

Comparison of health-related quality of life with different antitumor agents for advanced soft tissue sarcoma

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Research

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Abstract

Background During cancer treatment, maintenance and improvement of quality of life (QOL) are important, as is prolongation of overall survival. As the disease progresses, patients may experience a decline in QOL due to physical or mental changes. However, few studies have evaluated QOL longitudinally in advanced soft tissue sarcoma (STS) patients according to the antitumor agent. The purpose of this study was to compare health-related QOL (HRQOL) in patients with advanced STS receiving the combination regimen of doxorubicin and ifosfamide (AI) or three novel antitumor agents (pazopanib, trabectedin, eribulin).

Methods Twelve patients diagnosed with advanced STS who started chemotherapy between 2010 and 2017 at our hospital were enrolled. HRQOL was assessed using the European Organization on Research and Treatment of Cancer Quality-of-Life Core Questionnaire-30 (EORTC QLQ-C30) after three cycles of chemotherapy before assessing the effect of treatment. Global health status, a functional scale, and a symptomatic scale were compared for the AI regimen and the three novel antitumor agents.

Results The mean global health status score of the patients treated with the AI regimen was significantly different from that of those treated with one of the three novel antitumor agents (37.9 and 56.8, respectively). No significant differences were found in the five functional scores. The nausea and vomiting score was significantly different between the AI regimen and eribulin. The constipation score was significantly higher with the AI regimen, and the diarrhea score was significantly higher with pazopanib.

Conclusions Compared to the AI regimen, patients can continue treatment with one of the three innovative antitumor agents while maintaining QOL, even with progressive disease. In particular, of the three innovative antitumor agents compared to the AI regimen, patients treated with pazopanib were able to maintain social activities during treatment. In the second-line and subsequent treatments, we could not clearly show a different effect on maintenance of a better QOL among the three innovative drugs, so additional work in the future is needed. If we clarify which of the three drugs most affects QOL, recommendations can be made regarding treatment selection for the second-line and subsequent treatments.

Background

Soft tissue sarcomas (STSs) are rare malignant neoplasms that constitute fewer than 1.5% of all cancers, with an annual incidence of about 6 per 100,000 persons [1]. The largest study of the epidemiology of STSs in Japan, using data from the Bone and Soft Tissue Tumor Registry, a nationwide organ-specific cancer registry for bone and soft tissue tumors, showed that the number of STS patients has gradually increased [2]. Although wide resection is standard treatment for localized STS cases, the cumulative probability of local recurrence at 5 years is 12 to 25% [3–5]. Distant metastases at initial diagnosis are observed in 11.4% of cases [2], and the metastasis control rate at 5 years is 71% [4]. For

patients with advanced STS with development of local recurrence or distant metastasis, adjuvant chemotherapy is given. Adriamycin monotherapy [6] or the combination therapy of adriamycin and ifosfamide (AI) [7] is currently the standard option for first-line treatment of advanced STS. However, no standard therapy has been established for second-line and later treatment. Since 2012, three novel anticancer drugs, pazopanib, trabectedin, and eribulin, have been approved in Japan for second-line or later treatment of patients with advanced STS of any histologic subtype [8]. Pazopanib compared to placebo and trabectedin compared to dacarbazine significantly increase progression-free survival (PFS) of patients with advanced STS [9, 10]. However, neither pazopanib nor trabectedin show any improvement in overall survival (OS) [9, 10]. The clinical benefit of eribulin in advanced STS patients is a significant improvement in OS, but PFS was not improved in the eribulin arm compared with the dacarbazine arm [11]. With these three innovative antitumor agents, PFS or OS may be prolonged, but few studies have evaluated the quality of life (QOL) in patients with advanced STS who are receiving one of these three antitumor agents. For patients with advanced STS, suppressing disease progression with various treatments is important, but long-term studies are also critical to evaluate whether QOL is maintained.

Health-Related Quality of Life (HRQOL) is widely evaluated by patients themselves. In particular, the European Organization on Research and Treatment of Cancer Quality-of-Life Core Questionnaire-30 (EORTC QLQ-C30) is a well-known tool for assessment of HRQOL specifically for cancer patients [12]. The EORTC QLQ-C30 is also used for patients with localized STS of the extremities [13]. Furthermore, the HRQOL of patients administered any one of the three recent agents as second-line chemotherapy for advanced STS has been reported [14, 15]. However, in the same patients, no report has described the differences in HRQOL longitudinally from first-line to second-line and subsequent treatments. The primary objective of this report was to compare HRQOL longitudinally during first-line and second-line or subsequent treatment in patients with advanced STS. The secondary objective was to evaluate the difference in HRQOL according to second-line and subsequent therapeutic agents.

Patients And Methods

Patients

A total of 12 patients (eight males, four females) diagnosed with advanced STS who started chemotherapy between October 2010 and March 2017 at the Toyama University Hospital (Toyama, Japan) were enrolled in this study. The enrolled patients had distant metastasis at the initial visit or distant metastasis that developed during the clinical course. Combination therapy with AI (adriamycin 30 mg/m²/day ×2 days, ifosfamide 2 g/m²/day ×4-5 days) was started as the first-line chemotherapy, followed by second-line or subsequent chemotherapy. The patients had measurable metastatic lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). This study was approved by the Ethics Committee of Toyama University Hospital (Toyama, Japan), Database of Musculoskeletal Disease (No. 21-22), and Database of Musculoskeletal Tumor (No. 24-40). All 12 patients gave their written, informed consent for this study. The clinical characteristics of the patients are

shown in Table 1. The average age at the onset of chemotherapy was 52.3 (19-73) years. The histopathological subtypes were four undifferentiated pleomorphic sarcomas, two leiomyosarcomas, and one each of malignant solitary fibrous tumor, synovial sarcoma, alveolar soft part sarcoma, myxoid liposarcoma, clear cell sarcoma, and rhabdomyosarcoma. The most common metastatic site was the lung, and metastases also occurred to the spine and posterior mediastinum.

Chemotherapy

The AI regimen was given as the first-line chemotherapy to all 12 patients with advanced STS. The therapeutic effect of chemotherapy was judged by RECIST every three cycles, and in cases with progressive disease (PD), the regimen was switched to second-line treatment. Because no gold standard is available for the selection of the second-line therapeutic agent, the patient was given a description of treatment using pazopanib, trabectedin, and eribulin, which are novel therapeutic agents, and the patient selected from among them. Pazopanib (400-800 mg) is given orally once a day, with adverse events and blood tests checked on an outpatient basis every 2 weeks. Trabectedin (1.2 mg/m²) is administered as a 24-hour intravenous infusion every 21 days, and the patient must be hospitalized for 2 days. Eribulin (1.4 mg/m²) is administered as an intravenous infusion over 5 minutes on days 1 and 8 of every 21-day cycle. The treatment effect was evaluated every 3 months for each agent, with a switch to another agent when PD was determined. In cases of stable disease (SD) or partial response (PR), administration of the same agents was continued.

Assessment of HRQOL

HRQOL was evaluated using the EORTC QLQ-C30 [12]. The EORTC QLQ-C30 (version 3.0) consists of a 30-item questionnaire that addresses five functional domains (Physical, Role, Cognitive, Emotional, and Social domains), nine symptom scales (Fatigue, Pain, Nausea and Vomiting, Dyspnea, Appetite Loss, Sleep Disturbance, Constipation, Diarrhea, and Financial Difficulties), and one global health status. Items 29 and 30, which are related to global health status, are scored from 1 (very poor) to 7 (excellent). The remaining 28 items are evaluated in four categories (1, not at all; 2, a little; 3, quite a bit; 4, very much). According to the scoring manual, linear transformation is used to standardize the raw score. As a result, the overall scores range from 0 to 100. A higher mean score for global health status and the functional scale reflects a better level of functioning, but a higher mean score for symptoms reflects more problems.

Schedule of assessments

Evaluation of HRQOL using the EORTC QLQ-C30 questionnaire was performed after three cycles of each chemotherapy and before evaluating the therapeutic effect. When pazopanib was administered orally, QOL was evaluated after 3 months.

Statistical analysis

All statistical analyses were conducted using JMP statistical software (version 11; SAS Institute Inc., Cary, NC, USA), and $p < 0.05$ was considered to indicate a significant difference. Analysis of variance (ANOVA) followed by the Tukey-Kramer post-hoc test or the unpaired t-test was used to determine significance ($p < 0.05$ was considered significant) where applicable.

Results

Antitumor agent, number of cycles, and number of cases with each line

The AI regimen was started as first-line chemotherapy for all patients with advanced STS. The median number of cycles per patient was four. The therapeutic effect of chemotherapy was one case of PR, two cases of SD, and 10 cases of PD. The therapeutic effect in one case of leiomyosarcoma was PR, but esophagitis associated with severe vomiting occurred, and the AI regimen was discontinued after two cycles. For second-line treatment, pazopanib was administered to five patients, and the median duration of administration was 16 months. Trabectedin was started in four patients, and the median number of cycles was eight. Eribulin was administered to three patients, and the median number of cycles was four. Third-line treatment was conducted in nine patients. Pazopanib was administered to one patient for 4 months. Trabectedin was started in two patients, and the number of cycles was two and three. Eribulin was administered to six patients, and the median number of cycles was five. In addition, fourth-line treatment was started in six patients. Pazopanib was started in one patient and continued for 3 months. Trabectedin was started in five cases, and the number of cycles was 10, and eribulin was administered for nine cycles in one patient. After PD with the AI regimen, pazopanib was often started as second-line therapy, and eribulin was often administered as second- or third-line therapy (Table 2).

Global health status when receiving the AI regimen and second-line or subsequent treatments

The mean global health status score of the 12 patients treated with the AI regimen was 37.9 (standard deviation [SD] = 19.1, 95% confidence interval [CI]: 25.0, 50.7). The mean global health status score of the 12 patients who received second-line therapy, nine who received third-line, and seven who received fourth-line was 56.8 (SD = 21.0, 95% CI: 47.5, 66.1), which was significantly higher than the score with the AI regimen as first-line chemotherapy (Student's t-test, $p = 0.017$, Table 3).

Difference in global health status between first-line therapy and each antitumor agent after second-line therapy

The mean global health status scores of the six patients treated with pazopanib, the eight patients treated with trabectedin, and the seven patients treated with eribulin were 51.4 (SD = 13.4, 95% CI: 37.4, 65.4), 58.3 (SD = 25.5, 95% CI: 39.4, 77.3), and 59.5 (SD = 23.3, 95% CI: 38.0, 81.1), respectively. The difference of the global health status score between the AI regimen and three innovative antitumor agents was not significant (single-factor ANOVA, $p = 0.11$).

Evaluation of the EORTC QLQ-C30 functional scale for each antitumor agent

The results for the functional scale are shown in Table 4. The mean physical functioning score was 68.5 (SD = 21.7) with the AI regimen, 73.3 (SD = 21.9) with pazopanib, 74.8 (SD = 24.4) with trabectedin, and 71.4 (SD = 23.6) with eribulin. The mean emotional functioning score was 68.9 (SD = 26.9) with the AI regimen, 73.6 (SD = 20.7) with pazopanib, 82.4 (SD = 21.0) with trabectedin, and 81.0 (SD = 20.2) with eribulin. The mean role functioning score was 54.5 (SD = 19.8) with the AI regimen, 77.8 (SD = 20.2) with pazopanib, 74.1 (SD = 26.5) with trabectedin, and 71.4 (SD = 28.4) with eribulin. The mean cognitive function score exceeded 80 with all antitumor agents, indicating that the patients maintained good cognitive function. The mean social functioning score was 47.2 (SD = 26.3) with the AI regimen, 81.0 (SD = 12.5) with pazopanib, 61.9 (SD = 26.4) with trabectedin, and 66.7 (SD = 26.2) with eribulin. The social function scores were significantly different between the AI regimen and pazopanib with ANOVA followed by the Tukey-Kramer post-hoc test.

Evaluation of the EORTC QLQ-C30 symptomatic scale for each antitumor agent

The results of the symptoms scale are shown in Table 5. The mean fatigue score was 46.5 (SD = 29.7) with the AI regimen, 38.9 (SD = 28.8) with pazopanib, 34.6 (SD = 21.1) with trabectedin, and 36.5 (SD = 27.8) with eribulin; no significant difference was present among these antitumor agents. The mean nausea and vomiting score was 47.0 (SD = 34.8) with the AI regimen, 16.7 (SD = 14.9) with pazopanib, 37.0 (SD = 32.0) with trabectedin, and 11.9 (SD = 12.6) with eribulin; a significant difference was found between the AI regimen and eribulin (ANOVA, $p = 0.047$). The mean pain score was 39.4 (SD = 34.4) with the AI regimen, 25.0 (SD = 13.9) with pazopanib, 24.1 (SD = 26.5) with trabectedin, and 35.7 (SD = 29.5) with eribulin. The mean dyspnea score was less than 30 with all drugs, and few patients developed dyspnea. The mean insomnia score was the highest with the AI regimen, at 39.4 (SD = 36.0), and the lowest with pazopanib, at 16.7 (SD = 18.3); the difference was not significant. The mean appetite loss score was higher than 40 with the AI regimen and trabectedin, and the lowest score was 11.1 (SD = 17.2) with pazopanib. During AI treatment, appetite tended to decrease compared with pazopanib (ANOVA, $p = 0.061$). The mean constipation score was higher than 40 with the AI regimen. With the other antitumor agents, the constipation score was less than 30. In particular, the constipation score with the AI regimen was significantly higher than with pazopanib and with eribulin (ANOVA, $p = 0.007$). The mean diarrhea score with pazopanib was 61.1 (SD = 44.3), which was significantly higher than with the AI regimen and with eribulin (ANOVA, $p = 0.028$). The mean financial difficulties score was slightly higher than 50 with pazopanib and with eribulin, even though these drugs were given as outpatient treatment. However, the difference among these antitumor agents was not significant.

Discussion

For most of advanced STS patients, anthracycline-based chemotherapy, primarily with doxorubicin (adriamycin), either as monotherapy or in combination with ifosfamide, is considered first-line treatment [16]. Three innovative drugs, pazopanib, trabectedin, and eribulin, have been developed as candidates for second-line and subsequent treatment [16]. Innovative anticancer drugs such as pazopanib, trabectedin, or eribulin may prolong PFS or OS in patients with advanced STS [9–11], but simultaneously,

maintenance and improvement in QOL during survival is important. In a recent report on the efficacy of therapeutic interventions, not only the traditional endpoints of tumor response and survival, but also QOL evaluation were included as primary endpoints in cancer clinical trials [14]. The mean global health status score of advanced STS patients treated with pegylated liposomal doxorubicin, which has less hematological toxicity and cardiotoxicity than doxorubicin, was 53.8 [17]. The mean global health status score was 65.2 in advanced STS patients treated with eribulin [18], and approximately 60 to 65 with pazopanib treatment [14]. In the present study, the differences in QOL due to different antitumor agents were evaluated in the same patients for the first time. We found no significant difference among each treatments (AI regimen, pazopanib, trabectedin, eribulin) in the global health status. When the three innovative drugs are considered as one group and analyzed relative to the AI regimen, the global health status score of the group (mean score; 56.8) is significantly higher than that of the AI regimen. The reason for the absence of a significant difference in the global health status score among the AI regimen, pazopanib, trabectedin, and eribulin was attributed to the small number of patients receiving each treatment, which ranged from seven to 12. We did observe a significant difference in global health status scores when we compared two arm of treatments, AI regimen vs. a group of three innovative agents. When the disease progresses during treatment with the first-line regimen, innovative anticancer drugs are started. In the present study, despite progression of disease activity, with the start of a new anticancer agent compared to the first-line treatment, the average global health status score was better. Furthermore, the global health status score in patients receiving new antitumor agents has not been described in reports of clinical trials of new therapeutic agents so far [14, 18]. Therefore, innovative antitumor agents may be able to be continued while maintaining QOL, even in patients with disease progression. In this study, we found no significant difference in the global health status score among the three innovative antitumor agents. However, analysis of a large number of cases may reveal which of the three innovative antineoplastic agents is most beneficial for maintaining QOL. Our results suggest a new viewpoint for selection of an antitumor drug for the second-line and subsequent treatments.

We found no significant differences in the four functional scales except for the social function scale according to the different treatments. Patients with advanced STS had a significantly higher social functional scale during treatment with pazopanib compared to treatment with the AI regimen. If an STS patient is a young or middle-aged person with a job, pazopanib can be continued as outpatient treatment without the patient feeling a sense of loss in society, leading to maintenance of QOL. However, because the social functional scale was not significantly different among the three innovative antitumor agents, we could not clearly identify which of the second-line and subsequent therapies could be continued while maintaining the patient's social role. In a previous report describing the data of EORTC QLQ-C30 for a population of about 3,000 Swedish persons, including people with various health conditions ranging from healthy persons to patients with chronic diseases and/or malignant tumors, the mean functional score ranged from 70 to 97 for most people [19]. Compared with this large amount of Swedish data, in the present study, the mean social function score of advanced STS patients treated with the AI regimen was 47.2, which means that QOL was quite low in the family and workplace during treatment with the AI regimen. This low social functional scale may be related to adverse events that are a result of AI

treatment. Both doxorubicin and ifosfamide have been classified as moderate emetic risk antineoplastic agents by the American Society of Clinical Oncology (ASCO) Antiemetic Guideline Update Committee [20]. In a previous report, fatigue, nausea, and vomiting in children and adolescents who received adriamycin or ifosfamide affected depressive symptoms and behavior changes during cancer treatment [21]. The EORTC QLQ-C30 symptomatic scale in this study also identified fatigue, nausea and vomiting, appetite loss, and constipation with the AI regimen, each of which had a score of 45 or more. A large study of HRQOL measured by EORTC QLQ-C30 in the Swedish population showed that the mean symptomatic scale score was less than 40 [19]. Therefore, high symptom scale scores during treatment with the AI regimen may reflect low QOL during treatment. Alternatively, the symptom scale scores of advanced STS patients treated with pazopanib, trabectedin, or eribulin may have been low only for scales related to the characteristic side effects of each drug. The characteristic adverse event of pazopanib is diarrhea, that of trabectedin is nausea and vomiting, and that of eribulin is appetite loss. Therefore, QOL may be maintained and improved by taking sufficient countermeasures against the adverse events that are characteristic of each drug. Because drug selection for second-line and subsequent lines for advanced STS is not clearly defined, these QOL data can help with drug selection at the beginning of second-line therapy.

Our study has some limitations. First, the study was conducted at a single center with a small population. A larger number of patients or a multicenter study is needed to confirm the present findings. Second, in this study, QOL was evaluated only once during three cycles after the start of treatment. To ascertain the effect on QOL, QOL should be evaluated at several points after starting administration of drugs.

Conclusions

Compared to the AI regimen, patients could maintain QOL while taking one of three innovative antitumor agents, even if the patient showed PD. In particular, of the three innovative antitumor agents compared to the AI regimen, patients treated with pazopanib were able to maintain a social role during treatment. During the second-line and subsequent treatments, we could not clearly show a difference in the effect on QOL among the three innovative drugs, so additional work is needed. If we are able to clarify which drugs affect QOL, recommendations can be made regarding treatment selection for the second-line and subsequent treatments. Furthermore, we may improve QOL in advanced STS patients by controlling the specific adverse events that are characteristic of each of the three novel antitumor agents.

Abbreviations

QOL

quality of life, STS:soft tissue sarcoma, HRQOL:health-related QOL, AI:doxorubicin and ifosfamide, EORTC QLQ-C30:European Organization on Research and Treatment of Cancer Quality-of-Life Core Questionnaire-30, PFS:progression-free survival, OS:overall survival, RECIST 1.1:Response Evaluation Criteria in Solid Tumors version 1.1, PD:progressive disease, SD:stable disease, PR:partial response, ASCO:American Society of Clinical Oncology

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Toyama University Hospital (Toyama, Japan), Database of Musculoskeletal Disease (No. 21-22), and Database of Musculoskeletal Tumor (No. 24-40).

Consent for publication

All 12 patients gave their written consent for this report.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KS and TY made substantial contributions to conception and design. KS was responsible for the acquisition or analysis and interpretation of data. KW provided advice on the data analysis. KS, TY, and KW were involved in the treatment with antitumor agents. KY and MK were involved in drafting the manuscript or revising it critically for important intellectual content. KS made critical revisions to the article for important intellectual content. All the authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Tables

Table 1. Clinical characteristics of advanced STS patients

Case	Age (years)/ Sex	Occupation	Histology	Primary site	AJCC Stage*	Development of metastasis	Metastatic site	Outcome (survival#)
1	50/M	Office worker	Malignant SFT	Lower leg	IV		Lung	DOD (48)
2	66/M	None	Leiomyosarcoma	Shoulder	IV		Lung	DOD (48)
3	41/F	Office worker	ASPS	Forearm	IV		Lung	DOD (97)
4	50/M	Government official	Synovial sarcoma	Ankle	IIIB	+	Lung	AWD (48)
5	64/M	Self-employed	UPS	Lumbar	IV		Lung	DOD (41)
6	44/F	Office worker	Myxoid liposarcoma	Thigh	IIIB	+	Mediastinal	DOD (48)
7	19/M	Office worker	UPS	Mediastinal	IIIB	+	Lung	AWD (65)
8	57/M	Office worker	Rhabdomyosarcoma	Retroperitoneum	IV		Lung	AWD (65)
9	39/F	Office worker	Leiomyosarcoma	Pelvic	IV	+	Lung	DOD (19)
10	58/M	None	UPS	Lumbar	IIIB	+	Lung	NED (21)
11	73/M	None	UPS	Shoulder	IIIB	+	Spine	DOD (27)
12	68/F	Housewife	Clear cell sarcoma	Thigh	IV		Lung	DOD (22)

M: male, F: female, SFT: solitary fibrous tumor, ASPS: alveolar soft part sarcoma, UPS: undifferentiated pleomorphic sarcoma, AJCC: American Joint Committee on Cancer, DOD: dead of disease, AWD: alive with disease, NED: no evidence of disease, * Clinical stage according to AJCC classification at the initial diagnosis, # survival is shown in months.

Table 2. Number of cases and median cycles by antitumor agent in each treatment line

	1st line		2nd line		3rd line		4th line	
	Cases	Cycles	Cases	Cycles	Cases	Cycles	Cases	Cycles
AI regimen	12	4						
Pazopanib			5	16 M	1	4 M	1	3 M
Trabectedin			4	8	2	2.5	5	10
Eribulin			3	4	6	5	1	12
Total of cases	12		12		9		7	

AI: adriamycin plus ifosfamide, M: months

The number of cycles of pazopanib was expressed in months over the period of taking the drug.

The median cycles are represented by the number of cycles for the case when the number of cases was one, and the average number of cycles when the number of cases was two.

Table 3. Mean scores for the EORTC QLQ-C30 global health status according to the antitumor agent

	Mean	Min, max	SD	95% CI	p value
AI regimen	37.9	8.3, 66.7	19.1	25.0, 50.7	0.0174*
second-line and subsequent treatment	56.8	25.0, 100	21.0	47.5, 66.1	
Pazopanib	51.4	33.3, 66.7	13.4	37.4, 65.4	0.58#
Trabectedin	58.3	25.0, 83.3	25.5	39.4, 77.3	
Eribulin	59.5	33.3, 100	23.3	38.0, 81.1	

AI: adriamycin plus ifosfamide, Min: minimum score, max: maximum score, SD: standard deviation,

CI: confidence interval

* p value was calculated with the Student's *t*-test for the scores between the AI regimen and second-line and subsequent treatment.

p value was calculated with single-factor ANOVA for the scores among pazopanib, trabectedin, and eribulin.

Table 4. Mean scores for the EORTC QLQ-C30 functional scales according to the antitumor agent

	Statistic	AI regimen	Pazopanib	Trabectedin	Eribulin	p value*
Physical functioning	Mean	68.5	73.3	74.8	71.4	0.937
	Min, max	40, 100	53.3, 100	33.3, 100	33.3, 100	
	SD	21.7	21.9	24.4	23.6	
	95% CI	53.9, 83.1	50.3, 96.3	56.0, 93.6	49.6, 93.3	
Role functioning	Mean	54.5	77.8	74.1	71.4	0.179
	Min, max	33.3, 100	50, 100	33.3, 100	33.3, 100	
	SD	19.8	20.2	26.5	28.4	
	95% CI	41.2, 67.9	56.6, 99.0	53.7, 94.4	45.2, 97.7	
Emotional functioning	Mean	68.9	73.6	82.4	81.0	0.556
	Min, max	25, 91.7	58.3, 100	50, 100	50, 100	
	SD	26.9	20.7	21.0	20.2	
	95% CI	50.9, 87.0	51.9, 95.3	66.3, 98.6	62.2, 99.7	
Cognitive functioning	Mean	80.3	83.3	87.0	83.3	0.834
	Min, max	66.7, 100	66.7, 100	50, 100	50, 100	
	SD	14.6	14.9	16.2	19.2	
	95% CI	70.5, 90.1	67.7, 99.0	74.6, 99.5	65.5, 100	
Social functioning	Mean	47.2	81.0	61.9	66.7	0.037
	Min, max	16.7, 100	66.7, 100	33.3, 100	33.3, 100	
	SD	26.3	12.5	26.4	26.2	
	95% CI	31.0, 63.4	70.3, 91.6	38.8, 85.0	46.4, 86.9	

AI: adriamycin plus ifosfamide, Min: minimum score, max: maximum score, SD: standard deviation,

CI: confidence interval

* p value was calculated with ANOVA for each score among treatments.

Table 5. Mean scores for EORTC QLQ-C30 symptomatic scales according to the antitumor agent

	Statistic	AI regimen	Pazopanib	Trabectedin	Eribulin	p value*
Fatigue	Mean	46.5	38.9	34.6	36.5	0.773
	Min, max	11.1, 88.9	0, 66.7	11.1, 66.7	0, 66.7	
	SD	29.7	28.8	21.1	27.8	
	95% CI	26.5, 66.4	8.7, 69.1	18.3, 50.8	10.8, 62.2	
Nausea and vomiting	Mean	47.0	16.7	37.0	11.9	0.047
	Min, max	0, 100	0, 33.3	0, 100	0, 33.3	
	SD	34.8	14.9	32.0	12.6	
	95% CI	23.6, 70.4	1.0, 32.3	12.4, 61.7	0.3, 23.6	
Pain	Mean	39.4	25.0	24.1	35.7	0.598
	Min, max	0, 100	0, 33.3	0, 83.3	0, 83.3	
	SD	34.4	13.9	26.5	29.5	
	95% CI	16.3, 62.5	10.4, 39.6	3.7, 44.4	8.4, 63.0	
Dyspnea	Mean	30.3	22.2	29.6	23.8	0.937
	Min, max	0, 66.7	0, 66.7	0, 66.7	0, 66.7	
	SD	34.8	34.4	26.1	25.2	
	95% CI	6.9, 53.7	-13.9, 58.4	9.6, 49.7	0.5, 47.1	
Insomnia	Mean	39.4	16.7	25.9	23.8	0.478
	Min, max	0, 100	0, 33.3	0, 66.7	0, 66.7	
	SD	36.0	18.3	27.8	31.7	
	95% CI	15.2, 63.6	-2.5, 35.8	4.6, 47.3	-5.5, 53.1	
Appetite loss	Mean	51.5	11.1	44.4	23.8	0.061
	Min, max	0, 100	0, 33.3	0, 100	0, 66.7	
	SD	34.5	17.2	33.3	31.7	
	95% CI	28.3, 74.7	-6.9, 53.1	18.8, 70.1	-5.5, 53.1	
Constipation	Mean	45.5	11.1	25.9	9.5	0.007
	Min, max	0, 100	0, 33.3	0, 33.3	0, 33.3	
	SD	30.8	17.2	14.7	16.3	
	95% CI	24.8, 66.2	-6.9, 29.2	14.6, 37.2	-5.5, 24.6	
Diarrhea	Mean	30.3	61.1	29.6	14.3	0.028
	Min, max	0, 66.7	0, 100	0, 66.7	0, 33.3	
	SD	23.4	44.3	20.0	17.8	
	95% CI	14.6, 46.0	14.6, 107.6	14.2, 45.0	-2.1, 30.8	
Financial difficulties	Mean	33.3	50.0	37.0	52.4	0.387
	Min, max	0, 66.7	0, 100	0, 66.7	0, 100	
	SD	21.1	27.9	20.0	37.8	
	95% CI	19.2, 47.5	20.7, 79.3	21.6, 52.4	17.4, 87.3	

AI: adriamycin plus ifosfamide, Min: minimum score, max: maximum score, SD: standard deviation,

CI: confidence interval

* p value was calculated with ANOVA for each score among treatments.