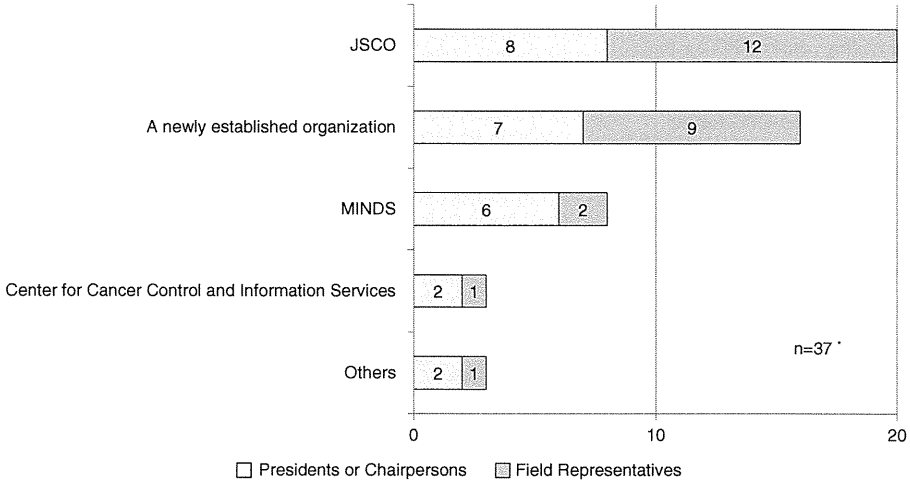


Fig. 3 Appropriate third-party organization for distribution of public research funds. Q13: "Which would be an appropriate third-party organization (multiple answers allowed)?" *37 respondents who replied "Distribute appropriately to each academic society by a third-party organization" in Q12. *JSCO* Japan Society of Clinical Oncology, *MINDS* Medical Information Network Distribution Service

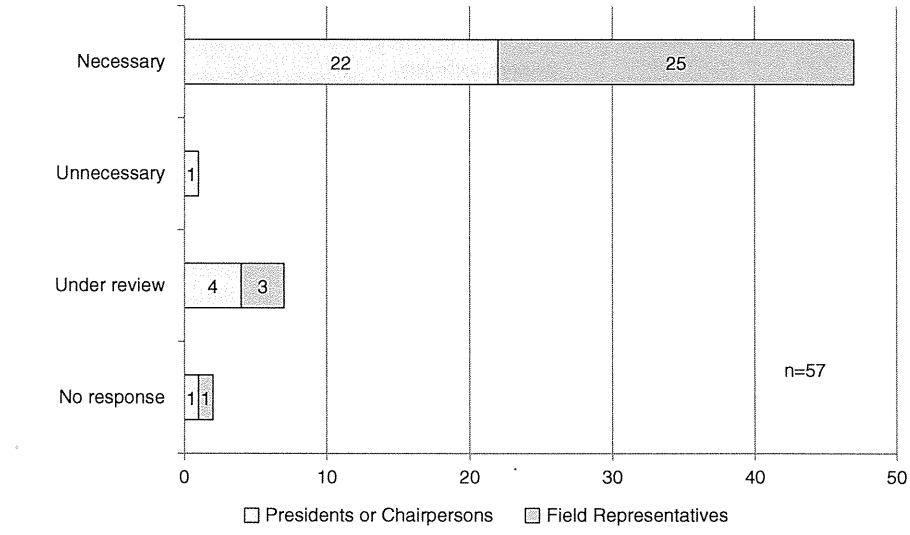


Fig. 4 Demand for a comprehensive publication site of cancer CPG. Q16: "Do you think that a comprehensive publication site of cancer CPG such as NCCN is necessary?" *CPG* Clinical Practice Guidelines, *NCCN* National Comprehensive Cancer Network

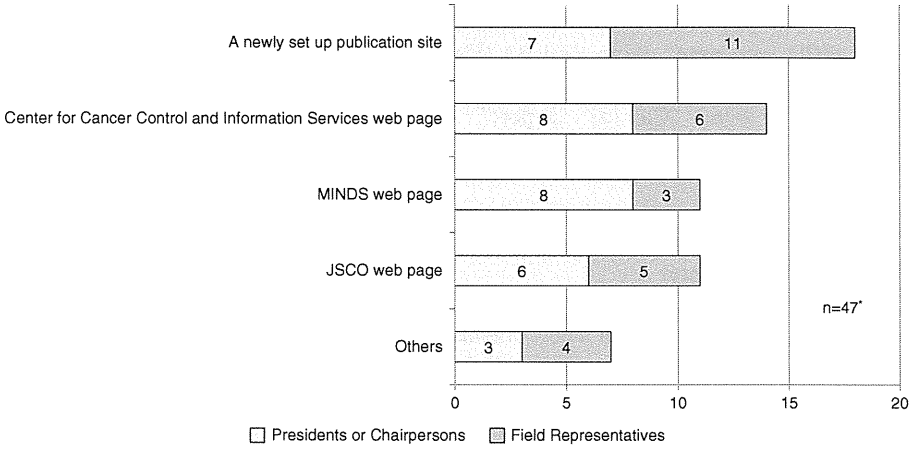


Fig. 5 Appropriate web site to exhibit cancer CPG comprehensively. Q17: "Where should a comprehensive publication site of cancer CPG be set up (multiple answers allowed)?" *47 respondents who replied that it was "necessary" for a comprehensive guidelines publication site in Q16. *JSCO* Japan Society of Clinical Oncology, *MINDS* Medical Information Network Distribution Service

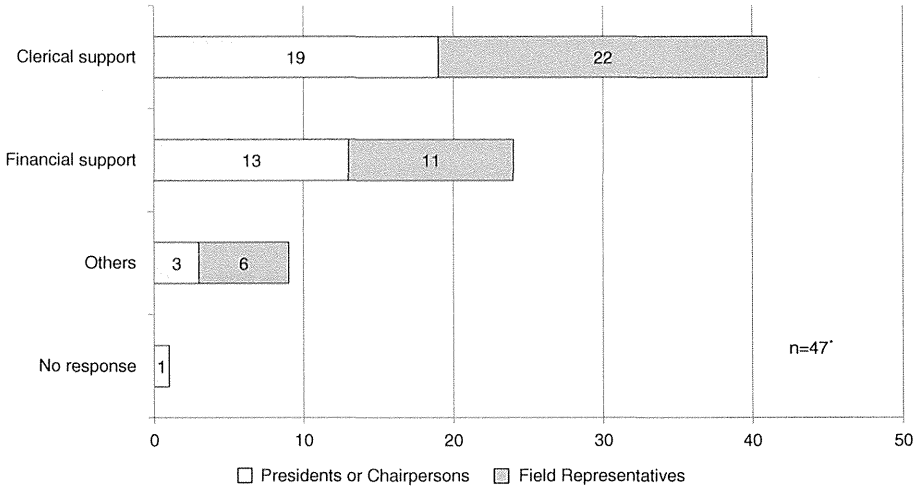


Fig. 6 Requirements for providing cancer CPG for the comprehensive publication site. Q18: "What do you require to provide cancer CPG for the comprehensive publication site (multiple answers allowed)?" *47 respondents who replied that it was "necessary" for a comprehensive publication site in Q16

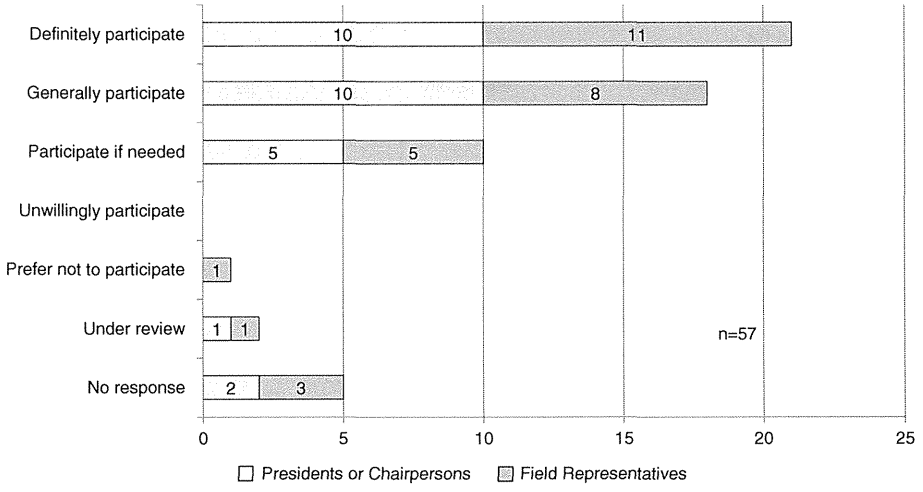


Fig. 7 Participation in a newly established organization for collaboration among academic parties. Q20: "If an organization were to be newly established in order to facilitate collaboration among academic parties dealing in cancer CPG, would your academic society participate in it?"

were as follows: "A newly set-up publication site" (38.3 %); "Center for Cancer Control and Information Services web page" (29.8 %); and "MINDS web page" and "JSCO web page" (both 23.4 %) (Fig. 5). Requirements for providing guidelines to the comprehensive publication site were "Clerical support" (87.2 %) and "Financial support" (51.1 %) (Fig. 6).

Participation in an organization for collaboration among academic parties

We have thought all along that a new organization needs to be established in order to facilitate collaboration among parties involved in cancer CPG. With regard to participation in a newly established organization, the responses were as follows: "Definitely participate" (36.8 %); "Generally participate" (31.6 %); "Participate if needed" (17.5 %); "Unwillingly participate" (0 %); and "Prefer not to participate" (1.8 %) (Fig. 7).

Dissociation of responses between "Presidents or Chairpersons" and "Field Representatives"

A large dissociation was not observed between the responses from "Presidents or Chairpersons" and "Field Representatives". However, there were slight differences in responses to questions 13 and 17. For question 13, the number of responses for "JSCO", "a newly established organization" and "MINDS" was almost the same from "Presidents or Chairpersons", while "JSCO" had the largest number of responses from the "Field Representatives" (Fig. 3). For question 17, the number of responses for "A newly set-up publication site", "Center for Cancer Control and Information Services web page" and "MINDS web page" were almost the same from "Presidents or

Chairpersons", while "A newly set-up publication site" had the largest number of responses from the "Field Representatives" (Fig. 5).

Discussion

Academic societies develop guidelines in their special fields with high-level academic policy. They have voluntarily engaged in the development of the guidelines as a social contribution, recognizing this as one of their missions. However, financial support from public research funds is thought to be required in order to maintain the development and publication of cancer CPG because a disparity in the financial foundation apparently exists among academic societies. Regarding the question of financial support, 80.7 % of respondents indicated "Have partial financial support from public research funds". The reason for seeking "partial support" rather than "full support" may be to maintain autonomy. Most Japanese CPG are purely based on scientific evidence and so they differ from the guidelines of the National Institute for Health and Care Excellence (NICE) in the UK. NICE guidelines are developed based on cost–effectiveness in addition to evidence and consequently reflect national policies [2].

As for the desirable flow of public research funds, many respondents replied that those funds should be distributed to each academic society through a third-party organization. Concerning a third-party organization, more than half of the respondents answered that JSCO would be appropriate. JSCO is a multidisciplinary academic society of oncology and its membership concurrently belongs to many specialized societies for various cancers. In 2006–2007, JSCO participated in a research program funded by the Health and Labour Sciences Research Grant as the secretariat for developing and publishing guidelines for seven sites of cancers. Subsequently, JSCO has collaborated with various academic societies, and the JSCO Cancer Guidelines Evaluation Committee has evaluated guidelines submitted from these societies [3]. Through this experience, JSCO has become familiar with the inner workings of each academic society and possesses comprehensive coordination skills. These JSCO characteristics may be the reason respondents suggested JSCO as a suitable third-party organization to distribute public research funds. Another reason may be that JSCO, unlike MINDS and the Center for Cancer Control and Information Services, is a purely academic organization and independent of national policies.

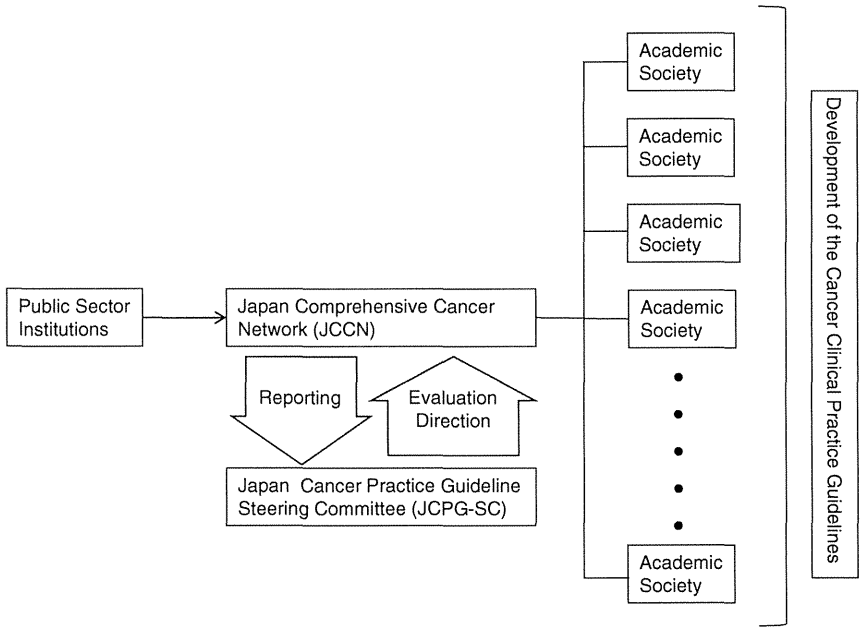
As for the publication of cancer CPG, over 80 % of respondents selected "Necessary" for a comprehensive site like NCCN, where CPG for various cancers are consolidated. Concentrating all cancer CPG at one site can accomplish the following: (1) improvement of the convenience of access for cancer CPG; (2) standardization of the guideline formats; and (3) regular updating of cancer CPG. As for the setting up of the comprehensive site, the highest number of respondents answered "A newly set-up publication site"; however, there were no answers which reached 50 %. Limited to the "Presidents and Chairpersons", the numbers of responses for "A newly set-up publication site", "Center for Cancer Control and Information Services web page" and "MINDS web page" were almost the same. At this time, opinions are obviously divided.

If the comprehensive publication site is established, most of the academic societies will need clerical and financial support as a requirement for providing guidelines. Consequently, the organization responsible for the management of the comprehensive publication site has to meet these requirements. We have to arrange where the comprehensive site should be set up to take account of the description above.

Concerning answers for participation in an organization to facilitate collaboration among parties involved in cancer CPG, 86.0 % of respondents replied "Definitely participate" or "Generally participate" or "Participate if needed". This result may reflect the fact that academic societies: (1) currently face difficulty in grasping the entire structure of a project that aims to develop and publish the guidelines; and (2) need regulations for providing guidelines and the flow of funds. Based on our findings in this study, we propose that the public research funds be collected initially in one organization and distributed to each academic society appropriately, and then that the societies provide their guidelines for a comprehensive publication site. Additionally, the establishment of a new external organization is desired in order to facilitate collaboration among the various parties. We suggest the flow of public funds and process for providing guidelines shown in Figs. 8 and 9. In this paper, we call the organization responsible for collecting both public research funds and guidelines the "Japan Comprehensive Cancer Network (JCCN)" and the external organization responsible for facilitating collaboration among the various parties the "Japan Cancer Clinical Practice Guideline Steering Committee (JCPG-SC)". An overview of the details follows:

Appropriate collection and distribution of public research funds (Fig. 8)

To distribute financial support in the right amount and at the right time, it is necessary to grasp the progress status of development, updating, and publication of guidelines for



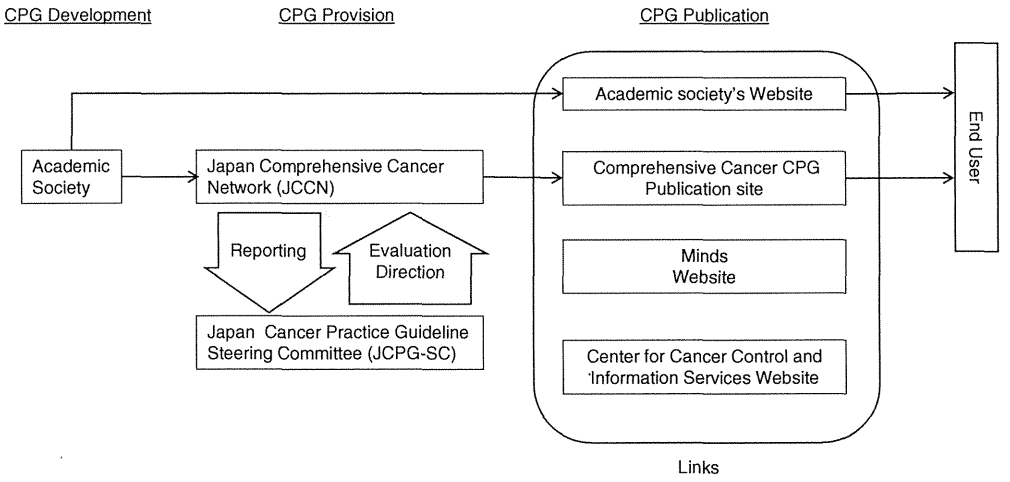


Fig. 8 Flow of public research funds for developing cancer clinical practice guidelines

Fig. 9 Flow of cancer clinical practice guidelines from academic society to end users

each type of cancer while understanding the inner workings of each individual academic society. Public research funds have been distributed for guidelines for each type of cancer directly from the public sector but this may not be ideally efficient because public sector institutions need to keep track of the progress status in the development of each guideline every fiscal year. Moreover, academic societies have to handle the administrative process themselves. We believe that the ideal structure would be to collect public research funds at JCCN and subsequently distribute them to each academic society, considering the current state of guideline development. This structure will allow each academic society to receive the right amount of funds at the right time.

Concentration of guidelines and consolidation of the publication site (Fig. 9)

Many guidelines for various types of cancers are posted on the JSCO and MINDS websites. However, theses web sites cannot be called comprehensive sites because neither JSCO or MINDS website has all-cancer CPG. Furthermore, the irregular updating of cancer CPG may cause confusion for the end users. Therefore, the most effective action is to amalgamate the latest version of all-cancer CPG and consolidate the publication site into JCCN. This will allow the establishment of a convenient and highly reliable comprehensive publication site for cancer CPG.

Obligations of the Japan Comprehensive Cancer Network (JCCN)

Obligations of the JCCN are as follows: (1) to keep track of the inner workings of each academic society, including clerical ability and financial foundation; (2) to grasp the progress status of guideline development and publication; and (3) to distribute the right amount of financial support to each academic society. JCCN will also be expected to manage the comprehensive publication site for cancer CPG. From the perspective that the guidelines be developed based on evidence, JCCN should ideally be a purely academic organization independent of the public sector. In future, we need to hold discussions focused on whether to establish JCCN as a completely new organization or entrust these tasks to a pre-existing academic organization.

Establishment of an external organization to evaluate and direct JCCN (Figs. 8, 9)

Collection of research funds and concentration of cancer CPG at JCCN will improve the efficiency of administrative management. Subsequently, objective evaluation and direction will be needed in terms of the following: (1) fairness in fund distribution and management; and (2) convenience and reliability of the publication site. Consequently, it is necessary to establish a new external organization, JCPG-SC, which has these roles. We propose that JCPG-SC be composed of representatives from academic societies, the Center for Cancer Control and Information Services, JSCO and MINDS, as well as experts dealing with the development of cancer CPG. JCCN has the obligation to report their undertaking to JCPG-SC, while at the same time JCPG-SC has the responsibility to evaluate and direct the management of JCCN.

Conclusion

A new organizational structure is proposed in this paper in order to facilitate the continuous development and publication of cancer CPG. We believe this structure enables the distribution of appropriate financial support and makes possible the establishment of a highly convenient comprehensive publication site.

Acknowledgments This project was made possible by the following Health and Labour Sciences Research Grants: (i) "Study on Database Construction of Cancer Information and Medical Facilities Database to provide useful Information for Patients, Families and the Public" (Principal Researcher: Fumihiko Wakao, 2007–2009), (ii) "Study on improving the quality of Cancer Information and Medical Facilities Database to provide useful Information for the Public" (Principal Researcher: Fumihiko Wakao, 2010–2012) and (iii) "Research on Effectiveness of Cancer Clinical Practical Guidelines from the Perspective of the Cancer Registry: Changes in Clinical Practice Trends and Treatment Outcome" (Principal Researcher: Koichi Hirata, 2012–2013). We are grateful to all the respondents who belong to academic societies developing cancer CPG. The 23 societies which cooperated with the questionnaire survey were the following: Japanese Gastric Cancer Association, The Japan Society of Hepatology, Japanese Study Group on GIST, Japan Society for Oral Tumors, The Japanese Orthopaedic Association, Japan Society of Obstetrics and Gynecology, Japan Society of Gynecologic Oncology, Japanese Society of Pediatric Oncology, The Japanese Society of Pediatric Hematology, The Japan Esophageal Society, Japan Pancreas Society, The Japanese Urological Association, The Japanese Society of Hematology, Japanese Society for Cancer of the Colon and Rectum, Japanese Society of Hepato-Biliary-Pancreatic Surgery, Japan Society for Head and Neck Cancer, The Japanese Breast Cancer Society, Japan Neurosurgical Society, The Japan Lung Cancer Society, Japanese Dermatological Association, Japanese Society for Palliative Medicine, Japanese Society for Radiation Oncology and Japanese Society of Hospital Pharmacists.

Conflict of interest Masahiko Nishiyama received a research grant from Yakult Honsha Co., Ltd. (Tokyo, Japan). The other authors declare that they have no conflict of interest.

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Case Reports in Oncology

Case Rep Oncol 2014;7:692–699

DOI: 10.1159/000368714
Published online: October 22, 2014

1662–6575/14/0073–0692$39.50/0
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Efficacy of Enteral Supplementation Enriched with Glutamine, Fiber, and Oligosaccharide on Mucosal Injury following Hematopoietic Stem Cell Transplantation

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Key Words

Glutamine · Fiber · Oligosaccharide · GFO · Mucosal injury · Hematopoietic stem cell transplantation

Abstract

The combination of glutamine, fiber and oligosaccharides (GFO) is thought to be beneficial for alleviating gastrointestinal mucosal damage caused by chemotherapy. A commercial enteral supplementation product (GFO) enriched with these 3 components is available in Japan. We performed a retrospective study to test whether oral GFO decreased the severity of mucosal injury following hematopoietic stem cell transplantation (HSCT). Of 44 HSCT patients, 22 received GFO and 22 did not. Severity of diarrhea/mucositis, overall survival, weight loss, febrile illness/documented infection, intravenous hyperalimentation days/hospital days, engraftment, acute and chronic GVHD, and cumulative incidence of relapse were studied. Sex, age, performance status, diagnosis, disease status, and treatment variables were similar in both groups. There were fewer days of diarrhea grade 3–4 in patients receiving GFO than in those who did not (0.86 vs. 3.27 days); the same was true for days of

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mucositis grade 3–4 (3.86 vs. 6.00 days). Survival at day 100 was 100% in the GFO group, but only 77.3% for the patients not receiving GFO ($p = 0.0091$, log-rank test). Weight loss and the number of days of intravenous hyperalimentation were better in the GFO group ($p < 0.001$ and $p = 0.0014$, respectively). Although not significant, less gut bacterial translocation with *Enterococcus* species developed in the GFO group ($p = 0.0728$) than in the non-GFO group. Other outcomes were not affected. To the best of our knowledge, this is the first comparative clinical study of GFO supplementation to alleviate mucosal injury after allo-HSCT. We conclude that glutamine, fiber and oligosaccharide supplementation is an effective supportive therapy to decrease the severity of mucosal damage in HSCT.

Introduction

Gastrointestinal mucosal injury is one of the most serious complications resulting from the conditioning regimens required for allogeneic hematopoietic stem cell transplantation (HSCT). It causes significant morbidity and may affect prognosis, because disruption of the gastrointestinal mucosal barrier facilitates translocation of microorganisms and/or endotoxins into the blood stream and increases mortality [1]. In this context, appropriate mitigation of gastrointestinal mucositis might improve the survival rate after HSCT.

Earlier studies comparing nutritional support with and without glutamine supplementation for patients with mucositis after HSCT were conducted because many investigators considered glutamine to be essential in critical illnesses such as radiation-induced colitis, sepsis, trauma, and burns [2–4]. These and other studies suggest that glutamine may exert a protective effect on the gut mucosal barrier and increase short-term survival after HSCT [5–7]. Standard total parenteral nutrition (TPN) does not contain glutamine because of its instability during heat sterilization and prolonged storage [8]. Additionally, glutamine for TPN, such as L-alanyl-L-glutamine dipeptide, is not available in Japan.

Both dietary fiber and oligosaccharide are also promising candidates for dietary supplements protecting against gastrointestinal mucosal injury induced by HSCT conditioning regimens. Dietary fiber plays an important role in controlling diarrhea, improving the restoration of bowel function, and reducing infection, thereby improving the prognosis of critically ill patients [9]. Oligosaccharide is thought to have beneficial effects by suppressing pathogenic bacteria in the colon [10]. Thus, the combination of glutamine, fiber and oligosaccharides (GFO) could be expected to protect against gastrointestinal mucosal injury in HSCT patients. Dietary fiber can also be fermented into short-chain fatty acids by bowel microflorae, which can protect the intestinal barrier and prevent bacterial translocation [9].

Currently, a commercial enteral GFO supplementation product is available in Japan. Recent investigations have revealed that this GFO preparation prevented gut bacterial translocation to the mesenteric lymph nodes in a murine model of bacterial overgrowth [11], and Joo et al. [9] reported that GFO has suppressive effects on mucosal damage in a murine ulcerative colitis model [12].

This study tests the hypothesis that enteral supplementation with GFO ameliorates gut injury induced by HSCT conditioning regimens and improves patient short-term survival in a retrospective analysis.

Patients and Methods

Patients

Patients who underwent stem cell transplantation at Sapporo Medical University Hospital between January 2009 and April 2011 were analyzed retrospectively with institutional review board approval. Patients were eligible for transplantation if they had any hematological malignancies at high risk for relapse and if suitable related or unrelated bone marrow/peripheral blood donors had been available within a reasonable period relative to their disease condition. Patients who had end-stage cardiac dysfunction (left ventricular ejection fraction <35%), pulmonary dysfunction (SpO2 <90% in room air), or active serious infection at the time of transplantation were not eligible. All patients gave written informed consent.

Conditioning Regimens and Graft-versus-Host Disease Prophylaxis

Conditioning regimens were either conventional or reduced-intensity conditioning (RIC) regimens. Conventional conditioning included the combination of busulfan 16 mg/kg and cyclophosphamide (CY) 120 mg/kg or total body irradiation 12 Gy and CY 120 mg/kg. RIC involved the use of fludarabine as a substitute for or in association with the conventional regimen drugs. Graft-versus-host disease (GVHD) prophylaxis regimens included the combination of FK506 and short-term methotrexate (MTX) or cyclosporine and short-term MTX. The first-line treatment for acute GVHD was prednisolone 1–2 mg/kg for all patients.

GFO administration

GFO was purchased from Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan). One pack of GFO (15 g) has 36 kcal and contains 3 g of glutamine, 5 g of dietary fiber, 1.5 g of oligosaccharide, and 1.2 mg of sodium. Two packages of GFO dissolved in 200 ml of water were administered to patients orally 3 times per day beginning 7 days prior to the start of conditioning and continued until 28 days after transplantation. Administration was stopped if vomiting occurred. TPN, conditioning chemotherapy, medication and transfusions were administered through a central venous catheter. While the neutrophil count remained $<0.5 \times 10^9$/l, patients were nursed in reversed isolation.

Evaluation of Enteral Supplementation Enriched with GFO

Diarrhea and oral mucositis were assessed using Common Terminology Criteria for Adverese Events (CTCAE) version 4.0. Diarrhea was classified as grade I when the incidence was below 4 episodes per day relative to baseline, as grade II when the incidence was 4–6 episodes per day over baseline, as grade III when the incidence was >7 episodes per day over baseline, as grade IV when life-threatening consequences occurred, and as grade V when the patient died. Mucositis (oral) was classified as grade I when the patients was asymptomatic or only had mild symptoms (intervention not indicated), as grade II when moderate pain was experienced, not interfering with oral intake (modified diet indicated), as grade III when severe pain interfering with oral intake occurred, as grade IV when life-threatening consequences were found (urgent intervention indicated), and as grade V when the patient died. The mean and highest grades and durations were then calculated for analysis. The number of days and severity of diarrhea, mucositis, weight loss, fever (>38.5 °C), TPN, episodes of microbiologically-documented infections, and hospital days were collected.

Selection of Matched Controls and Matching Variables

A matched-pair control group (no GFO supplement) for patients who used GFO was obtained from our historical database from 2006 to 2008. The controls were individually matched to the cases at a 1:1 ratio. Matching was attempted for the following criteria applied in the order they are listed: age at transplantation (<55 vs. ≥55 years), ECOG performance status (0 or 1), disease status (standard vs. high risk; i.e. patients with acute leukemia, chronic myeloid leukemia, malignant lymphoma in complete remission, and myelodysplastic syndromes (refractory anemia) were categorized as standard risk, and all others as high risk), pretransplant conditioning (conventional vs. RIC), GVHD prophylaxis (FK- vs. cyclosporine-based), and graft source (bone marrow vs. peripheral blood). To avoid any potential selection bias, matching was blinded, and only the patients' ID and pretreatment variables were known.

Statistical Analysis

Data were entered into a computerized database and analyzed by either Fisher's exact test or a χ^2 test for categorical data and the Mann-Whitney U test for non-categorical data. The data analyzed between groups were as follows: (1) average diarrhea/mucositis score; (2) overall survival; (3) body weight loss; (4) febrile illness/documented infection; (5) intravenous hyperalimentation days/hospital days; (6) time to neutrophil engraftment; (7) incidences of acute and chronic GVHD, and (8) cumulative incidence of relapse.

The probabilities of overall survival were estimated and plotted using the Kaplan-Meier method. Data analysis was performed using GraphPad Prism version 5.0b (GraphPad Software Inc., San Diego, Calif., USA). The level of significance in all cases was set at $p < 0.05$.

Results

Patient Characteristics

Twenty-two patients who underwent stem cell transplantation and received GFO supplementation were analyzed. A matched-pair control group (no GFO supplementation) was obtained from our historical database. The characteristics of these two groups are summarized in table 1. There was no difference between them with regard to sex ($p = 0.75$), age ($p = 0.53$), ECOG performance status ($p = 0.62$), underlying diagnoses ($p = 0.55$), disease status ($p = 1.0$), conditioning regimen ($p = 0.93$), GVHD prophylaxis ($p = 0.66$), and graft source ($p = 1.0$).

Clinical Outcomes

Clinical outcomes are shown in table 2. There were no differences in the maximum diarrhea ($p = 0.68$) or mucositis ($p = 0.20$) grades. However, a statistically significant reduction in the number of days of diarrhea grade 3–4 ($p = 0.001$) or grade 2 ($p = 0.0001$) and days of mucositis grade 3–4 ($p = 0.033$) was apparent in the GFO-supplemented group. GFO administration also prevented weight loss ($p < 0.001$) and reduced the number of days of intravenous hyperalimentation ($p = 0.001$). There were no differences in the number of days with fever (>38.5 °C; $p = 0.41$) or microbiologically-documented infections ($p = 0.71$), all of which were bloodstream infections: 3 methicillin-resistant *Staphylococcus aureus* (MRSA) and 1 methicillin-resistant *Staphylococcus epidermidis* (MRSE) in the GFO group, and 2 *Enterococcus faecium*, 1 *Enterococcus faecalis*, 1 methicillin-resistant *S. aureus*, and 1 methicillin-resistant *S. epidermidis* in the group without GFO supplementation. GFO administration did not affect the number of hospital days ($p = 0.88$). Next, we analyzed the impact of GFO on clinical parameters of HSCT, especially the time to engraftment, incidence and severity of acute/chronicGVHD and relapse rate. We found no differences between the two groups in this respect (data not shown). However, an apparent benefit was observed in the GFO group regarding the survival rate 100 days after HSCT (100 vs. 77.3%, $p = 0.0091$, log-rank test) as shown in figure 1. There were 5 deaths during the first 100 days after HSCT in the group without GFO due to refractory disease in 2 cases, sepsis in 2 cases, and pneumonia in 1 case. Median survival time was 530 versus 416 days ($p = 0.6871$) in the GFO and non-GFO group, respectively.

Discussion

In the present study, we documented the beneficial effects of GFO in protecting against mucosal injury, decreasing weight loss and days of intravenous hyperalimentation, and

increasing short-term survival after HSCT (table 2; fig. 1). Conditioning chemotherapy and irradiation for HSCT evoke severe diarrhea and this adversely affected early therapy-related mortality. We observed that severe diarrhea was particularly improved in the GFO-supplemented group. Thus, it was considered that a reduction of therapy-related early mortality had been achieved. In fact, there were 2 patients who died from *Entercoccus* species infection due to bacterial translocation in the early phase after HSCT in the non-GFO group, although GFO supplementation neither suppressed the incidence of documented infection nor shortened the febrile period (table 2). However, gut bacterial translocation, such as that of *Enterococcus* species *(E. faecium* or *E. faecalis)*, tended not to develop in the GFO group ($p = 0.0728$ relative to the control group). This suggested that GFO supplementation reduces gut mucosal injury and sepsis caused by enterococci in HSCT patients. Oligosaccharides included in GFO are prebiotics which have beneficial effects on commensal bacteria. Furthermore, we used a lactobacillus preparation (Biofermin-R, Biofermin Pharmaceutical Co. Ltd., Japan) as a probiotic in all patients. Since we observed mucosal injury less frequent and of shorter duration, we conclude that GFO and probiotics have synergistic effects (i.e. they are so-called 'synbiotics') and were able to ameliorate mucosal injury caused by the conditioning regimen.

Contrasting observations regarding the efficacy of oral glutamine [13] for amelioration of chemotherapy-associated mucositis could be related to a different route and schedule of glutamine administration in those studies. Anderson et al. [1] reported the efficacy of low-dose oral glutamine on oral mucosal injury during autologous bone marrow transplantation [14]. The dose of glutamine used in our study is comparatively higher than the average dietary intake (2–5 g/day) and almost the same as used by Anderson et al. A 2-gram oral dose of glutamine can significantly raise (0.1 mM difference) blood glutamine levels for about 1 h [15]. Since GFO contains 3 g of glutamine per pack, effects seen with the dose used in our study may be related to absorbed glutamine. Patients on GFO received an average of 32.4 g (2.16 per pack) per day, containing 6.48 g of glutamine, 10.8 g of dietary fiber, and 3.24 g of oligosaccharide. In the present study, using a relatively high dose of glutamine, fiber, and oligosaccharide, no GFO-related toxicity was found. GFO supplementation was well tolerated by the patients, and no allergic reactions were documented.

Oral glutamine appears to reduce GVHD and i.v. glutamine may increase the risk of relapse, according to a meta-analysis of studies of glutamine supplementation [7]. In our study, GFO supplementation neither suppressed the incidence of acute or chronic GVHD nor increased the relapse rate. However, these findings are based on a small number of patients. For definitive conclusions, larger well-designed prospective trials are required.

To the best of our knowledge, this is the first retrospective comparative clinical study of mucosal injury in allogeneic stem cell transplantation using GFO. We conclude that GFO supplementation is an effective supportive therapy to decrease the severity of mucosal injury in HSCT, which is a cause of morbidity associated with this treatment. Comparison of GFO with glutamine alone is planned for the future.

Acknowledgements

We appreciate the assistance of the physicians, physician assistants, nurses and support staff on the transplantation units and nutritional support team.