International Journal of Clinical Oncology (2024) 29:1081–1087
https://doi.org/10.1007/s10147-024-02572-6

SPECIAL ARTICLE

Effectiveness and safety of primary prophylaxis with G-CSF for patients with Ewing sarcomas: a systematic review for the Clinical Practice Guidelines for the Use of G-CSF 2022 of the Japan Society of Clinical Oncology

Takeshi Hirose[1] · Mamoru Ito[2] · Kenji Tsuchihashi[2] · Yukinori Ozaki[3] · Hiroshi Nishio[4] · Eiki Ichihara[5] · Yuji Miura[6] · Shingo Yano[7] · Dai Maruyama[8] · Tetsuhiro Yoshinami[9] · Nobuyuki Susumu[10] · Munetaka Takekuma[11] · Takashi Motohashi[12] · Eishi Baba[13] · Nobuaki Ochi[14] · Toshio Kubo[15] · Keita Uchino[16] · Takahiro Kimura[17] · Yutaro Kamiyama[18] · Shinji Nakao[19] · Shinobu Tamura[20] · Hitomi Nishimoto[21] · Yasuhisa Kato[22] · Atsushi Sato[23] · Toshimi Takano[3] · Makoto Endo[1]

Received: 5 May 2024 / Accepted: 10 June 2024 / Published online: 21 June 2024

Abstract

Background Multidrug chemotherapy for Ewing sarcoma can lead to severe myelosuppression. We proposed two clinical questions (CQ): CQ #1, "Does primary prophylaxis with G-CSF benefit chemotherapy for Ewing sarcoma?" and CQ #2, "Does G-CSF-based intensified chemotherapy improve Ewing sarcoma treatment outcomes?".

Methods A comprehensive literature search was conducted in PubMed, Cochrane Library, and Ichushi web databases, including English and Japanese articles published from 1990 to 2019. Two reviewers assessed the extracted papers and analyzed overall survival (OS), febrile neutropenia (FN) incidence, infection-related mortality, quality of life (QOL), and pain.

Results Twenty-five English and five Japanese articles were identified for CQ #1. After screening, a cohort study of vincristine, ifosfamide, doxorubicin, and etoposide chemotherapy with 851 patients was selected. Incidence of FN was 60.8% with G-CSF and 65.8% without; statistical tests were not conducted. Data on OS, infection-related mortality, QOL, or pain was unavailable. Consequently, CQ #1 was redefined as a future research question. As for CQ #2, we found two English and five Japanese papers, of which one high-quality randomized controlled trial on G-CSF use in intensified chemotherapy was included. This trial showed trends toward lower mortality and a significant increase in event-free survival for 2-week interval regimen with the G-CSF primary prophylactic use compared with 3-week interval.

Conclusion This review indicated that G-CSF's efficacy as primary prophylaxis in Ewing sarcoma, except in children, is uncertain despite its common use. This review tentatively endorses intensified chemotherapy with G-CSF primary prophylaxis for Ewing sarcoma.

Keywords Granulocyte colony-stimulating factor · Ewing sarcoma · Chemotherapy · Adverse effects

Introduction

Ewing sarcoma is a malignant tumor that can occur in either the bone or soft tissue and is the third most common primary malignant bone tumor after osteosarcoma and chondrosarcoma [1]. The typical age of onset is teenage years, and about 60–80% of Ewing sarcoma cases occur in children, adolescents, and young adults under 20 years of age [2]. Ewing sarcoma is characterized by the proliferation of small round cells and specific fusion genes, including *EWSR1-FLI1* and *EWSR1-ERG* [3].

Localized Ewing sarcoma can be treated with a combination of chemotherapy and surgery. Radiation therapy can be used to achieve durable local control in unresectable Ewing tumors. Notably, some reports have shown local control differences between radiation and surgery [4, 5]; decisions regarding the optimal local control method should be based on patient characteristics and prognosis-related factors.

Currently, multi-agent regimens for Ewing sarcoma, primarily anthracyclines, alkylating agents, and topoisomerase

Extended author information available on the last page of the article

inhibitors, are common; those posing a high risk of myelosuppression are also prevalent. The typical regimen for curative treatment is vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide (VDC/IE) [6]. VDC/IE was administered repeatedly at 3-week intervals according to the original protocol. However, in recent years, an enhanced regimen, repeated at 2-week intervals, has been developed based on the premise of primary prophylactic administration of granulocyte colony-stimulating factor (G-CSF) [7].

The use of G-CSF as a supportive care medication aims to prevent chemotherapy-induced and febrile neutropenia (FN). When used appropriately, G-CSF can improve chemotherapy outcomes, leading to increased benefits such as a reduced incidence of complications such as FN and associated death, improved quality of life (QOL), and prolonged survival. However, G-CSF also has negative effects, such as pain, the burden of hospital visits, and drug costs. Therefore, its use should be considered carefully if its benefits remain unclear.

The American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) 2010 guidelines, and National Comprehensive Cancer Network (NCCN) guidelines, while not specific to Ewing sarcoma, recommend primary prophylaxis when FN incidence exceeds 20%. Yet, definitive evidence for this threshold remains unestablished. The guidelines do not detail the benefits of intensified chemotherapy for primary prophylaxis with G-CSF in adult Ewing sarcoma patients [8–12].

In Japan, the primary prophylactic administration of G-CSF is not covered by insurance, except for some cancers, and the therapeutic administration of G-CSF for FN is the mainstream treatment. A total of 42 members of The Working Group for the Revision of Guidelines for the Proper Use of G-CSF evaluated each question (Clinical Practice Guidelines for the Use of G-CSF, 2022, Japan Society of Clinical Oncology). Even for cancer types and regimens with scant evidence and undefined recommendations, we have prepared a reference to assist in evaluating the risk–benefit balance in each scenario.

This systematic review assessed the effectiveness and safety of primary prophylaxis with G-CSF, in addition to chemotherapy, in patients with Ewing sarcoma.

Patients and methods

Data searching and screening

A systematic review, adhering to the "Medical Information Network Distribution Service (Minds) Handbook for Clinical Practice Guideline Development 2014" [13] and "Minds Clinical Practice Guideline Development Guide 2017" [14, 15], was conducted utilizing PubMed, Ichushi web (Japan Medical Abstracts Society database), and the Cochran Library databases. The search, conducted in April 2020, utilized MeSH keywords including "Ewing sarcoma" and "G-CSF," covering publications dated from 1990/01/01 to 2019/12/31 in English and Japanese (Supplementary Tables S1, S2). Relevant literature from other databases was incorporated based on the judgment of a systematic review team. According to titles and abstracts, an initial screening was independently conducted by two systematic review team reviewers (TH and MI) to identify ineligible reports (Fig. 1a, b). The second screening entailed a detailed evaluation of chosen articles against inclusion and exclusion criteria, entailing full-text reading, recording exclusion reasons, and omitting duplicates. Disagreements were resolved by consensus among the co-authors. Articles that met the selection criteria were further scrutinized for quality reporting data as described below.

Selection criteria

The inclusion criteria encompassed randomized controlled trials (RCT,) non-RCTs, cohort, and case–control trials with adults diagnosed with Ewing sarcoma, requiring the treatment group to have undergone standard intensive induction therapy. Exclusion criteria consisted of guidelines, reviews, letters, abstract-only publications, laboratory studies, systematic reviews, meta-analyses, and grey literature.

Quality of evidence

Following the second screening, a systematic review team member independently reassessed the articles and extracted data using standardized data abstraction forms. The evidence from individual studies on critical outcomes within the clinical questions posed by the guideline creation was categorized based on study design and quality. Critical outcomes included duration of neutropenia or thrombocytopenia, infection-related mortality, disease progression/recurrence, overall survival (OS), and adverse events such as musculoskeletal pain. The authors determined the outcomes under the Population, Intervention, Comparator, and Outcome (PICO) frameworks for the benefits and harms of prophylactic G-CSF. Conflicts and questions were resolved by the team leader (M.E.). Evidence level was evaluated per outcome across studies by design, considering bias risk, inconsistency, imprecision, indirectness, and publication bias. Literature quality and evidence body were assessed via the GRADE approach and categorized into "strong," "medium," "weak," or "very weak" [16].

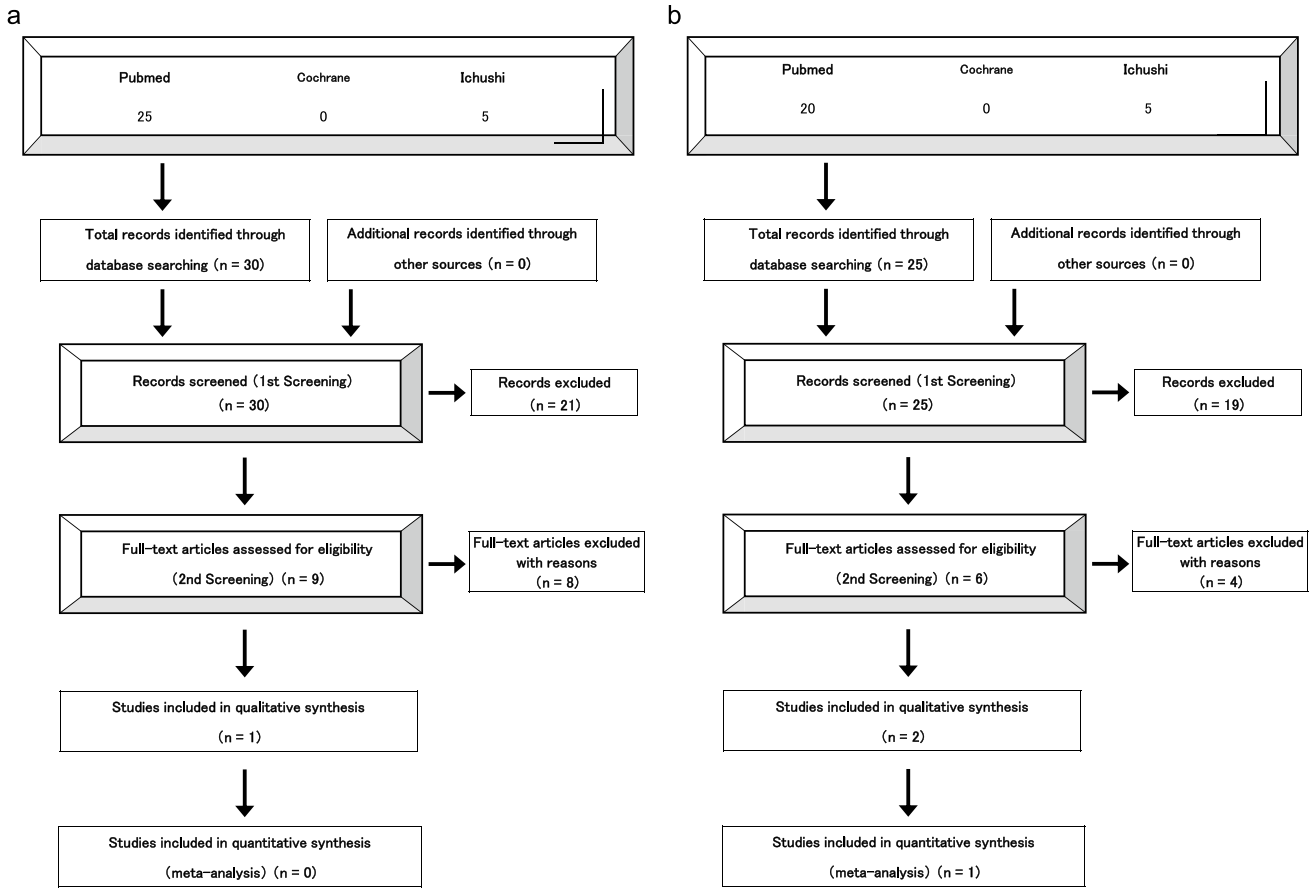

Fig. 1 Flow diagram of literature search. **a** Clinical question #1. **b** Clinical Question #2

PICO setting

Our study addressed these clinical questions (CQs): #1: "Does primary prophylaxis with G-CSF benefit chemotherapy for Ewing sarcoma?" #2: "Does G-CSF-based intensified chemotherapy improve Ewing sarcoma treatment outcomes?".

Regarding CQ #1, PICO consisted of the following: (P) patients, which included patients with Ewing sarcoma receiving chemotherapy; (I) intervention, which included the use of G-CSF as primary prophylaxis; (C) comparison, which did not use G-CSF as primary prophylaxis; (O) outcomes, which included (i) OS; (ii) incidence of FN; (iii) mortality rate from infection; (iv) QOL; and (v) pain. As for CQ #2, PICO was composed of (P) patients, which include patients with Ewing sarcoma receiving chemotherapy, (I) intervention, which includes the use of intensified chemotherapy based on the premise of G-CSF as primary prophylaxis, (C) comparison, which is conventional and not intensified chemotherapy, and (O) outcomes, which include (i) OS, (ii) incidence of FN, (iii) mortality rate for infection, (iv) QOL, and (v) pain.

Results

In CQ #1, 25 articles in English and five in Japanese were listed using PubMed and Ichushi, respectively. After initial screening, nine out of 30 papers were selected based on titles and abstracts. Following this, a full-text review for eligibility narrowed the selection to one cohort study for further analysis. The working group deliberated on converting CQ into future research questions (FQ) because of insufficient data obtained. In this guideline shows, FQ is defined as those for which the systematic review could not be completed due to lack of evidence or other reasons, and for which evidence-based recommendations could not be provided among the foreground questions based on important clinical issues. All questions were designated as CQs at the beginning of the revision work, but CQs and FQs were classified according to the status of subsequent systematic reviews.

A total of 851 patients who underwent VIDE chemotherapy were included (Table 1) [17]. Safety data from 4746 courses of VIDE in 851 patients were collected and compared in terms of the interval between VIDE courses, dose deviations, supportive therapy (G-CSF), incidence of

Table 1 Studies selected for each clinical question

CQ	Author	Study design	Number of patients	Interventions (Int)	Comparison (Com)	Overall survival	Incidence of febrile neutropenia	Mortality rate for infection	Quality of life	Pain
#1	Juergens	Cohort study	851	VIDE chemotherapy with total 4746 courses	The interval, dose variability, the occurrence of AR	842 alive/851	60.8% (with G-CSF) VS 65.8% (without G-CSF) (not statistically evaluated)	(Incidence of infection) 54.7% (with G-CSF) VS 61.0% (without G-CSF) (not statistically evaluated)	–	–
#2	Womer	Randomized controlled trial	568	284 patients with filgrastim (VDCIE) every 14 days	284 Patients with filgrastim (VDCIE) every 21 days	83% (Int) VS 77% (Com) ($p = 0.056$)	7.3% (Int) VS 6.2% (Com) (no important difference)	(Incidence of infection with neutropenia) 4.7% (Int) VS 4.6% (Com) (no important difference)	–	–
#2	Marina	Randomized controlled trial	53	25 patients with G-CSF (VDCIE) including high-dose cyclophosphamide	28 patients with G-CSF (VDCIE) including standard-dose cyclophosphamide	–	–	–	–	–

– not mentioned, *VIDE* Vincristine, Ifosfamide, Doxorubicin, and Etoposide, *AR* adverse reaction, *G-CSF* granulocyte colony-stimulating factor, *VDCIE* Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide, *Int* intervention, *Com* comparison

adverse reactions per course, sex, and age. The incidences of FN and infection were 60.8% and 54.7%, respectively, when G-CSF was administered. In contrast, when G-CSF was not administered, the incidence rates of FN and infection were 65.8% and 61.0%, respectively. No statistical analyses were performed. In the cohort of 851 patients, nine fatalities occurred, with five potentially linked to VIDE therapy (three from sepsis, two unspecified). The absence of data on OS, pain, and QOL precluded direct evaluation of CQ #1 outcomes from this review. Consequently, CQ #1 was reclassified as an FQ, restating it as "Primary prophylaxis with G-CSF's efficacy in Ewing sarcoma remains uncertain outside pediatric cases, though it is commonly administered during curative treatment."

CQ #2 was investigated using two databases, PubMed and Ichushi, which yielded 20 articles in English and five in Japanese. Following the initial screening based on title and abstract, six of the 25 papers were considered relevant and subjected to full-text evaluation. Only two studies met the eligibility criteria after the second screening, both of which were RCTs. However, one study compared a dose-intensification regimen that was not commonly used in clinical practice and was deemed inappropriate for inclusion in a systematic review [18]. Another study was a high-quality RCT that examined the use of G-CSF to increase treatment intensity and was considered the basis of the current standard of care for Ewing sarcoma [7]. Following a thorough literature review, the working group responsible for CQ #2 conducted a systematic review.

An RCT comparing every 3-week vs. every 2-week VDC/IE chemotherapy cycle enrolled 568 eligible patients. Filgrastim was used as primary prophylaxis in both groups. The study's primary endpoint was event-free survival (EFS), and the HR for EFS was 0.74 (95% CI 0.54–0.99, $p = 0.048$), indicating a statistically significant increase in EFS with every 2-week treatment. Regarding OS outcomes, the hazard ratio (HR) for biweekly versus triweekly cycles was 0.69 (95% CI 0.47–1.0, $p = 0.056$), indicating a trend toward reduced mortality risk, although the difference was statistically insignificant. OS was not the primary endpoint, and the study was not designed to test its superiority. The findings of this study have established biweekly chemotherapy cycles as the standard in clinical practice. However, the evidence strength is constrained, being derived from a single RCT, resulting in a "weak" rating for OS. Notably, FN incidence appeared elevated in biweekly-treated patients; 7.3% and 6.2% in biweekly and triweekly respectively. Although no statistical validation was provided in the literature, we calculated the odds ratio, which was 1.19 (95% CI 0.99–1.43, $p = 0.067$ [Fisher's exact test]). In assessing a single RCT, evidence strength for FN was rated as weak. Mortality included one infection-related death in the biweekly

group, with none in the triweekly group. A larger number of events would be needed for a more accurate assessment.

Since this was a single RCT, the strength of the evidence was judged to be very weak based on mortality due to infection. Regarding QOL and pain, studies on this topic were not identified, making it unassessable.

Although no evidence-based assessment of patient values and preferences has been made, there may be variations in the perception of desirable and undesirable effects such as pain. An evidence-based cost and resource evaluation was unfeasible; therefore, we estimated G-CSF costs and assessed if the benefits justified the expenditures and resources involved. Although only one RCT was included in the systematic review, the benefits outweighed the harms of intensified chemotherapy based on primary prophylaxis with G-CSF in treating Ewing sarcoma.

Finally, a draft recommendation, "Weakly recommend intensified chemotherapy based on primary prophylaxis with G-CSF in treating Ewing sarcoma," was presented to the recommendation decision meeting based on the systematic review report. After discussion and voting by a working group of 25 members (23 physicians, one nurse, and one pharmacist), a consensus was reached, with 24 of the 25 members agreeing to participate in the draft.

Discussion

Currently, multiple-drug regimens centered on anthracyclines, alkylating agents, and topoisomerase inhibitors are frequently used for the treatment of Ewing sarcoma, and treatments with a high risk of FN are widely administered. The typical regimen selected for curative treatment is VDC/IE, and the incidence of FN without primary G-CSF prophylaxis ranges from 49.0% to 72.5% [19, 20]. In clinical practice, G-CSF is widely administered as primary prophylaxis during VDC/IE therapy, considering the incidence of FN described above. Additionally, as explained above for CQ#2, the VDC/IE treatment interval was shortened from 3 to 2 weeks based on the assumption of primary prophylactic administration of G-CSF, which is the standard of care for localized Ewing sarcoma.

However, to date, ASCO guidelines, ESMO guidelines 2010, and NCCN guidelines have not explicitly addressed Ewing sarcoma, and primary prophylactic administration is recommended when the incidence of FN is 20% or higher [8–10]. Therefore, to our knowledge, this is the first systematic review to summarize the efficacy of G-CSF administration in Ewing sarcoma.

As a result, only one systematic review of the literature on the primary prophylactic administration of G-CSF is available. A cohort study of 851 VIDE-treated patients with Ewing sarcoma showed that FN and infection incidence rates with and without G-CSF were 60.8%, 54.7%, 65.8%, and 61.0%, respectively, with no significant differences.

Next, we examine the content of the extracted literature for CQ#2. While it comprised a single RCT, its high quality warranted a systematic review, thus defining CQ#2. The HRs for OS and EFS were 0.69 and 0.74, respectively, for every 2 weeks compared with every 3 weeks, showing a trend toward lower mortality for OS and a statistically significant increase in EFS.

Many guidelines worldwide recommend using G-CSF based on the assumption of a "20% of FN incidence rate" cutoff, which lacks scientific evidence. The working group for the revision of the guideline has been discussing the recommendation of using G-CSF and has decided to abandon the assumption of a "20% FN incidence rate" and to evaluate the evidence for each question scientifically. This was the first attempt to create guidelines based on scientific evidence. During the development process, there was a lack of evidence comparing individual cancer types and regimens with or without G-CSF, and there is room for improvement, including the setting of questions, in future revisions of the guidelines.

This systematic review had some limitations. First, only a few reports on these CQs are available. Second, more detailed information on QOL, musculoskeletal pain, and other symptoms must be provided. Sufficient evidence on QOL and bone pain in most cancer subtypes does not exist in the Clinical Practice Guidelines for the Use of G-CSF 2022. Therefore, this FQ needs to be addressed. Third, different regimens for Ewing sarcoma were used in clinical situations, even between CQ #1 and CQ #2.

In conclusion, this study examined primary prophylaxis with G-CSF in Ewing sarcoma. In our systematic review, we assessed patient outcomes with CQ #1 and CQ #2. The benefit of primary prophylactic G-CSF in Ewing sarcoma, apart from pediatric cases, remains uncertain, yet it is commonly used in curative therapies. "Intensified cancer drug therapy with G-CSF as primary prophylaxis in Ewing sarcoma receives a weak recommendation."

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-024-02572-6.

Acknowledgements We extend our gratitude to Natsuki Fukuda for her dedicated work at the Japan Society of Clinical Oncology's administrative office, to Masahiro Yoshida for his methodological advice in establishing this guideline, and to the literature search team members, Natsuki Narita and Yuko Mitsuoka, for their support. We also thank Editage (www.editage.jp) for English language editing.

Author contributions All the authors contributed to the conception and design of this study. T.H. and M.E. wrote the manuscript draft, and all the authors reviewed and commented on the manuscript.

Data availability Data associated with this systematic review can be accessed from the corresponding author upon reasonable request.

Declarations

Conflict of interests Kenji Tsuchihashi received honoraria from Ono Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, and Novartis Pharma. Yukinori Ozaki received honoraria from Daiichi-Sankyo, Pfizer, Chugai, Lilly, and Kyowa Kirin. Eiki Ichihara received honoraria from Eli Lilly and research funding from MSD, Ono Pharmaceutical, Jansen Pharma, and Takeda Pharmaceutical. Yuji Miura received honoraria from Ono Pharmaceutical, MSD, Takeda Pharmaceuticals, Eisai, Bristol Myers Squibb, and research funding from Ono Pharmaceutical and MSD. Shingo Yano received research funding from Otsuka Pharmaceutical. Dai Maruyama received honoraria from Ono Pharmaceutical, Janssen Pharma, Nippon Shinyaku, Eisai, Mundipharma, Kyowa Kirin, Chugai Pharmaceutical, Zenyaku, MSD, SymBio, Sanofi, AbbVie, Takeda Pharmaceutical, AstraZeneca, Bristol Myers Squibb, and Genmab, and research funding from Amgen, Astellas Biopharma, Novartis, Kyowa Kirin, Ono Pharmaceutical, Chugai Pharmaceutical, Janssen Pharma, Takeda Pharmaceutical, Otsuka Pharmaceutical, Sanofi, Astellas, Bristol Myers Squibb, AbbVie, Eisai, MSD, Taiho Pharmaceutical, AstraZeneca, Eli Lilly, and Genmab. Tetsuhiro Yoshinami received honoraria from Kyowa Kirin, Pfizer, Chugai Pharmaceutical, Eli Lilly, MSD, AstraZeneca, and Eizai. Takashi Motohashi received honoraria from AstraZeneca, Chugai Pharmaceutical, and Myriad Genetics. Eishi Baba received honoraria from Chugai Pharmaceutical and Daiichi-Sankyo, and research funding from Taiho Pharmaceutical and Chugai Pharmaceutical. Toshio Kubo received honoraria from Chugai Pharmaceutical. Takahiro Kimura received honoraria from Sanofi. Shinji Nakao received honoraria from Kyowa Kirin. Atsushi Sato received honoraria from Chugai Pharmaceutical, and Taiho Pharmaceutical, and research funding from Chugai Pharmaceutical, and Taiho Pharmaceutical. Toshimi Takano received honoraria from Daiichi-Sankyo, Chugai Pharmaceutical, and Eli Lilly. The other authors certify that no conflicts of interest exist in relation to this article.

References

1. Ogura K, Higashi T, Kawai A (2017) Statistics of bone sarcoma in Japan: report from the bone and soft tissue tumor registry in Japan. J Orthop Sci 22(1):133–143
2. Widhe B, Widhe T (2000) Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. J Bone Joint Surg Am 82(5):667–674
3. Sankar S, Lessnick SL (2011) Promiscuous partnerships in Ewing's sarcoma. Cancer Genet 204(7):351–365
4. Bacci G, Ferrari S, Longhi A et al (2004) Role of surgery in local treatment of Ewing's sarcoma of the extremities in patients undergoing adjuvant and neoadjuvant chemotherapy. Oncol Rep 11(1):111–120
5. Indelicato DJ, Keole SR, Shahlaee AH et al (2008) Long-term clinical and functional outcomes after treatment for localized Ewing's tumor of the lower extremity. Int J Radiat Oncol Biol Phys 70(2):501–509
6. Grier HE, Krailo MD, Tarbell NJ et al (2003) Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 348(8):694–701
7. Womer RB, West DC, Krailo MD et al (2012) Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol 30(33):4148–4154
8. Crawford J, Caserta C, Roila F et al (2010) Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 21(Suppl 5):v248-251
9. NCCN (2022) NCCN Clinical Practice Guidelines in Oncology Hematopoietic Growth Factors Version 1.2022
10. Smith TJ, Bohlke K, Lyman GH et al (2015) Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33(28):3199–3212
11. Crawford J, Caserta C, Roila F (2010) Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 21(Suppl 5):v248-251
12. (Guidelines®) NCPGN (2022) Hematopoietic Growth Factors Version 1.2022
13. Morizane T, Yoshida M, Kojimahara N (2014) Medical information network distribution service (Minds) handbook for clinical practice guideline development 2014 (in Japanese). Igaku Shoin, Tokyo
14. Minds Manual Developing Committee (2017) Minds manual for clinical practice guideline development 2017 (in Japanese). Japan Council for Quality Health Care, Tokyo
15. Kojimahara NNT, Morizane T (2017) Minds Manual for Guideline Development 2017. Japan Council for Quality Health Care
16. Guyatt GH, Oxman AD, Vist GE et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926
17. Juergens C, Weston C, Lewis I et al (2006) Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer 47(1):22–29
18. Marina NM, Pappo AS, Parham DM et al (1999) Chemotherapy dose-intensification for pediatric patients with Ewing's family of tumors and desmoplastic small round-cell tumors: a feasibility study at St. Jude Children's Research Hospital. J Clin Oncol 17(1):180–190
19. Chin M, Yokoyama R, Sumi M et al (2020) Multimodal treatment including standard chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide for the Ewing sarcoma family of tumors in Japan: results of the Japan Ewing Sarcoma Study 04. Pediatr Blood Cancer 67(5):e28194
20. Wexler LH, DeLaney TF, Tsokos M et al (1996) Ifosfamide and etoposide plus vincristine, doxorubicin, and cyclophosphamide for newly diagnosed Ewing's sarcoma family of tumors. Cancer 78(4):901–911

Authors and Affiliations

Takeshi Hirose[1] · Mamoru Ito[2] · Kenji Tsuchihashi[2] · Yukinori Ozaki[3] · Hiroshi Nishio[4] · Eiki Ichihara[5] · Yuji Miura[6] · Shingo Yano[7] · Dai Maruyama[8] · Tetsuhiro Yoshinami[9] · Nobuyuki Susumu[10] · Munetaka Takekuma[11] · Takashi Motohashi[12] · Eishi Baba[13] · Nobuaki Ochi[14] · Toshio Kubo[15] · Keita Uchino[16] · Takahiro Kimura[17] · Yutaro Kamiyama[18] · Shinji Nakao[19] · Shinobu Tamura[20] · Hitomi Nishimoto[21] · Yasuhisa Kato[22] · Atsushi Sato[23] · Toshimi Takano[3] · Makoto Endo[1]

✉ Makoto Endo
endo.m.a40@m.kyushu-u.ac.jp

1 Department of Orthopaedic Surgery, Kyushu University, 3-1-1 Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan

2 Department of Hematology, Oncology and Cardiovascular Medicine, Kyushu University, Fukuoka, Japan

3 Department of Breast Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

4 Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan

5 Center for Clinical Oncology, Okayama University Hospital, Okayama, Japan

6 Department of Medical Oncology, Toranomon Hospital, Tokyo, Japan

7 Division of Clinical Oncology/Hematology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

8 Department of Hematology Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

9 Department of Breast and Endocrine Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan

10 Department of Obstetrics and Gynecology, International University of Health and Welfare Narita Hospital, Chiba, Japan

11 Department of Gynecology, Shizuoka Cancer Center, Shizuoka, Japan

12 Department of Obstetrics and Gynecology, Tokyo Women's Medical University Hospital, Tokyo, Japan

13 Department of Oncology and Social Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

14 Department of General Internal Medicine 4, Kawasaki Medical School, Okayama, Japan

15 Department of Allergy and Respiratory Medicine, Okayama University Hospital, Okayama, Japan

16 Department of Medical Oncology, NTT Medical Center Tokyo, Tokyo, Japan

17 Department of Urology, The Jikei University School of Medicine, Tokyo, Japan

18 Department of Clinical Oncology/Hematology, The Jikei University School of Medicine, Tokyo, Japan

19 Department of Hematology, Faculty of Medicine, Institute of Medical Pharmaceutical and Health Sciences, Kanazawa University, Ishikawa, Japan

20 Department of Hematology/Oncology, Wakayama Medical University, Wakayama, Japan

21 Department of Nursing, Okayama University Hospital, Okayama, Japan

22 Department of Drug Information, Faculty of Pharmaceutical Sciences, Shonan University of Medical Sciences, Kanagawa, Japan

23 Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Aomori, Japan