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Original research article

The protective effects of *Bacillus licheniformis* preparation on gastrointestinal disorders and inflammation induced by radiotherapy in pediatric 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 evident adverse reaction [13]. Recently, there are still few data

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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%