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Safety of Endostar in combination with chemotherapy in patients with cancer

Running title: Safety of Endostar with chemotherapy for cancer

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Abstract

Background: A number of studies indicated the benefits and safety of Endostar in combination with chemotherapy in cancer, but the exact real-life safety of Endostar is

poorly known. This study aimed to assess the safety of Endostar in combination with chemotherapy in patients with cancer in a real-life setting in China.

Methods: This was a retrospective study of patients treated with Endostar in combination with chemotherapy in the Chinese PLA General Hospital (Beijing, China) from 1st January 2006 to 31st December 2017. All data were obtained from the Hospital Information System (HIS). Laboratory abnormalities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Bleeding events and wound healing complications after surgery associated with Endostar were evaluated based on case records.

Results: A total of 825 patients were included. There were no patients used Endostar alone in real-life settings. Overall, anemia occurred in 74.5% of the assessed patients, thrombocytopenia occurred in 29.0%, abnormal white blood cell count occurred in 54.5%, abnormal liver function occurred in 13.8%, and increased creatinine occurred in 1.2%. No definite bleeding events and wound healing complications after surgery associated with Endostar were found based on case records. Most laboratory AEs were of grade 1-2. Lung cancer, osteosarcoma and doxorubicin-based chemotherapy was associated with an increased risk of grade ≥ 3 abnormal white blood cell count ($P < 0.05$). The total dose of Endostar was not associated with severe AEs (grade ≥ 3) of thrombocytopenia and abnormal white blood cell count.

Conclusion: The occurrence of AEs during treatment with Endostar in combination with chemotherapy differed across different tumor types and chemotherapy regimens. No new unexpected AEs relating to Endostar were observed from this study. The total dose of Endostar was not associated with increased risk of severe AEs (grade ≥ 3) of thrombocytopenia and abnormal white blood cell count when used in combination with chemotherapy in the real-life setting.

Key words: lung cancer; liver cancer; osteosarcoma; Endostar; adverse events.

Background

Cancer is currently one of the leading causes of global deaths with its incidence and mortality rates both increased dramatically over the past few decades[1]. In 2018, there was an estimated 18.1 million new cancer cases and 9.6 million cancer deaths worldwide[1], with lung cancer as the most common diagnosis (11.6%) and cause of death (18.4%). These data highlight the challenges in cancer prevention and screen as well as the urgent need for new and effective treatment modalities.

Angiogenesis is a process encountered in solid tumors and is necessary to provide optimal nutrient and oxygen supplies to the cancer cells, and targeting angiogenesis is a viable option to delay cancer growth[2-4]. Endostatin is a 20-kD internal fragment of collagen XVIII with anti-angiogenesis properties[5]. Endostar, which is recombinant human Endostatin purified from transgenic *Escherichia coli*, was approved in 2005 in China for the treatment of advanced non-small cell lung cancer (NSCLC) in combination with platinum-based chemotherapy, with improved treatment response rates[6, 7]. A meta-analysis showed that the relative improvement in the objective response rate (ORR) due to Endostar in patients with NSCLC was 74% compared with placebo and combined with chemotherapy[8]. A number of studies also indicated the benefits of Endostar in liver cancer [9] and osteosarcoma[10, 11].

With anti-angiogenesis drugs, safety could be a concern. Treatment-related adverse events (AEs) including cardiovascular toxicity[12], proteinuria, hypertension, hemorrhagic events, and neutropenia[13, 14] have been previously reported. A meta-analysis of Endostar showed that Endostar combined with chemotherapy did not

increase the incidence and severity of leukopenia, thrombocytopenia, anemia or nausea/vomiting in patients with NSCLC, compared with chemotherapy alone. In addition, no increased risk was observed for other common AEs. Nevertheless, data for Endosta rare mostly from selected patients from lung cancer trials [8, 15-17].Data from other cancer types and from real-life clinical practice are limited. Real-life studies are an essential component of evidence-based medicine, allowing informed decision-making based on the balance between effectiveness and safety[18]. Therefore, this study aimed to assess the safety of Endostar in combination with chemotherapy in patients with various types of cancer in a real-life setting.

Methods

Study design and patients

This was a retrospective study of patients treated with Endostar for cancer in the Chinese PLA General Hospital (Beijing, China) from 1st January 2006 to 31st December 2017. The study was approved by the ethics committee of the Chinese PLA General Hospital. The need for written informed consent was waived by the committee.

The major inclusion criteria were: 1) locally advanced and metastatic solid tumor such as NSCLC, liver cancer, osteosarcoma and so on, confirmed by histology or cytology; 2) have baseline and treatment plan records; 3) have used Endostar (Manufactured by Shandong Sincere Bio-pharmaceutical Co.,Ltd.) for the treatment of solid tumor during the study period; 4) have received Endostar at least once; 5) have hematology or laboratory examination records within 30 days after the administration of Endostar.

The major exclusion criteria were: 1) non-solid tumor such as hematological malignancy; 2) no baseline or treatment plan records available; 3) have not used Endostar during the study period; 4) no hematology or laboratory examination records within 30 days after the administration of Endostar.

Data collection and outcomes

All data of patients who were prescribed and administered Endostar, including the patients' basic information, results of laboratory test, dose of Endostar, case records, *etc* were identified and retrieved from the Hospital Information System (HIS) of the Chinese PLA general hospital.

The outcomes for the study were the occurrence of laboratory adverse events (AEs), including abnormal blood cell parameter (hemoglobin level, leukocyte and platelet count) hepatic and renal function, and cases records of AEs associated with Endostar including bleeding events (pneumorrhagia, hemoptysis, nasal hemorrhage, gingival bleeding), wound healing complications (dehiscence, ecchymosis, surgical site bleeding, delayed union). All AEs were graded according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0)[19].

Statistical analysis

Categorical data are presented as numbers and percentages. Continuous variables are presented as mean \pm standard deviation or median (interquartile range (IQR)), as appropriate based on the Kolmogorov-Smirnov test. For subgroup analysis, descriptive safety data were summarized by main cancer type (lung, osteosarcoma and liver), main chemotherapy regimen (platinum-based and doxorubicin-based regimen) and total dose of Endostar (≤ 210 mg and >210 mg). The association of Endostar administration with grade ≥ 3 thrombocytopenia or abnormal white blood cell count was assessed using univariable and multivariable Cox models. The standard dose for

1 complete cycle of Endostar administration was 210 mg and therefore the total dose of Endostar was classified as ≤ 210 mg vs. > 210 mg. Due to event number restriction, no Cox regression analysis was performed for anemia, abnormal hepatic and renal functions. SAS 9.4 (SAS Institute, Cary, NY, USA) was used for statistical analysis. P values < 0.05 were considered statistically significant.

Results

Characteristics of the patients

During the study period, a total of 825 patients had available hematology or laboratory test data at baseline and during 30-day follow-up (Table 1). There were no patients used Endostar alone in real-life settings. The median age was 50 (IQR: 28-59) years and 72.1% were male. Liver cancer, lung cancer, osteosarcoma represented 18.3%, 23.0%, and 19.6% of the patients, respectively. Among the 825 patients, 136 (16.5%) received platinum monotherapy, 257 (31.2%) received platinum-based combination therapy, and 132 (16.0%) received doxorubicin-based combination therapy. The number of Endostar cycles was one in 87 (10.5%) patients, two in 226 (27.4%), and more than two in 512 (62.1%). The median total dose of Endostar was 495 mg (inter-quartile range: 195-870 mg). 583 (70.7%) patients received Endostar by intravenous drip (Drip). 51 (6.2%) patients received Endostar by continuous intravenous pumping (Pump). 174 (21.1%) patients received Endostar by other methods including intracatheter arterial chemoembolization, thoracic injection, peritoneal injection and hypodermic injection.

Overall AEs

Overall, anemia occurred in 74.5% of the assessed patients, thrombocytopenia occurred in 29.0%, abnormal white blood cell count in 54.5% (decreased white blood

cell (WBC) in 52.7% and neutropenia in 39.2%), abnormal liver function in 13.8% (increased alanine transaminase (ALT) in 11.8%, increased aspartate aminotransferase (AST) in 5.3%, and increased bilirubin in 2.4%), and increased creatinine in 1.2% (Table 2). Most laboratory AEs were of grade 1-2. Grade 3-4 anemia, thrombocytopenia and abnormal WBC occurred in 10.2%, 9.8% and 22.9% patients respectively. Specifically, grade 3-4 decreased WBC occurred in 20.9% patients and neutropenia occurred in 15.8% patients. Grade 3-4 abnormal liver function and kidney function tests occurred in 0.8% and 0% patient respectively. Based on the case records, no definite bleeding events and wound healing complications after surgery associated with Endostar were found. No patients had fatal AEs in the present study.

Subgroup AE

Figure 1 shows that the frequency of overall anemia was highest for osteosarcoma (80.5%), followed by lung cancer (74.2%) and liver cancer (64.7%). The frequency of overall thrombocytopenia was the highest in patients with liver cancer (46.3%), followed by osteosarcoma (33.3%), and lung cancer (19.6%). The frequencies of overall abnormal WBC count, decreased white blood cell and neutropenia were highest with osteosarcoma (77.6%, 76.9% and 61.2%), followed by lung cancer (52.5%, 48.6% and 35.8%), and liver cancer (30.9%, 28.9% and 24.8%). The frequency of overall abnormal liver function test, increased ALT and increased AST were the highest for osteosarcoma (17.4%, 17.4% and 9.3%), followed by lung cancer (9.1%, 6.1% and 0%). The frequency of increased bilirubin was low for both lung cancer (3.0%) and osteosarcoma (0%). The frequency of increased creatinine was the highest for liver cancer (6.7%), followed by lung cancer (0%), and osteosarcoma (0%).

Figure 2 shows that when comparing platinum-based with doxorubicin-based regimens, the frequencies of overall anemia (76.1% vs. 0%), thrombocytopenia (33.2% vs. 24.1%), increased creatinine (2.8% vs. 0%) and increased bilirubin (2.8% vs. 1.4%) were higher for platinum-based regimens whereas the frequencies of overall abnormal white blood cell count (67.9% vs. 39.0%; decreased WBC: 67.9% vs. 36.7%; neutropenia: 44.5% vs. 28.2%) and abnormal liver function test (15.3% vs. 2.8%; increased ALT: 13.9% vs. 0%; increased AST: 5.6% vs. 0%) were higher for doxorubicin-based regimens.

Figure 3 shows that when comparing low-total dose of Endostar (≤ 210 mg) with high-total dose of Endostar (> 210 mg), the frequencies of overall thrombocytopenia (34.9% vs. 26.9%), increased bilirubin (3.6% vs. 1.9%) and increased creatinine (7.1% vs. 0.5%) were higher for low-total dose of Endostar whereas the frequencies of overall anemia (77.4% vs. 68.1%), abnormal white blood cell count (64.4% vs. 33.6%; decreased WBC: 62.5% vs. 31.9%; neutropenia: 45.6% vs. 25.9%) and abnormal liver function test (13.5% vs. 3.6%; increased ALT: 13.0% vs. 3.6%; increased AST: 6.0% vs. 0%) were higher for high-total dose of Endostar.

Factors associated with severe AEs when using Endostar in combination with chemotherapy

When considering all patients, no factors were found to be associated with severe thrombocytopenia (Table 3). Lung cancer and osteosarcoma (as compared with liver cancer) and doxorubicin-based chemotherapy (as compared with platinum-based chemotherapy) were associated with an increased risk of seriously abnormal white blood cell count (Table 3). Total dose of Endostar was not associated with increased risk of severe thrombocytopenia or seriously abnormal white blood cell count when used in combination with chemotherapy (Table 3).

Discussion

A number of studies indicated the benefits and safety of Endostarin combination with chemotherapy in solid tumors[8-11, 15, 16], but the exact real-life safety of Endostar is poorly known. Therefore, this study aimed to assess the safety of Endostar in combination with chemotherapy in patients with cancer in a real-life setting. The results suggested that no new unexpected AEs relating to Endostar were observed when used in combination with chemotherapy.

Endostar has been approved in 2005 for the treatment of NSCLC in China, but it has not yet been approved in other countries. Therefore, all data from clinical trials and real-world studies are from the Chinese populations. The present study has a large sample size compared with the available real-world studies. A real-world study of 88 patients with sensitizing mutation negative NSCLC showed that Endostar combined with platinum-based doublet chemotherapy improved survival, but at the cost of higher occurrence of AEs[20]. A real-world study of 14 patients with pancreatic neuroendocrine tumors showed that the most common grade 1-2 AEs were neutropenia (43%) and leucopenia (21%)[21]. A real-world study of 23 patients with advanced mucosal melanoma showed that the most common severe AEs of Endostar with chemotherapy were leucopenia (13%), thrombocytopenia (13%), anemia (4%), nausea and vomiting (4%), and elevated transaminase (4%)[22]. A large study of 2725 patients with NSCLC showed that Endostar added to standard NCCN-recommended chemotherapy improved treatment response without resulting in excess AEs[17]. In the present real-world study, grade 3-4 anemia occurred in 10.2% of the assessed patients, thrombocytopenia occurred in 9.8%, abnormal white blood cell count occurred in 22.9%, abnormal liver function occurred in 0.8%, increased

creatinine occurred in 0% and no definite bleeding events and wound healing complications after surgery associated with Endostar were found based on case records. This is generally consistent with the available real-world data, as well as with the data from the clinical trials [8-11, 15, 16].

In the present study, the pattern of laboratory AEs seems to vary with the type of cancer. Indeed, the frequencies of thrombocytopenia (46.3%) and abnormal kidney function test (6.7%) were the highest in patients with liver cancer, while the frequencies of anemia (80.5%), abnormal white blood cell count (77.6%) and abnormal liver function test (17.4%) were the highest for osteosarcoma. Multivariable analysis showed that lung cancer and osteosarcoma were associated with increased risk of abnormal white blood cell count, as compared with liver cancer ($P < 0.01$). Previous studies have showed that Endostar combined with chemotherapy in liver cancer is associated with leucopenia and liver function damage [9], while Endostar combined with chemotherapy in lung cancer did not increase the toxicity of chemotherapy alone [8, 15], and Endostar in osteosarcoma showed myelosuppression and transient elevation of liver enzymes [10]. Of course, the differences in AE patterns might be due to disease stage, affected organs, preconditioning regimens, and especially concurrent chemotherapy, among others. Notably, in the present study, over 90% patients with liver cancer and over 80% patients with lung cancer were treated with platinum-based chemotherapy, whereas over 80% of patients with osteosarcoma were treated with doxorubicin-based chemotherapy. Additional studies are necessary to determine the exact AE patterns of Endostar in combination with chemotherapy across different cancer types. Interestingly, a study showed that Endostar could decrease the occurrence of nasopharyngeal mucosal necrosis in

patients with nasopharyngeal carcinoma who received chemoradiotherapy[23]. Potential protective effects of Endostar should also be investigated.

The occurrence of laboratory AEs of Endostar with different total dose was also investigated in this study. Descriptive results showed that the frequencies of overall thrombocytopenia (34.9%) and increased creatinine (7.1%) were higher for low-total dose of Endostar (≤ 210 mg) while the frequencies of overall anemia (77.4%), abnormal white blood cell count (64.4%) and abnormal liver function (13.5%) were higher for high-total dose of Endostar (> 210 mg). Multivariable analysis showed that the total dose of Endostar was not associated with increased risk of severe thrombocytopenia or seriously abnormal white blood cell count ($P > 0.05$). As for the occurrence of laboratory AEs of Endostar when combined with different chemotherapy regimens, the present study suggests that the frequencies of thrombocytopenia (33.2%) and abnormal kidney function test (2.8%) were the highest for platinum-based regimens, whereas the frequencies of abnormal white blood cell count (67.9%) and abnormal liver function test (15.3%) were the highest for doxorubicin-based regimens. Doxorubicin-based regimens were associated with an increased risk of seriously abnormal white blood cell count ($P < 0.05$) compared with platinum-based regimens. In fact, those patterns are more similar to the already known AE patterns of platinum- vs. doxorubicin-based chemotherapies[24-27], suggesting that the AEs of the chemotherapy part of the treatment are likely to be more significant than the AEs from Endostar. Additional studies are necessary to discriminate between Endostar-specific AEs, chemotherapy-specific AEs, and AEs that arise from the combination of the two. Other regimens should also be investigated. For example, a study of the combination of Endostar with taxane-based regimens in

breast cancer showed that the vast majority of patients experienced neutropenia (80.7%) and leukopenia (77.2%)[28].

This study has limitations. It was a single-center, retrospective study, and the data that could be analyzed were limited to those available in the database. Second, not all patients received laboratory examinations before and after administration of Endostar and a bias could be introduced. For example, patients with lung cancer were more likely to undergo blood testing, as well as those receiving multiple doses of Endostar. Third, all patient in the present study used Endostarin combination with chemotherapy and no controls were included. Finally, the high diversity in individual treatment regimens may introduce some confounding (e.g., dose and type). Only a general classification was used for the present study.

Conclusion

The occurrence of AEs during treatment with Endostar in combination with chemotherapy differed across different tumor types and chemotherapy regimens. No new unexpected AEs relating to Endostar were observed from this study. The total dose of Endostar was not associated with increased risk of severe AEs (grade \geq 3)of thrombocytopenia and abnormal white blood cell count when used in combination with chemotherapy.

List of abbreviations

AEs, adverse events

ALT, alanine transaminase

AST, aspartate aminotransferase

CTCAE 4.0, Common Terminology Criteria for Adverse Events version 4.0

HIS, Hospital Information System

IQR, interquartile range

NSCLC, non-small cell lung cancer

ORR, objective response rate

WBC, white blood cell

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Chinese PLA General Hospital. The need for written informed consent was waived by the committee.

Consent for publication

Not applicable.

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

All authors declare that they have no competing interests.

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Authors' contributions

DXW conceived and coordinated the study, designed, performed and analyzed the experiments, wrote the paper. DHG, MZ, LX, XWH and TLW carried out the data collection. DXW, DHG, MZ and CHZ carried out data analysis and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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Figure legends

Figure 1. Occurrence of laboratory adverse events (grades 1-4) during treatment with Endostarin combination with chemotherapy for lung cancer, osteosarcoma, and liver cancer. (A) Anemia. (B) Thrombocytopenia. (C) Decreased WBC. (D) Neutropenia.

(E) Increase ALT. (F) Increased AST. (G) Increased bilirubin. (H) Increased creatinine. No grade 5 AE occurred. WBC, white blood cell; ALT, alanine transaminase; AST, aspartate aminotransferase.

Figure 2. Occurrence of laboratory adverse events (grades 1-4) during treatment with Endostarin combination with platinum-based and doxorubicin-based chemotherapies. (A) Anemia. (B) Thrombocytopenia. (C) Decreased WBC. (D) Neutropenia. (E) Increase ALT. (F) Increased AST. (G) Increased bilirubin. (H) Increased creatinine. No grade 5 AE occurred. WBC, white blood cell; ALT, alanine transaminase; AST, aspartate aminotransferase.

Figure 3. Occurrence of laboratory adverse events (grades 1-4) during treatment with low-total dose (≤ 210 mg) and high-total dose (> 210 mg) of Endostar. (A) Anemia. (B) Thrombocytopenia. (C) Decreased WBC. (D) Neutropenia. (E) Increase ALT. (F) Increased AST. (G) Increased bilirubin. (H) Increased creatinine. No grade 5 AE occurred. WBC, white blood cell; ALT, alanine transaminase; AST, aspartate aminotransferase.

Figures

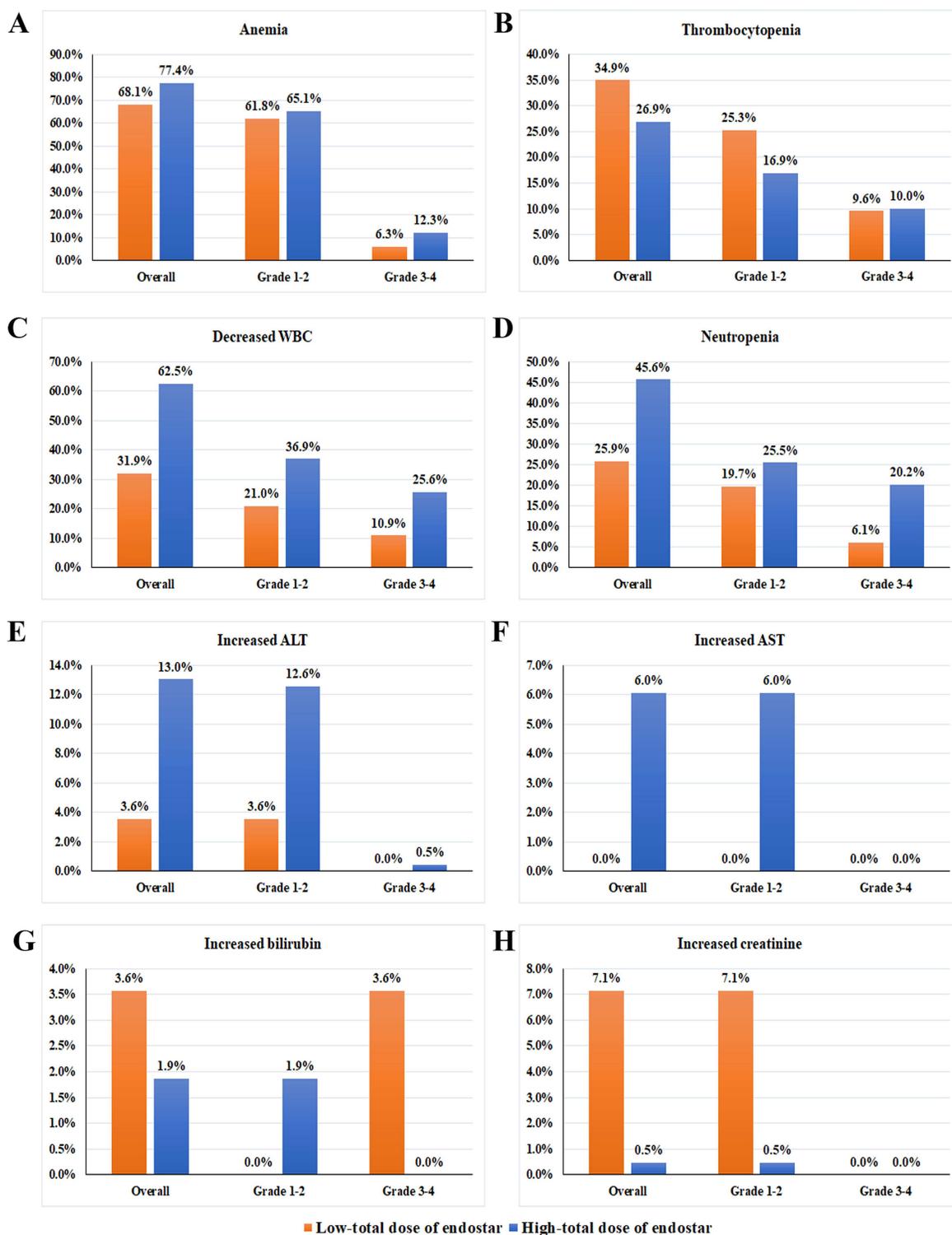


Figure 1

Occurrence of laboratory adverse events (grades 1-4) during treatment with low-total dose (≤ 210 mg) and high-total dose (> 210 mg) of Endostar. (A) Anemia. (B) Thrombocytopenia. (C) Decreased WBC. (D)

Neutropenia. (E) Increase ALT. (F) Increased AST. (G) Increased bilirubin. (H) Increased creatinine. No grade 5 AE occurred. WBC, white blood cell; ALT, alanine transaminase; AST, aspartate aminotransferase.

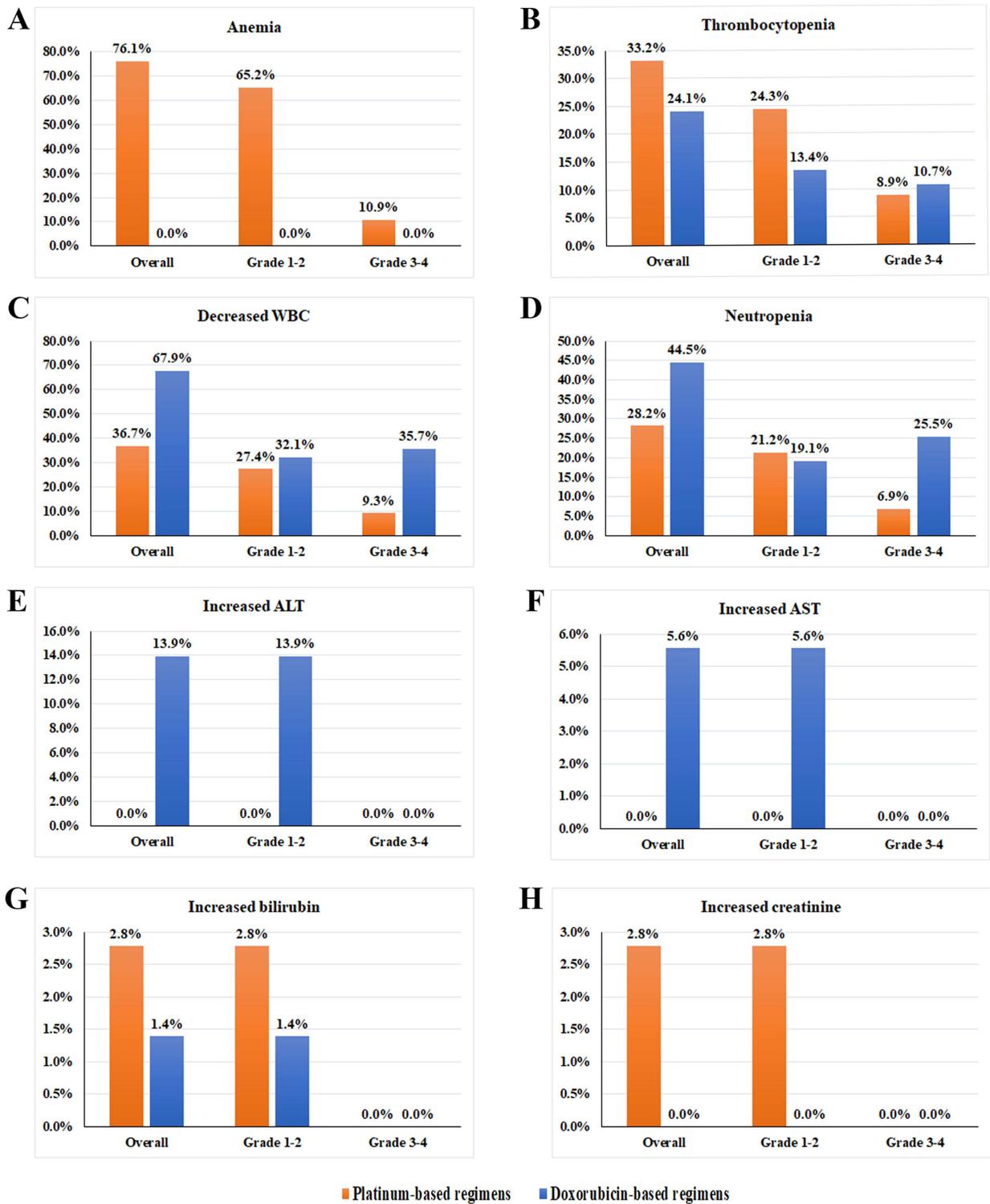


Figure 2

Occurrence of laboratory adverse events (grades 1-4) during treatment with Endostarin combination with platinum-based and doxorubicin-based chemotherapies. (A) Anemia. (B) Thrombocytopenia. (C) Decreased WBC. (D) Neutropenia. (E) Increase ALT. (F) Increased AST. (G) Increased bilirubin. (H)

Increased creatinine. No grade 5 AE occurred. WBC, white blood cell; ALT, alanine transaminase; AST, aspartate aminotransferase.

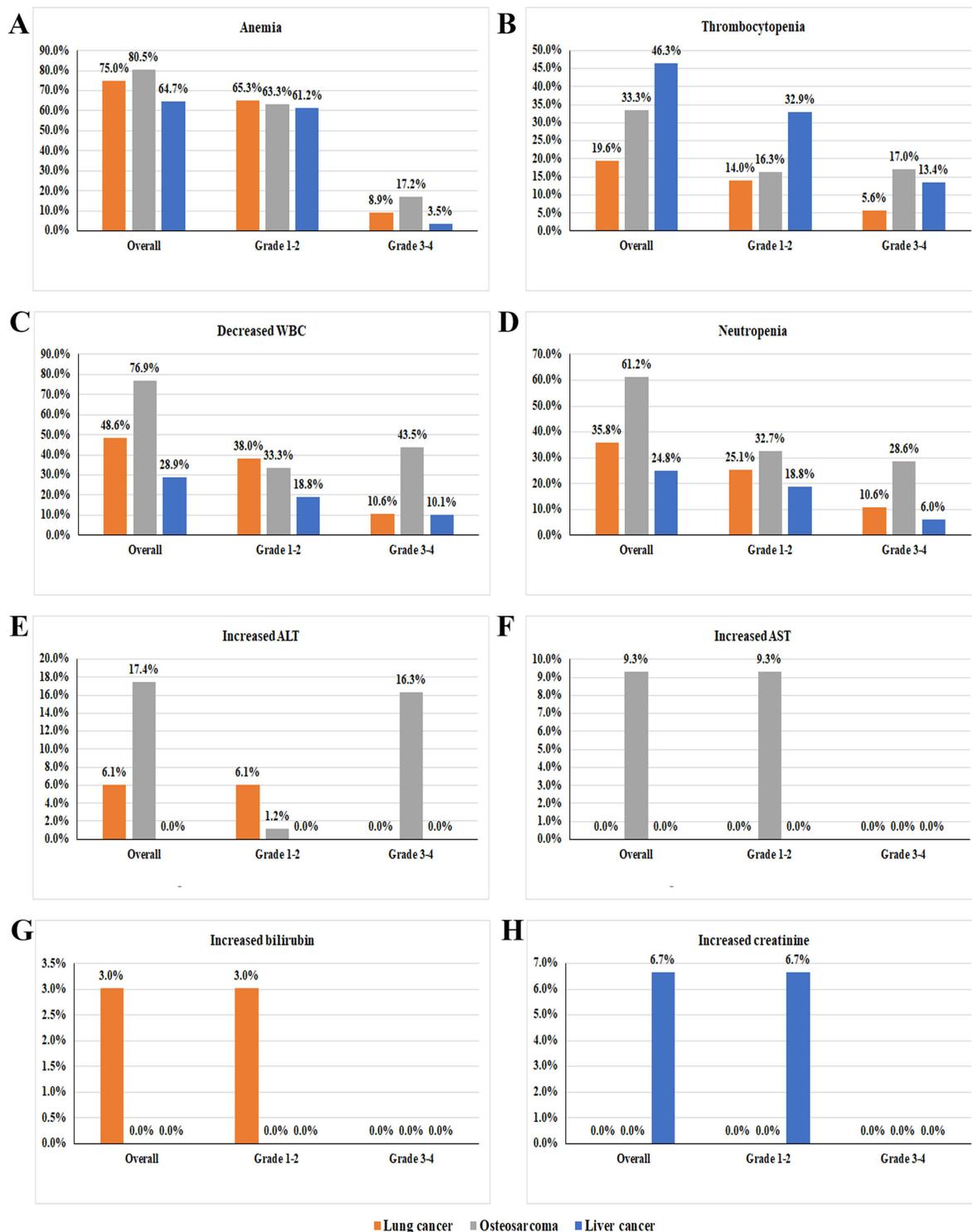


Figure 3

Occurrence of laboratory adverse events (grades 1-4) during treatment with Endostarin combination with chemotherapy for lung cancer, osteosarcoma, and liver cancer. (A) Anemia. (B) Thrombocytopenia. (C) Decreased WBC. (D) Neutropenia. (E) Increase ALT. (F) Increased AST. (G) Increased bilirubin. (H)

Increased creatinine. No grade 5 AE occurred. WBC, white blood cell; ALT, alanine transaminase; AST, aspartate aminotransferase.