REGULAR ARTICLE

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A double blind RCT to examine the safety and efficacy of *Lactobacillus rhamnosus* GG in pediatric febrile neutropenia

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Key Points

- The probiotic was safe but showed poor gut colonization, indicating that higher doses or alternative strains may be needed.
- Probiotic supplementation led to a small, nonsignificant reduction in FN incidence.

Studies have shown that dysbiosis precedes febrile neutropenia (FN). This study evaluated whether oral supplementation with *Lactobacillus rhamnosus* GG could reduce FN incidence in children receiving myelosuppressive chemotherapy during the period of expected neutropenia. Children aged 2 to 18 years were stratified by diagnosis (leukemia or solid tumor) and randomly assigned to probiotic or placebo before their first chemotherapy cycle. The intervention continued for 30 days and 14 days respectively in children with leukemia and solid tumors. Patients were monitored for FN until the next chemotherapy cycle and for adverse events for 1 week after intervention. Stool samples from 7 randomly selected patients underwent 16S rRNA sequencing. Eighty patients were randomized (36 probiotic and 44 placebo). FN occurred in 18 (50%) probiotic and 23 (52%) placebo patients (risk ratio, 0.95 [confidence interval, 0.62-1.47]; P = .83). No significant differences were observed in time to FN or antibiotic duration. No *Lactobacillus* bacteremia was detected. Stool sequencing revealed suboptimal probiotic colonization at the dose used. Probiotic supplementation led to a small, nonsignificant reduction in the FN incidence but was safe and feasible. Lack of colonization suggests a need to optimize the dose or select a different probiotic for future studies.

Introduction

Febrile neutropenia (FN) is a common complication of cancer treatment, with an incidence of 35% to 48% in acute myeloid leukemia (AML) cases at diagnosis and 13% to 30% during acute lymphoblastic leukemia (ALL) induction chemotherapy.[1]

Evidence suggests dysbiosis precedes the onset of development of FN. The microbiome metabolizes complex carbohydrates to produce short chain fatty acids, which maintain epithelial tight junctions and upregulate PPARγ (peroxisome proliferators–activated receptor γ). PPARγ activity maintains an anerobic environment at the epithelial surface suppressing the over growth of facultative anaerobes.[2] Chemotherapy gut dysbiosis eliminates the epithelial hypoxia causing an alteration in the gut microbial community from obligate to facultative anaerobes.[2-5] Studies show that intestinal domination of *Enterococci* and *Streptococci* result in an increased risk of FN.[6]

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The data sets generated during and/or analyzed during the current study are available from the corresponding author, Aditya Kumar Gupta (adivick@gmail.com), on reasonable request.

The full-text version of this article contains a data supplement.

In 2016, Ladas et al showed that supplementation of probiotics in children undergoing hematopoietic stem cell transplant is both safe and feasible.[7]

Lactobacillus rhamnosus GG (LGG) was first isolated in the 1980s by Gorbach and Goldin.[8] The complete genome sequence of LGG was determined by 2009 by Morita et al using the Sanger method.[9] LGG has been studied extensively in conditions such as health care associated diarrhea, functional abdominal pain, irritable bowel syndrome, and inflammatory bowel disease.[10,11] Human studies in cancer patients using LGG are limited. One study in 2007 testing LGG supplementation for chemotherapy related diarrhea in colorectal cancer showed excellent compliance and a reduction in radiotherapy induced grade 3 and 4 diarrhea, whereas another trial in 2023 showed less promising results.[12,13]

The rationale for selection of LGG in our study included resistance to cotrimoxazole (used as routine pneumocystis pneumonia prophylaxis in our unit) and data from our unit which showed reduced *Lactobacilli* levels in the stool of patients with neutropenic enterocolitis (NEC).[14]

Methods

Study design and participants

This single-center randomized, double blind, placebo control trial was conducted at a tertiary care center in New Delhi, India. Children eligible for randomization were those aged between 2 and 18 years of age who were to be started on chemotherapy, with >20% expected incidence of FN or classified as highly myelosuppressive.[15-17]

Patients who had received any chemotherapy prior to randomization were excluded, as were patients having gastrointestinal tract pathologies at presentation (eg, intestinal obstruction or malabsorption). Patients documented to have taken probiotics in the 6 months prior to randomization were also excluded.

Ethical approval for the study was obtained from the institute ethics committee, and the trial has been registered on Clinical Trials Registry of India (approval number REF/2022/01/051080).

Intervention

Children eligible for enrollment in our center included children with acute lymphoblastic leukemia (receiving intermediate or high-risk induction), AML, soft tissue sarcomas, retinoblastoma (receiving neoadjuvant chemotherapy), neuroblastoma (high-risk chemotherapy), Ewing sarcoma and osteosarcoma. Informed consent was obtained from parents/legally appointed representatives of all children who were enrolled. Children were randomized using variable block randomization and stratified based on whether they were being treated for leukemia or a solid tumor.

Sachets of LGG mouth melt granules were provided each containing 1×10^9 colony forming units (CFU). The dose was based on the study by Ladas et al[7] (10^8 CFU/kg) and the number of sachets was determined according to weight bands. Placebo preparations were identical in appearance, taste, and smell.

The intervention was started on day 1 of the chemotherapy protocol. In children with leukemia, the intervention was continued for 30 days or till the patient was ready for the next protocol, whichever was earlier. In children with solid tumors, the intervention was continued for 14 days or till the absolute neutrophil count was >500/μL, whichever was earlier. Standard of care was continued as per unit protocols (prophylactic cotrimoxazole for all patients and voriconazole for AML, no antibacterial prophylaxis, betadine gargles, general hygiene, and asepsis measures) in both groups. Granulocyte colony stimulating factor was administered as per unit protocol for patients with solid tumors at 5 μg/kg starting 24 hours after chemotherapy till count recovery (Figure 1).

Patients receive chemotherapy on outpatient basis in our center for solid tumors as well as leukemia, provided they are judged to be clinically stable and in the absence of any other oncological indications (eg, tumor lysis). The patients were followed up physically during all outpatient and day-care visits, as well as telephonically twice a week for compliance and any adverse events.

Fever episodes were assessed by 2 clinicians to exclude any possible noninfectious causes, and after the episode was determined to be FN, the intervention was withheld, blood cultures taken (aerobic cultures on brain heart infusion and anerobic in Robertson cooked meat broth) and broad spectrum IV antibiotics initiated as per the unit policy. In case of children with a gastrointestinal focus, the intervention was stopped permanently but in others it was restarted after ensuring that the blood culture did not grow *Lactobacillus.*

For quality control of the intervention, at the start, midway and end of the study, a sample of probiotic as well as the placebo sachets were cultured to ensure viable *Lactobacillus* growth in 1 group and absence of growth of other commensals or pathogens in both groups. Children were followed up for adverse events till a week after stopping the intervention.

The patients, primary investigator, and all those involved in patient assessment, patient care, data collection, and analysis were blinded throughout the study.

Stool 16-S RNA sequencing was planned to check if the probiotic supplementation translated into gut colonization, and to check for alpha diversity of the samples. Stool samples were collected sequentially from patients who had good compliance, (ie, having consumed >80% of the prescribed sachets), who completed the intervention. The number of patients who underwent stool sequencing was limited due to funding to only 7 patients. Stool samples were collected within 24 hours of completion of the intervention and were transported using dry ice to the laboratory. The sequencing was done using the Illumia MiSeq platform (Roche Diagnostic Corporation, Indianapolis, IN). The amplicons of 16 S V3-V4 were generated from the DNA using nested PCR (KAPA Hyperplus kit, Roche Diagnostic Corporation) to prepare a library. The libraries were normalized, pooled and sequenced, using a V3 500 cycle kit to generate 0.1 million reads per sample with 250 base-pair read length. Data analysis was performed via the Qiime2 Pipeline (Open source, version 2020.8.0). Taxonomic assignment of the 16S rRNA segments were done using Naïve Bayes taxonomic classifiers which were trained using the primer set for the V3-V4 hypervariable regions, using the silva-138-99seqs.qza database.

Outcomes

The primary outcome of this study was the proportion of patients developing FN in both arms, during the study period (that is from

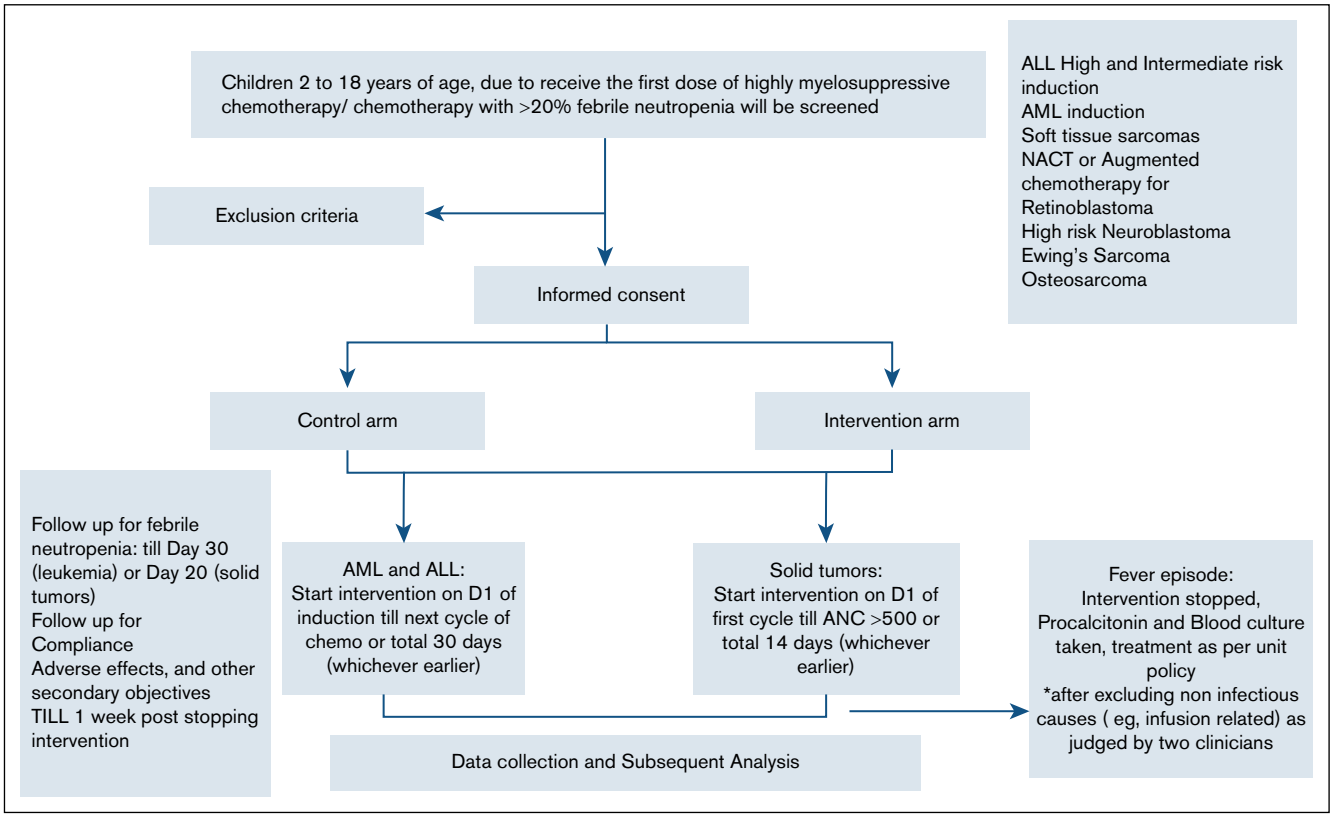

Figure 1. Study flow. ANC, absolute neutrophil count; NACT, neo adjuvant chemotherapy.

start of chemotherapy to day 30 in children with leukemias and day 21 in children with solid tumors).

Secondary outcomes included the proportion of patients developing radiologically confirmed NEC (defined as ultrasound or computed tomography evidence of bowel wall thickening of >3 mm, a dilated cecum or other colonic segment, an inflammatory mass, pericolonic inflammation, or pneumatosis intestinalis) on a background of fever, abdominal pain, and neutropenia,[18-20] as well as the proportion of adverse effects, duration of antibiotics, and time to development of FN in both arms. All grade 3 and 4 adverse effects were reviewed by a data safety and monitoring board.

Statistical analysis

A randomized controlled trial by Wada et al[21] showed an absolute reduction of 24% in proportion of patients developing FN (68% in placebo and 44% in probiotics), previous data from our center showed a 47% weighted incidence of FN in children with leukemia and solid tumors receiving myelosuppressive chemotherapy, and with a proposed a 20% absolute reduction in the proportion of patients developing FN the sample size was 212 patients; and with a 24% proposed absolute reduction the sample size was 124 patients. We enrolled 80 patients from March 2022 to September 2023.

Statistical analysis was performed using Stata BE 18 from StataCorp LLC (Texas, 2023). Data were checked for normality using the Shapiro Wilk test. Pearson χ^2 test was used to evaluate differences between independent groups for categorized variables provided all the events per variable in the expected table were >5, else Fisher exact test was applied. For continuous variables that are normally distributed, the unpaired *t* test was applied and if the data were nonparametric then Mann Whitney *U* test was used. Cox proportional hazards were calculated for time to development of the first episode of FN.

Results

Of the 138 patients screened, 80 patients were found to be suitable for inclusion, they were randomized in a 1:1 ratio using variable block randomization, 36 were randomized to the intervention arm and 44 to the control arm. The patient disposition is presented in the Figure 2.

Baseline characteristics

Age, sex, diagnosis, nutritional status, and socioeconomic classes were balanced between both the arms (Table 1). Nutritional status for children aged <5 years was assessed using World Health Organization charts for weight and for height, which defines severe malnutrition as less than −3 standard deviations (SD) of weight for height, moderate malnutrition between −2 and −3 SD, normal between −2 and +2 SD, overweight between +2 and +3 SD, and obese as greater than +3 SD. Socioeconomic classes were

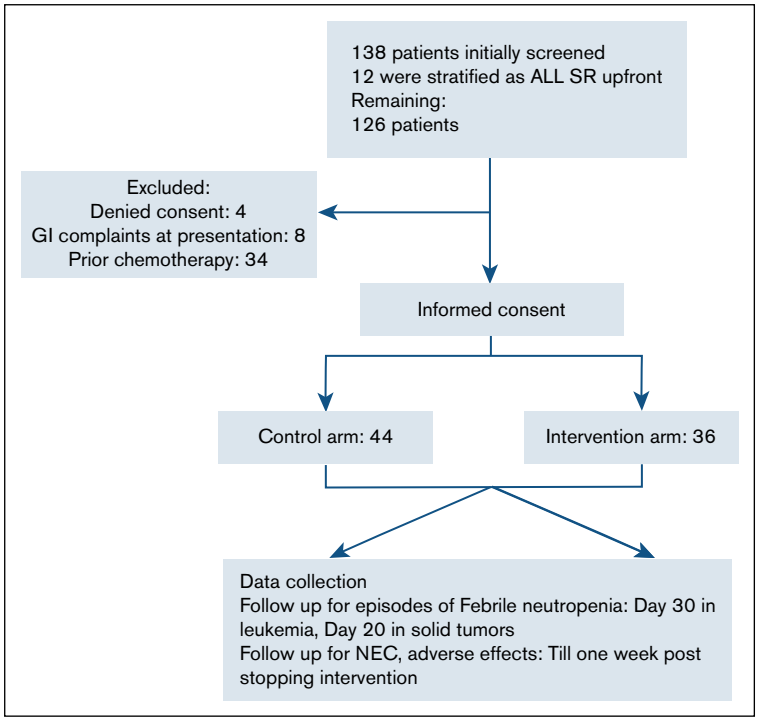

Figure 2. Patient disposition. NEC, neutropenic enterocolitis; SR, standard risk.

assigned as per modified Kuppuswamy socioeconomic scale, for the year 2023.[22]

Primary outcomes

Incidence of FN in the intervention arm was 50% with 18 patients developing FN in the period of observation. The incidence was slightly more in the control arm that is 52.3%, but the difference was not significant. The incidence of FN per 100 patient days in our study period was 2.1 in the control arm compared to 1.9 in the intervention arm (Table 2). Good compliance, as defined earlier, was achieved in 88.7% of all study patients; 31 (86.1%) in the intervention arm and 40 (90.9%) in the control arm. Details of focus of FN episodes are given supplemental Table 1.

Secondary outcomes

Radiologically proven NEC developed in 3 patients in the intervention arm and 2 in the control arm, the difference was not statistically significant. No patients in the intervention arm developed *Lactobacillus* culture-positive sepsis. Patients who developed FN with a gastrointestinal tract focus with no alternative organism isolated were 3 in the intervention arm and 5 in the control arm (Table 2). Of the 18 patients who developed FN in the intervention arm, the median duration of antibiotics was 10.5 days (interquartile range [IQR], 7-16), and of the 23 patients who developed FN in the control arm, the median duration of antibiotics was 7 days (IQR, 6-10). The difference was not statistically significant (Table 2). The focus of fever in both groups have been outlined in supplemental Table 1.

The time to first FN episode was compared in both groups using Cox proportional hazard and we found a hazard ratio of 1 and no significant difference (Figure 3).

Post hoc analysis

There were 2 deaths during the intervention period in the intervention arm and 3 in the control arm, and hemodynamic instability requiring either fluid bolus or inotropic support was seen in 2 patients in the intervention arm and 4 in the control arm. Respiratory support (either low flow oxygen, high flow oxygen, noninvasive mechanical ventilation, or ventilation) was required in 3 patients in the intervention arm and 4 patients in the control arm. None of these were statistically significant (Table 2).

Stool composition

Of the 7 samples sent for sequencing, 5 were intervention samples and 2 were control samples. The expected majority of gut microbiota is *Bacteroidetes* and *Firmicutes*,[23] but in our patients, both patients in the placebo arm showed dominance by *Desulfobacterota* (45% in patient 1 and 70% in patient 2). Of the patients in probiotic arm, dominant phyla were *Desulfobacteria* in 3 patients and *Firmicutes* in 2 patients. Only 1 patient (patient 6) showed the probiotic species in the stool sequencing, and it made up a small proportion of overall bacterial composition. Shannon index for alpha diversity, that is, diversity within a given sample was plotted for placebo and probiotic samples. Median (IQR) Shannon index for the placebo arm was 9.1 (8.9-9.3) and median (IQR) Shannon index for the probiotic arm was 9.3 (IQR, 6.1-9.4; supplemental Figures 1-4).

Discussion

This study explores the role of supplementation of LGG in the prevention of FN in children receiving myelosuppressive chemotherapy. A previous study by Wada et al[21] in 42 patients, using

Table 1. Baseline characteristics of the study patients

Characteristic	Intervention arm (36)	Control arm (44)
Age, mo: median (IQR)	66 (48-96)	60 (39-102)
Sex, n (%)		
Male	21 (58.3%)	31 (70.4%)
Female	15 (41.6%)	13 (29.6%)
Group, n (%)		
Leukemia	19 (52.7%)	24 (54.5%)
Solid tumor	17 (47.2%)	20 (45.4%)
Nutrition, n (%)		
Normal	27 (75.0%)	30 (68.1%)
Moderate malnutrition	8 (22.2%)	8 (18.2%)
Severe malnutrition	1 (2.7%)	4 (9.0%)
Overweight	0	2 (4.5%)
Leukemia (n)		
ALL	15	20
AML	4	4
Solid tumors (n)		
Retinoblastoma	8	14
Neuroblastoma	2	3
Ewing's/osteosarcoma	3	1
Soft tissue sarcoma	4	2
Socioeconomic class, n (%)		
Upper	2 (5.5%)	0
Upper middle	1 (2.7%)	3 (6.8%)
Lower middle	7 (19.4%)	10 (22.7%)
Upper lower	8 (22.2%)	14 (31.8%)
Lower	17 (47.2%)	17 (38.6%)
Prior antibiotic use	4 (0.1%)	2 (0.04%)
Days of neutropenia: median (IQR)	20.5 (15.2-28.5)	18 (12-31)

Table 2. Comparison of outcomes between the 2 groups

	Intervention arm (36)	Control arm (44)	*P* value
Number of patients with FN n (%)	18 (50.0%)	23 (52.3%)	Risk ratio with CI 0.95 (0.62-1.47) $P = .8$
Incidence of FN per 100 patient days	1.9	2.1	
Patients with radiologically defined NEC n (%)	3 (8.3%)	2 (4.5%)	$P = .32$
Patients with Lactobacillus culture positive sepsis n (%)	0	0	
Patients with GI focus FN with no other identified organism on culture n (%)	3 (8.3%)	5 (11.3%)	$P = .7$
Patients with possible bloodstream infection (no alternative focus and no other organism identified on culture) n (%)	5 (13.9%)	7 (15.9%)	$P = 1.0$
Gastrointestinal adverse effects CTCAE grade 3-5 n (%)	8 (22.2)	9 (20.4)	$P = .8$
Median duration of antibiotics (d) median (IQR)	10.5 (7-16)	7 (6-10)	$P = .07$
Patients with mortality during intervention n (%)	2 (5.5%)	3 (6.8%)	$P = 1.00$
Patients with hemodynamic instability n (%)	2 (5.6%)	4 (7.5%)	$P = .68$
Patients requiring respiratory support, n (%)	3 (8.3%)	4 (9.09%)	$P = 1.00$

CI, confidence interval; CTCAE, common terminology criteria for adverse events; GI, gastrointestinal.

Bifidobacterium breve showed promising results with significant reduction of FN episodes, days of fever, and duration of antibiotic therapy.

Our study is based on evidence suggesting that dysbiosis contributes to pathophysiology of FN.[4,24,25] "Intestinal dominance" which is the presence of any taxon of bacteria in a frequency of >30% of the overall composition of the gut microbiome, may cause FN, both because of direct translocation of the dominant bacteria as well as by causing changes in the gut microenvironment, leading to translocation of other pathogenic nondominant bacteria.[4,25] Data from our center by Sahoo et al found a significant decrease in the *Lactobacillus* population in stool samples of patients with NEC, and this decrease also predicted delayed recovery (in the form of prolonged duration of parenteral alimentation).[14]

Although there are studies to suggest a role of probiotics in chemotherapy and radiotherapy associated diarrhea and mucositis, fewer studies have investigated their efficacy in reducing FN.[26-28] Our study aimed to fill this gap in knowledge.

Studies by Mego et al have demonstrated safety of *Enterococcus faecium* in adults receiving intensive chemotherapy and colonization of stools at a dose of 18×10^9 CFU.[29,30] Ladas et al[7] demonstrated safety and 75% stool colonization when administering *L plantarum* at a dose of 1×10^8 CFU/kg in pediatric patients undergoing myeloablative hematopoietic stem cell transplant.

We used the same dose as Ladas et al[7] in our patients. We found that the incidence of FN and the number of episodes of FN during the study period was marginally better in the intervention arm but not significant. Our study also showed no episodes of bacteremia by the probiotic organism, and no increase in adverse effects, there was a longer median antibiotic duration among those who developed FN in the probiotic arm, however this was not statistically significant. These findings re-enforce the observation that probiotics can be safely administered in this population.[31]

Seven patients underwent stool 16S rRNA sequencing to determine the effect of LGG supplementation on the microbiome. We noted that out of the 5 patients in the intervention arm, only 1 patient had *Lactobacillus* detected in their stool sample. However, 16S rRNA sequencing carried out on stool samples from such a small subset and only a single time point may not truly be reflective of colonization, or lack thereof.

This is the second randomized control trial, and the first double blinded trial evaluating the role of probiotics in the prevention of FN, to our knowledge. Strengths of this study include stratification to include a spectrum of both solid tumors and leukemias, and ensuring good compliance of the intervention.

Some factors which could have influenced the results are regional variations in gut microbiome, prevalence of malnutrition as well as influence of diet. Extrapolating findings from another study from

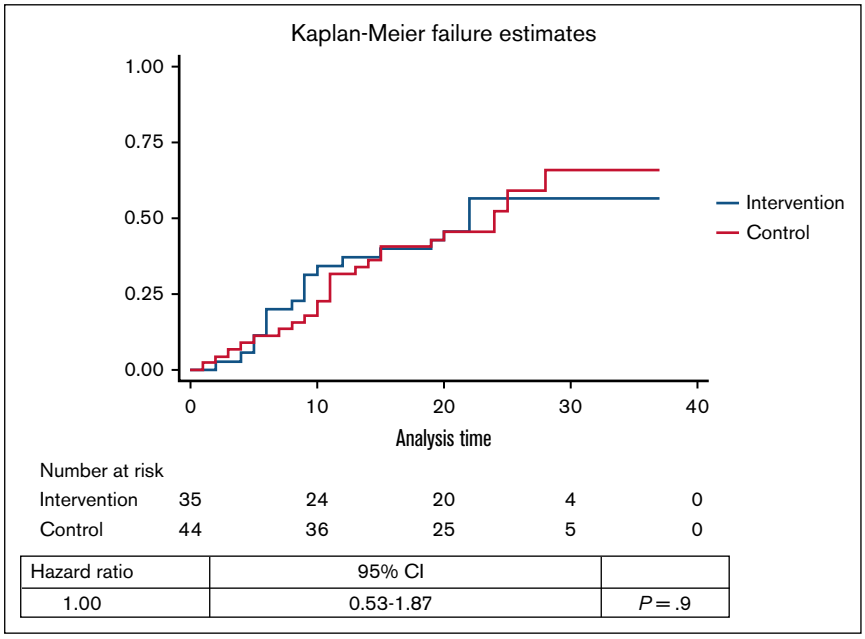

Figure 3. Time to first FN episode.

our center we believe that the consumption of *Lactobacillus*-rich food products such as curd, which is a staple in Indian diet, may have had a positive impact in prevention of FN and NEC in the placebo arm, thereby reducing the perceived benefit in the intervention arm (31 patients). Another key limitation of the study was the failure to attain the intended sample size.

We conclude that supplementation of probiotic LGG at the dose of 10^8 CFU/kg during the period of expected neutropenia did not lead to significant improvement in the incidence of FN in children aged 2 to 18 years receiving myelosuppressive chemotherapy when compared to placebo, however the administration of this probiotic at this dose appears to be both safe and feasible. Further studies are needed to determine optimal dose and choice of probiotic as well as the ideal method to monitor colonization.

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Tablets (India) Limited had no role in the design of the study, data collection, or analysis.

Authorship

Contribution: K.S., A.K.G., and R.C. contributed to the study conception and design; K.S. and S.B. carried out material preparation, data collection, and analysis; A.K.G., J.P.M., R.S., and R.M. were involved in patient care and supervision; V.D.B. assisted in quality control of materials; K.S. wrote the first draft of the manuscript with input from D.M. and P.P.; and all authors read, reviewed, edited, and approved the final manuscript.

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