestinal toxicity according to CTCAE 3.0 attributed to radiation therapy.

Toxicity grade	Experiment group(n = 80)					Control group(n = 80)					$\chi 2$	*P*
	I	II	III	IV	total	I	II	III	IV	total		
Nausea	13	24	13	3	53	10	29	21	6	66	5.542	0.019
Vomiting	5	13	10	0	28	6	21	13	2	42	4.978	0.026
Abdominal pain	5	12	10	8	35	7	23	20	12	62	19.087	0.000
Diarrhea	1	3	3	0	7	2	10	8	0	20	7.530	0.006
Mouth erythema or ulcer	6	3	0	0	9	7	10	5	0	22	6.762	0.009

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

following the manufacturer's instructions. Toxicity of radiation therapy was recorded during, at the end, and at 6, 12, 24, 36, 48, and 60 months after radiotherapy. Regular visits with follow-up imaging were scheduled every 3 months in the first 2 years after the end of RT, every 6 to 9 months in the third to fifth year, and annually thereafter. Complete response (CR) was defined as the total disappearance of visible residual tumor and CSF negative. Continuous CR (CCR) was defined as an absence of any evaluable disease during the entire observation time. Partial response (PR) was defined as a $\geq$ 50% decrease in tumor volume and CSF negative. Improvement (IMP) was defined as a 25%-50% decrease in tumor volume and/or CSF negative, stable disease (SD) was defined as a $<$ 25% decrease or increase, and progressive disease (PD) was defined as a $\geq$ 25% increase and/or CSF positive, as assessed by MRI and lumbar puncture [14]. PFS and OS are defined as progression-free survival and overall survival respectively. All items abbreviation are listed as Table 3.

2.4. Statistics

All data were performed at least three times and results were expressed as mean ±SD. Comparisons between two groups were determined with Chi square test or Student's *t*-test. Kaplan-Meier estimates and log-rank test were used for progression-free survival (PFS) and overall survival (OS) probability (±standard error [SE]). $P < 0.05$ was considered statistically significant ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$).

Table 3
Items abbreviation.

Abbreviation	
ZCS	*Bacillus licheniformis* preparation
CNST	central nervous system tumor
CSI	craniospinal irradiation
ET	Endotoxin
CRP	C-reactive protein
TNF-α	Tumor Necrosis Factor alpha
IL-1β	Interleukin 1 beta
IL-6	Interleukin-6
RT	RadioTherapy
Gy	Gray
ELISA	Enzyme-Linked ImmunoSorbent Assay
CR	Complete Response
CCR	Continuous CR
PR	Partial Response
IMP	Improvement
SD	Stable Disease
PD	Progressive Disease
PFS	Progression-Free Survival
OS	Overall Survival

3. Results

3.1. Protective effects of bacillus licheniformis preparation on gastrointestinal symptoms induced by RT in children with CNST

The common gastrointestinal disorders induced by radiation therapy were due to the imbalance of intestinal flora. There were approximately above 70% CNST pediatric patients suffered different degree of gastrointestinal symptoms, including nausea (56/80, 70%), vomiting (36/80, 45%), abdominal pain (55/80, 68.75%), diarrhea (18/80, 22.5%), and mouth erythema or ulcer (15/80, 18.75%) in control group (Table 2). To determine whether the treatment of ZCS can relieve this gastrointestinal disorders, the CNST patients received RT were administrated with ZCS which indicated as the experiment group (Table 2). Importantly, we observed a strongly decreased incidence at all grades of toxicity comparing to the control group. Thus it's demonstrated that ZCS displayed a markedly protective effects on the gastrointestinal toxicity.

3.2. Enhanced serum levels of ET, CRP and pro-inflammatory cytokines in patients after RT

Radiation would impair the intestinal barrier function, resulting in pathophysiological translocation of bacteria in intestinal tract into the systemic blood flow and contributing to the emergence of sepsis [15]. It is reported that certain mucosal cytokines are activated and the levels of TNF-α, IL-1β and IL-6 are significantly higher in radiation-induced proctosigmoiditis [16]. So we measured the serum levels of ET, CRP, TNF-α, IL-1β and IL-6 of the CNST patients. We found a low level of these cytokines in patients before radiotherapy, but there was a significant enhancement after they received RT treatment (Fig. 1). In agreement with this, the RT treatment in experiment group also markedly upregulated the serum level of ET, CRP and TNF-α, IL-1β, IL-6 (Fig. 2).

3.3. Bacillus licheniformis preparation dampened inflammatory response induced by RT in children with CNST

As we demonstrated above, the ZCS can relieve the gastrointestinal toxicity of the CNST patients. Moreover, it was clinically reported to balance the gastrointestinal flora, as well as acute and chronic enteritis, diarrhea and intestinal endotoxemia treatment. So we then assessed whether ZCS was available for decreasing the inflammation of CNST patients received RT. Expectedly, compared to the control group which did not receive ZCS, the enhancement of ET, CRP as well as TNF-α, IL-1β, IL-6 levels as a result of radiotherapy was substantially blocked by ZCS treatment (Fig. 3). Taken together, our data indicate that CNS made a key contribution to relieve the side-effects such as gastrointestinal disorders and inflammatory response caused by radiation therapy. And we attributes the CNS of relieving gastrointestinal toxicity partly to its anti-inflammatory reaction.

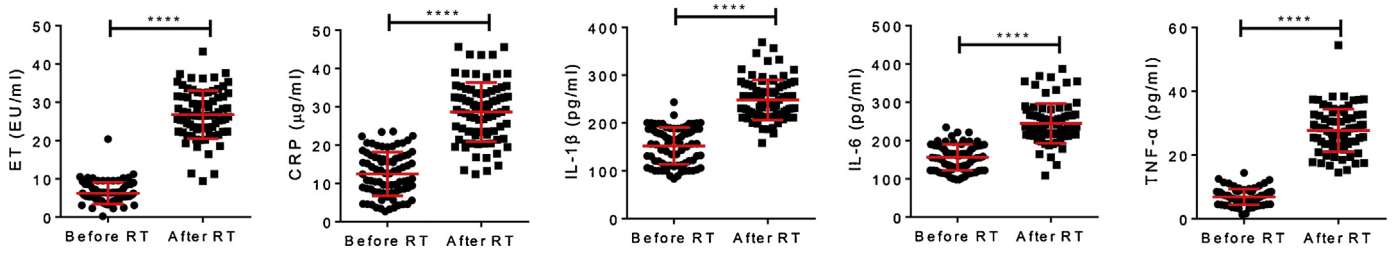

Fig. 1. ET, CRP and other cytokine levels of patients in control group before or after RT. ELISA analysis of ET, CRP, IL-1β, IL-6 and TNF-α compared with those of before radiation therapy. Data represents as mean ± SD, n = 80. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

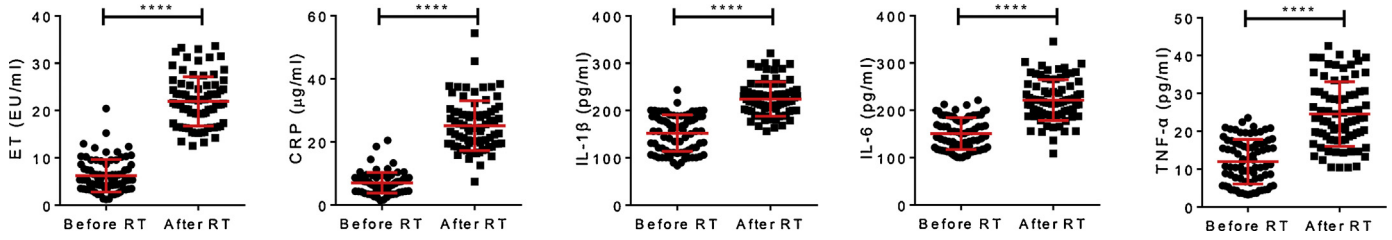

Fig. 2. ET, CRP and other cytokine levels of patients in experiment group before or after RT. ELISA analysis of ET, CRP, IL-1β, IL-6 and TNF-α compared with those of before radiation therapy. Data represents as mean ± SD, n = 80. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

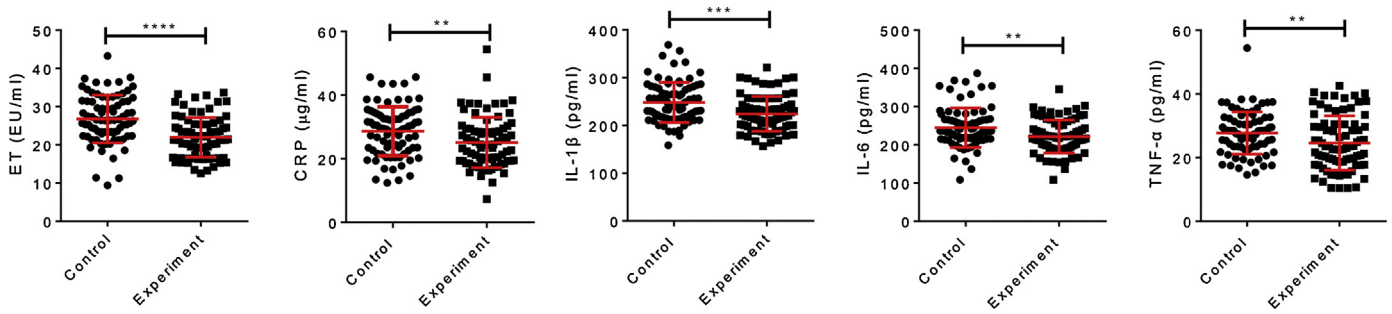

Fig. 3. ET, CRP and other cytokine levels of patients with RT in experiment and control group. ELISA analysis of ET, CRP, IL-1β, IL-6 and TNF-α in patients with Bacillus licheniformis preparation treatment compared with control group. Data represents as mean ± SD, n = 80. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

3.4. Tumor response and survival

After a mean follow-up of 2.8 years (0.2-4.9 years), one hundred and eight patients (67.5%) with CNST showed an objective tumor response to radiation therapy (Table 1). For all patients, the 3-year PFS (progression-free survival) and OS (overall survival) rates were 71.4% (±3.7%) and 80.0% (±3.6%); the 5-year PFS and OS rates were 50.7% (±6.1%) and 66.6% (±6.1%), respectively. Meanwhile, for experiment group patients, the 5-year PFS and OS rates were 55.0% (± 9.5%) and 63.5% (±10.1%), respectively. For control group patients, the 5-year PFS and OS rates were 48.3% (±7.9%) and 68.3% (± 7.8%), respectively (Fig. 4). However, the difference of OS and PFS between experimental and control group was not significant ($P = 0.659$, and 0.677). During the follow-up period, 24 patients relapsed in experimental group, and 31 relapsed in control experiment ($\chi^2 = 1.358$, $P = 0.159$) (Table 1).

4. Discussion

CNST are the most frequent solid tumors, causing higher prevalence of mortality in oncological children patients [17]. Almost all patients should undergo postoperative CSI and adjuvant chemotherapy [18]. However, patients receiving radiotherapy exhibit remarkable gastrointestinal symptoms due to imbalance in intestinal flora. Radiation would impair the intestinal barrier function and activate various cellular signaling pathways which resulted in expression of various cytokines like TNF-α, IL-1β, IL-2, IL-6, and IL-8 *in vivo* [16]. In this study, more than 70% of CNST children suffered from gastrointestinal symptoms. Moreover, different degree of inflammatory reaction occurred in almost all of the patients, and serum levels of ET, TNF-α, IL-1β, IL-6 and CRP significantly increased in our cohort. Although some patients did not manifested clinical symptoms, which indicated that inflammation induced by radiotherapy is much more frequent in such kind of patients.

Many clinical trials have implicated that probiotic therapy is beneficial against radiation-induced diarrhea or mucositis. It's reported that the use of probiotics could effectively control intestinal inflammation and prevent RT-induced gastrointestinal toxicity in cancer patients [12,19,20]. Additionally, Fuccio L and Guido A urgently proposed that it was time now using probiotics supplementation to prevent the gastrointestinal radiation-induced side effects [21]. But there are still few data about the effect of probiotics on gastrointestinal disorders and inflammation caused by CSI in CNST children.

Since *Bacillus licheniformis preparation* has been proved to be safe and beneficial [22], we prophylactically used ZCS probiotics to prevent the gastrointestinal symptoms and inflammatory reaction.

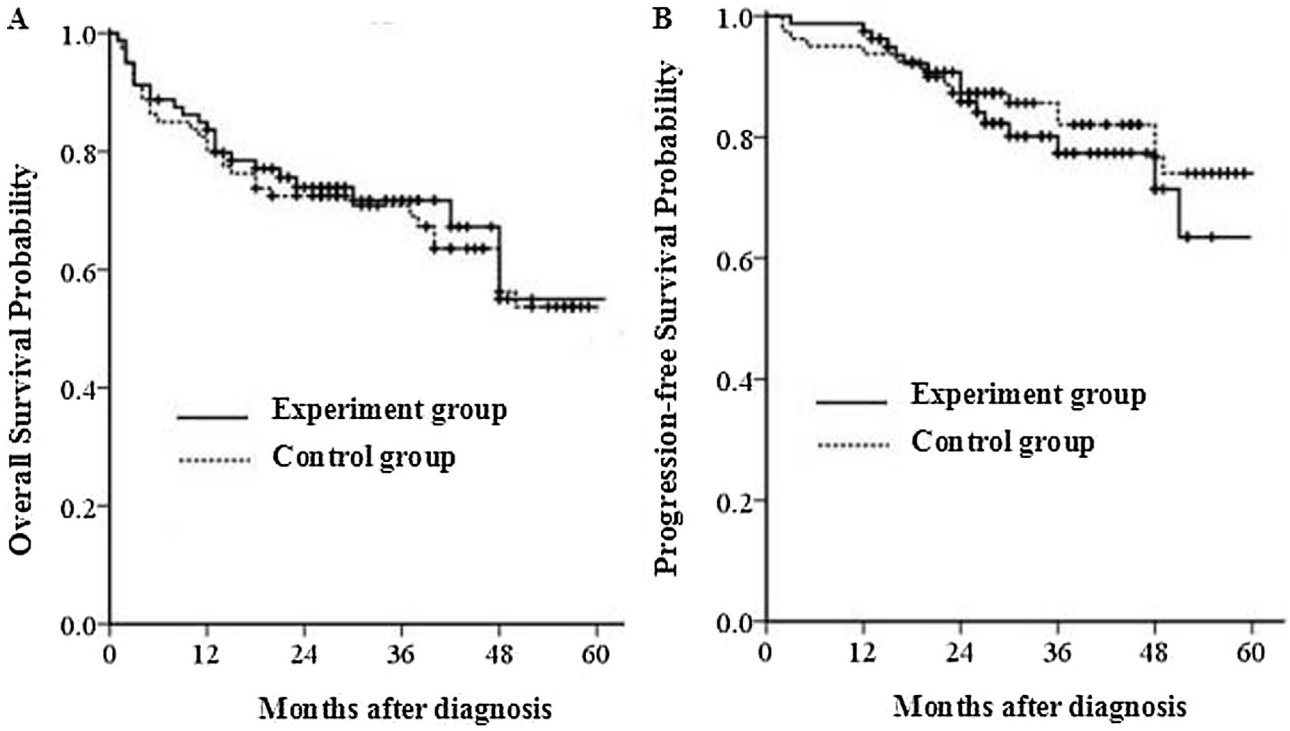

Fig. 4. Overall (A) and Progression-free (B) survival probability in patients with central nervous system tumor treated by radiation therapy.

We found that the experiment children which accepted the ZCS treatment significantly reduced serum levels of ET, CRP and TNF-α, IL-1β, IL-6 and relieved the gastrointestinal toxicity. ZCS could play the protective role through the following mechanisms(1) Antagonism (2) oxygen-capturing effect (3) Barrier effect (4) Immune function(5) Nutrition [13,23,24]. In our study, ZCS might inhibit the secretion of those pro-inflammatory cytokines and ultimately mitigate the gastrointestinal clinical symptoms.

Though probiotics can prophylactically extenuate the gastrointestinal toxicity and inflammatory cytokines production induced by radiation therapy, thereby improve the life quality of CNST patients during radiotherapy, we did not find that Probiotics (or *Bacillus licheniformis*) could markedly prolong the survival rate of CNST children and prevent the recurrence of tumor in this study. These might not exclude that follow-up time were too short, or probiotics' intake was less, and further observations were needed. On the other hand, gastrointestinal function well accompanys by increased immune system, so in the long term probiotics may contributes to tumor regression or inhibition and improve of survival rate.

Although bacteremia was not observed in clinical studies during radiation therapy, caution must be applied in cases of neutropenia and immunosuppression [10,25–27]. There are case reports of *Bifidobacterium longum* bacteremia in the literature [28]. Redman MG and colleagues demonstrated that 5 of 1530 cancer participants showed probiotic-related bacteraemia, fungaemia or positive blood cultures, but further evidence needs to be collected to determine whether probiotics provide a significant benefit for people with cancer [10]. ZCS as a viable *Bacillus licheniformis* probiotics, there is a potential risk of infection *in vivo* in patients with immunosuppression. In our study, myelosuppression was not found in all CSI patients and no one was infected with *Bacillus licheniformis* probiotics. For those children who receiving myelosuppressive chemotherapeutic regimens consecutively, the immune suppression should be monitor more closely with probiotic usage.

5. Conclusions

In summary, probiotics, as beneficial live microorganisms, may play a pivotal protective role in the pathogenesis of gastrointestinal symptoms induced by RT in pediatric patients with CNST. *Bacillus licheniformis* probiotics can regulate intestinal barrier function, innate immunity and intestinal repairmen. Prophylactically administrating ZCS during irradiation therapy for CNST patients can relieve RT-related symptoms and improve the life quality of cancer patients partly due to reducing the inflammatory reaction and gastrointestinal toxicity.

Conflict of interest

The authors declare no conflicts of interest.

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