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ORIGINAL ARTICLE

Meta-analysis of neutropenia or leukopenia as a prognostic factor in patients with malignant disease undergoing chemotherapy

Kohei Shitara · Keitaro Matsuo · Isao Oze · Ayako Mizota · Chihiro Kondo · Motoo Nomura · Tomoya Yokota · Daisuke Takahari · Takashi Ura · Kei Muro

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Abstract
Purpose We performed a systematic review and meta-analysis to determine the impact of neutropenia or leukopenia experienced during chemotherapy on survival.
Methods Eligible studies included prospective or retrospective analyses that evaluated neutropenia or leukopenia as a prognostic factor for overall survival or disease-free survival. Statistical analyses were conducted to calculate a summary hazard ratio and 95% confidence interval (CI) using random-effects or fixed-effects models based on the heterogeneity of the included studies.
Results Thirteen trials were selected for the meta-analysis, with a total of 9,528 patients. The hazard ratio of death was 0.69 (95% CI, 0.64–0.75) for patients with higher-grade neutropenia or leukopenia compared to patients with lower-grade or lack of cytopenia. Our analysis was also stratified by statistical method (any statistical method to decrease lead-time bias; time-varying analysis or landmark analysis), but no differences were observed.
Conclusions Our results indicate that neutropenia or leukopenia experienced during chemotherapy is associated with improved survival in patients with advanced cancer or hematological malignancies undergoing chemotherapy. Future prospective analyses designed to investigate the potential impact of chemotherapy dose adjustment coupled with monitoring of neutropenia or leukopenia on survival are warranted.

Keywords Chemotherapy · Neutropenia · Leukopenia · Prognostic factor · Meta-analysis

K. Shitara · A. Mizota · C. Kondo · M. Nomura · T. Yokota · D. Takahari · T. Ura · K. Muro
Department of Clinical Oncology,
Aichi Cancer Center Hospital, Chikusa-ku, Nagoya, Japan

K. Matsuo (✉) · I. Oze
Division of Epidemiology and Prevention,
Aichi Cancer Center Research Institute, 1-1 Kanokoden,
Chikusa-ku, Nagoya 464-8681, Japan
e-mail: kmatsuo@aichi-cc.jp

Introduction

Neutropenia or leukopenia induced by cytotoxic chemotherapy is a common adverse event in patients with cancer. In general, the recommended doses of cytotoxic agents are determined in dose-finding phase I studies. However, sample sizes in phase I studies are not large enough to examine individual differences in drug metabolism; therefore, toxicity profiles are likely to be highly variable [1]. In other words, the determined standard dose may be conservatively low for some patients with faster drug elimination times [1]. In support of this hypothesis, toxicities such as neutropenia or leukopenia experienced during chemotherapy have been reported to be associated with favorable clinical outcomes in several cancer types. Recently, we analyzed the neutropenia that occurs during first-line FOLFOX (infusional 5-fluorouracil/leucovorin and oxaliplatin) chemotherapy in patients with advanced colorectal cancer [2] or during second-line chemotherapy with weekly paclitaxel in patients with advanced gastric cancer [3], using time-varying covariate (TVC) analysis. Since several studies, including ours, have primarily been retrospective analyses that lacked a statistically testable hypothesis, we conducted the present meta-analysis to evaluate the prognostic impact of neutropenia or leukopenia on patients with advanced cancer undergoing chemotherapy with a statistical power much higher than that of each individual trial.

Patients and methods

Selection of studies

This study was performed to assess whether neutropenia or leukopenia has an important effect upon survival in patients with cancer undergoing chemotherapy. A systematic review and meta-analysis of published articles were performed. Two authors (KS and KM) conducted a literature search for trials through computer-based searches of the Medline database (January 1966 and May 20, 2010) and of abstracts from conference proceedings of the American Society of Clinical Oncology (1995–2010) and European Society for Medical Oncology (1995–2009).

Search keywords included "neutropenia", "leukopenia", "prognostic", and "chemotherapy". The search was also guided by a thorough examination of reference lists of original and review articles. No limitation based on language was defined. We included abstracts or unpublished data if sufficient information on study design, characteristics of participants, interventions, and outcomes was available.

Procedures

Two investigators (KS and KM) abstracted data, according to Quality of Reporting of Meta-analyses (QUORUM) guidelines. Each study was assessed for quality and potential bias using a structured checklist based on the Method for Evaluating Research and Guideline Evidence criteria [4]. Studies that met the following criteria were analyzed: patients with malignant disease treated with chemotherapy; prospective and retrospective analyses in randomized study or cohort study that evaluated neutropenia or leukopenia as a prognostic factor; and attainment of hazard ratio (HR) with 95% confidence interval (CI). Adverse events were assessed and recorded according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC; version 2 or 3), which have been adopted widely in cancer clinical trials, in as many cases as possible. For each study, the following information was extracted: first author's name; year of publication; study design (prospective or retrospective); number of enrolled patients; underlying malignant disease; median age; treatment regimen(s); methods of analysis, including specific analysis to decrease lead-time bias (i.e., landmark analysis or TVC analysis); methods of comparison (i.e., grade 0 vs. grade 1–4, grade 0–2 vs. grade 3–4, or mild vs. moderate); and HR and 95% CI for clinical outcome (overall survival or disease-free survival).

Statistical methods

For each study, a HR (and 95% CI) was derived according to neutropenia or leukopenia. If HRs according to both univariate and multivariate analysis were reported, HR in multivariate analysis was used in this analysis. To estimate a summary HR for death for patients with neutropenia or leukopenia, patients with lower-grade (grade 0, grade 0–2, or lowest tertile) versus higher-grade neutropenia or leukopenia were compared, since the cut-off values used to divide neutropenia or leukopenia into low versus high grades differed between studies. Some trials used tertiles without using NCI-CTC grades. For meta-analyses, both the fixed-effects model (weighted with inverse variance) and the random-effects model were used. Statistical heterogeneity among studies with the Q statistic was assessed, and inconsistency was quantified with the I^2 statistic. The assumption of heterogeneity was judged as invalid if $P < 0.1$. To investigate possible reasons for heterogeneity, subgroup analyses were performed by disease type or specific methods such as landmark analysis or TVC analysis, and meta-regression analyses were performed to test for variation in risk estimates by those variables. A cumulative meta-analysis was also performed. Publication bias was assessed by a funnel plot. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX, USA). All tests were 2-sided, and P values less than 0.05 were considered statistically significant.

Results

Selection of studies

A total of 753 potentially relevant reports were identified, of which 688 were initially excluded (Fig. 1). After a review of the remaining publications, 13 trials with sufficient data were identified for this meta-analysis, with a total of 9,528 patients [2, 3, 5–15]. Table 1 shows the baseline characteristics of patients from each trial. Malignant diseases included non-small cell lung cancer in three reports, breast cancer in three reports, gastric cancer in two reports, and colorectal cancer, uterine cervical cancer, ovarian cancer, esophageal cancer, and Hodgkin's lymphoma in one report each. Seven studies enrolled chemo-naive patients, one included pretreated patients, two evaluated chemotherapy in the adjuvant setting, and two assessed chemoradiotherapy for locally advanced disease. All studies used multivariate analysis to calculate HRs, and pretreatment neutrophil counts or leukocyte counts were included in five studies. Five studies used specific analysis methodology (landmark analysis in two and TVC analysis in three). Ten studies evaluated neutropenia, and three evaluated leukopenia. Six studies compared prognosis of patients without neutropenia or leukopenia to that of patients that experienced these cytopenias. Four studies compared patients

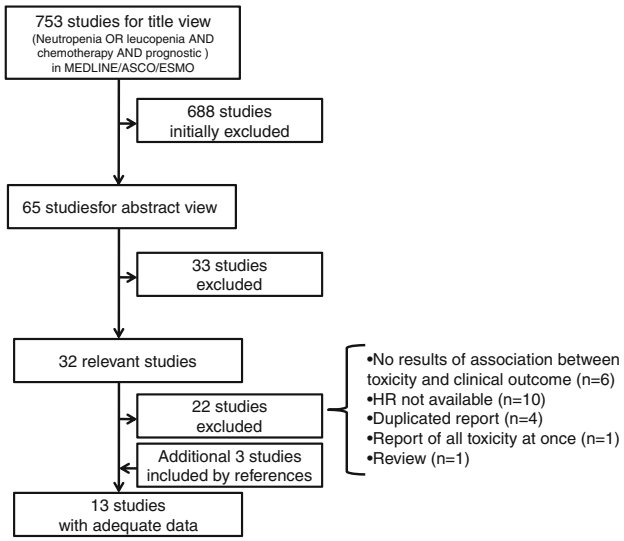

Fig. 1 Selection process for studies

with grade 0–2 versus grade 3–4 neutropenia. Two studies divided patients by tertile.

Survival analyses for neutropenia and leukopenia

The results of the meta-analysis revealed a combined estimate HR of 0.69 (95% CI, 0.64–0.75) (random-effects model) and 0.70 (95% CI, 0.65–0.75) (fixed-effects model). No apparent evidence for heterogeneity between these studies was detected ($P = 0.124$). A forest plot (Fig. 2) of the random-effects model analysis showed that eleven studies provided relatively similar HRs favoring higher-grade neutropenia or leukopenia, whereas the Kim et al. [11] and Miyoshi et al. [13] studies did not. The present analysis was also stratified by underlying disease (solid tumor in metastatic setting or solid tumor in adjuvant setting or hematologic malignancy; $P = 0.52$, Fig. 3), variable (neutropenia or leukopenia; $P = 0.55$), statistical method (landmark analysis or TVC analysis vs. without these methods; $P = 0.39$), and quality of report (low vs. high; $P = 0.46$); however, no differences were observed. Funnel plots showed that the possibility of bias is low (Fig. 4).

Discussion

We conducted the first meta-analysis to answer the question of whether patients with a higher grade of neutropenia or leukopenia during chemotherapy experienced superior survival compared to patients with lower-grade neutropenia or leukopenia. We found an approximately 30% risk reduction in mortality for patients with higher-grade cytopenias. Patients cannot be randomized to experience cytopenia or not, and so the only practical method of assessing the effect is by observational studies. These have a higher risk of bias than randomized trials, and so their results must be interpreted with caution, but well-conducted meta-analysis may reduce this risk. A lack of an obvious source of heterogeneity may support the consistency of our findings across heterogeneous methods of analysis, sites of malignancy, and clinical settings.

Based on our observation that patients who experience higher-grade neutropenia or leukopenia during chemotherapy have a better prognosis, we speculate that neutropenia, an indication of bone marrow suppression caused by a particular dose of a chemotherapeutic agent, may also be a surrogate marker that indicates that the same dose is adequate to provide an antitumor effect. Thus, lack of neutropenia or leukopenia may indicate a weak or absent biological effect by chemotherapy, which could possibly be caused by underdosing in an individual patient. Such underdosing may at least partly be the consequence of the methodology of phase I clinical trials in which the maximum tolerated dose (MTD) is selected according to body surface area (BSA) [7, 16]. Several studies have indicated that the pharmacokinetics of several cytotoxic drugs is poorly correlated with BSA due to inter-patient variability in metabolism (e.g., variability in enzymatic activity, genetic polymorphisms) [17–19]. If this inter-patient variability in pharmacokinetics is indeed a cause of underdosing, dose adjustment (increased or reduced) based on observed toxicity may be a possible solution. For example, dose increases of the epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab in the absence of skin toxicity have been shown to result in an improved objective response in patients with colorectal cancer [20].

Several other possible explanations in addition to chemotherapy dose may support the present findings. The first is the potential relationship between pretreatment neutrophil or leukocyte count and vulnerability to cytopenia during chemotherapy. Several reports have indicated that patients with high neutrophil or leukocyte counts prior to treatment might have a poor prognosis and be less likely to experience cytopenia during treatment [16, 21, 22]. However, our previous two studies [2, 3] and three other studies [8, 9, 12] included pretreatment neutrophil counts or leukocyte counts as adjusted factors, and these studies demonstrated that neutropenia or leukopenia experienced during chemotherapy was independently associated with prognosis. Therefore, this explanation is less likely to account for the findings of this meta-analysis.

Another possible explanation is that the association between cytopenia and prognosis is the result of bias introduced by the different analytical methods used in different studies. Since neutropenia does not exist prior to the initiation of chemotherapy, a false association between neutropenia and patient outcome might have been observed due to a

Table 1 Baseline characteristics of patients of the 13 included trials

Primary author	Year	Study type	Analysis	Disease	*n*	Setting	Treatment	Variable	Endpoint
Saarto [5]	1997	Prospective	MA	Breast	193	Adjuvant	AC, 5-FU	Leukopenia	DFS
Poikonen [6]	1999	Retrospective	MA	Breast	368	Adjuvant	CMF	Leukopenia	DFS
Di Maio [7]	2005	Prospective	MA with landmark[b]	NSCLC	1,265	Metastatic (1st-line)	GEM or VNR combinations	Neutropenia	OS
Klimm [8]	2005	Prospective	MA[a]	Hodgkin's lymphoma	4,626	1st-line	COPP/ABVD, BEACOPP ± RT	Leukopenia	FFTF
Yamanaka [9]	2007	Retrospective	MA[a] with TVC	Gastric	1,055	Metastatic (1st-line)	S-1	Neutropenia	OS
Pallis [10]	2008	Prospective	MA	NSCLC	858	Metastatic (1st-line)	GEM + DOC	Neutropenia	OS
Kim [11]	2009	Retrospective	MA	Cervical	107	Adjuvant	PTX + CBDCA + RT	Neutropenia	DFS
Kishida [12]	2009	Prospective	MA[a] with landmark	NSCLC	337	Metastatic (1st-line)	VNR + GEM followed by DOC vs. PTX + CBDCA	Neutropenia	OS
Miyoshi [13]	2009	Retrospective	MA	Esophageal	42	Preoperative	FP/FAP + RT	Leukopenia	OS
Shitara [2]	2009	Retrospective	MA[a] with TVC	Colorectal	153	Metastatic (1st-line)	FOLFOX ± BV	Neutropenia	OS
Kim [14]	2010	Retrospective	MA	Ovarian	179	Metastatic (1st-line)	PTX + CBDCA	Neutropenia	OS
Ishitobi [15]	2010	Retrospective	MA	Breast	103	Neoadjuvant	Epirubicin combination	Neutropenia	DFS
Shitara [3]	2010	Retrospective	MA[a] with TVC [c]	Gastric	242	Metastatic (2nd-line)	Weekly PTX	Neutropenia	OS

MA multivariate analysis, *TVC* time-varying covariate analysis, *NSCLC* non-small cell lung cancer, *AC* doxorubicin + cyclophosphamide, *5-FU* 5-fluorouracil, *CMF* cyclophosphamide + methotrexate + 5-fluorouracil, *C-MOPP* cyclophosphamide + vincristine + procarbazine + prednisone, *ABVD* adriamycin + bleomycin + vinblastine + dacarbazine, *BEA-COPP* bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisolone, *RT* radiotherapy, *VNR* vinorelbine, *GEM* gemcitabine, *DOC* docetaxel, *PTX* paclitaxel, *CBDCA* carboplatin, *DFS* disease-free survival, *OS* overall survival, *FFTF* freedom from treatment failure

[a] Pretreatment neutrophil counts or leukocyte counts were included

[b] Landmark analysis in 436 patients and out of landmark analysis in 829 patients

[c] TVC with landmark analysis in 202 patients

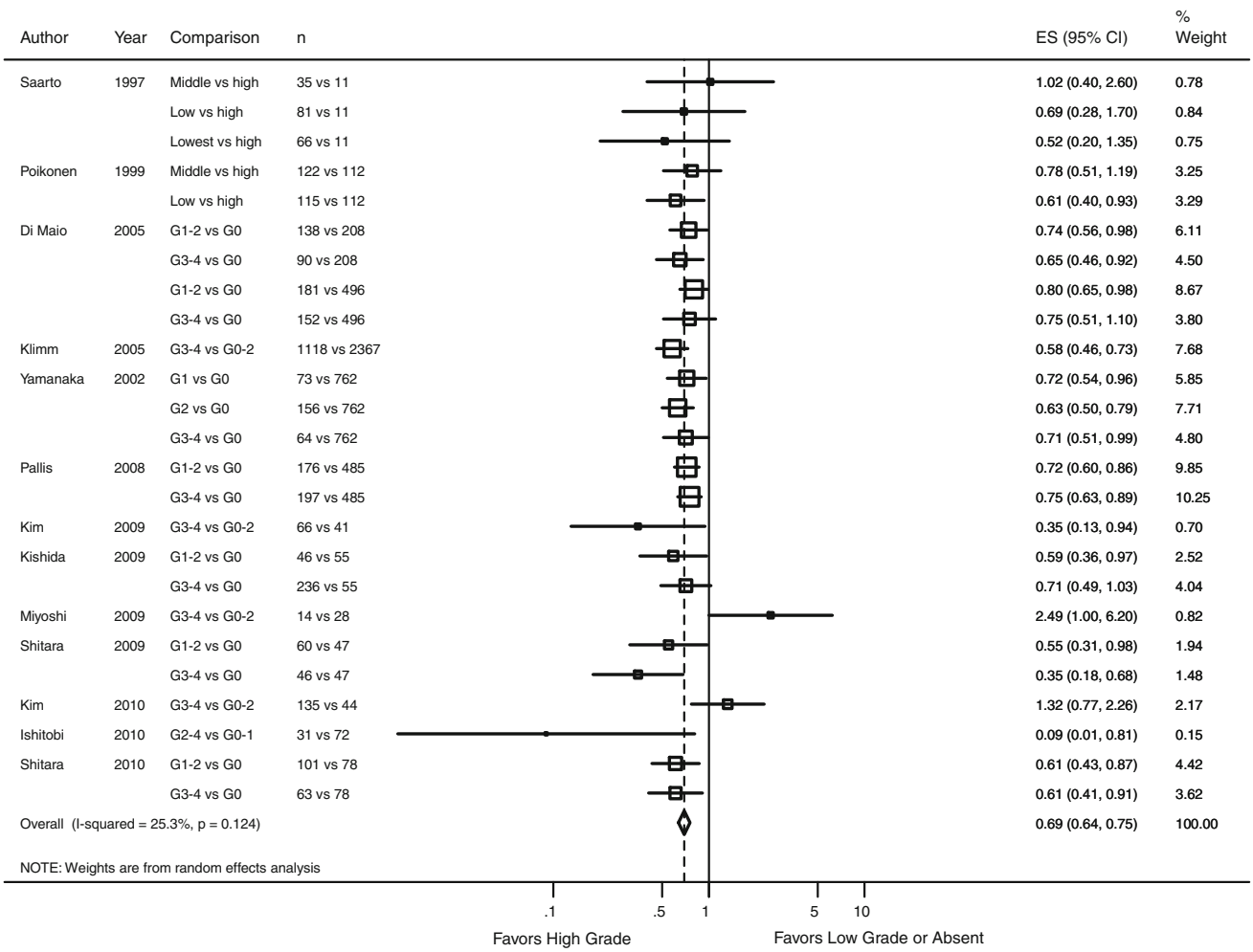

Fig. 2 Forest plots of hazard ratios. The size of the *gray markers* (*squares*) corresponds to the weight of the study in the meta-analysis. Combined hazard ratio was calculated using the random-effects model

higher incidence of neutropenia with increasing cycles of chemotherapy in patients with a better prognosis (lead-time bias). Therefore, some studies, including our previous studies, used landmark analysis and/or TVC analysis to decrease lead-time bias as much as possible. However, the present meta-analysis revealed the limited impact of survival analysis methods as shown by lack of significant heterogeneity. In our two previous studies in colorectal cancer [2] and gastric cancer [3], the majority of patients with neutropenia experienced their highest grade within 4 weeks of initiating treatment, and those who did not experience neutropenia during the first 4 weeks rarely experienced severe late-onset neutropenia. These observations support the possibility that false-positive association by lead-time bias is low and indicate that the impact of landmark analysis and/or TVC analysis is not high, as shown in this meta-analysis. The impact of neutropenia was shown in this study despite the treatment bias by severe neutropenia, which might reduce the effect of treatment by dose reduction or delay. Although the use of G-CSF was not evaluated in detail in each study, the possibility that G-CSF itself prolonged the survival of patients with neutropenia might be low.

This study has several methodological issues. Although the sample size was considered to be sufficient, the disease types and study settings were variable. Therefore, it is difficult to completely rule out potential heterogeneity across disease types. Second, the evaluation of neutropenia or leukopenia was performed differently in different studies; however, a lack of obvious heterogeneity among the results of different studies suggests this had little, if any, impact. Third, although most studies calculated HR using multivariate analysis, the variables used in multivariate analysis could have been insufficient. Fourth, although the funnel plot of our study suggested publication bias was low, there might be we did comprehensive literature search, the studies that failed to show an association between lack of neutropenia and outcome are less likely to have been published; therefore, this might have led to an exaggeration

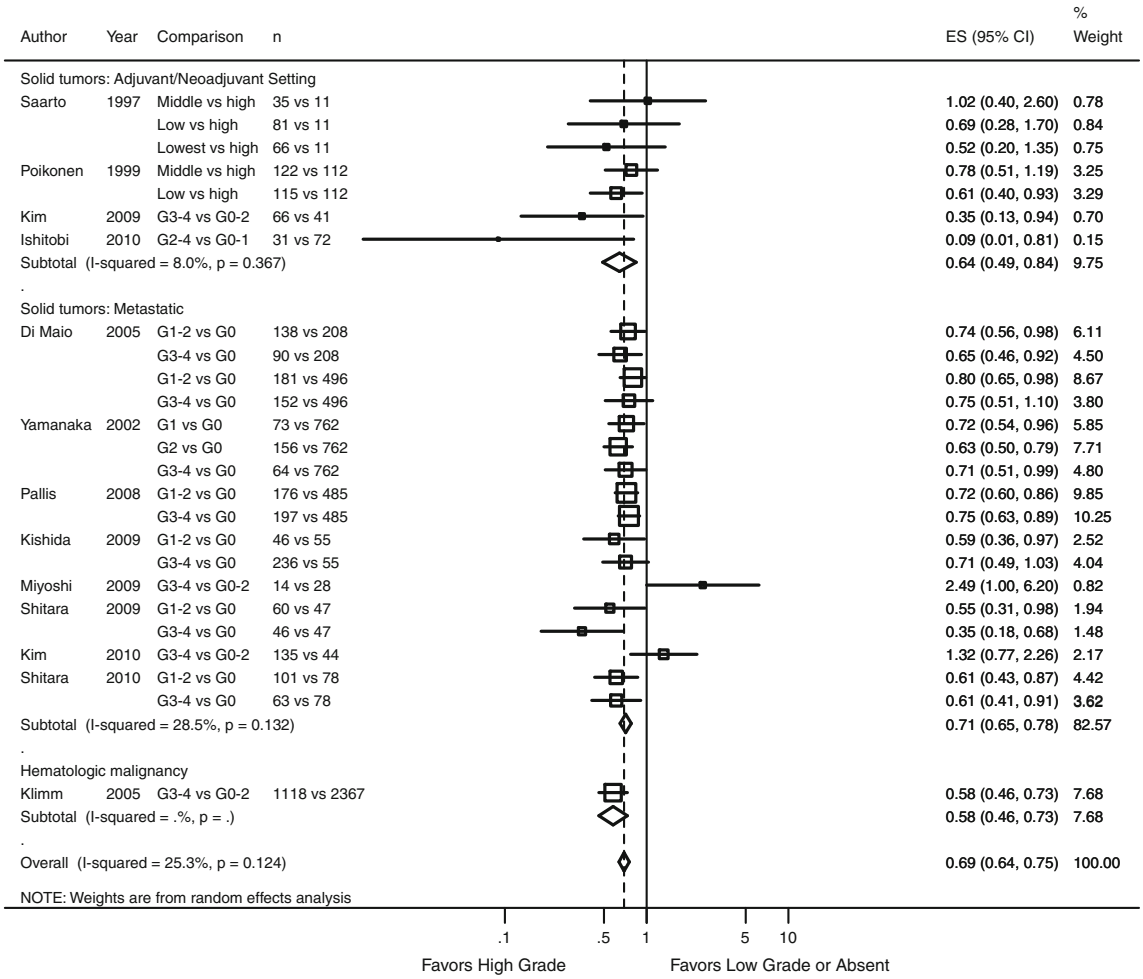

Fig. 3 Subset-analysis according to disease type

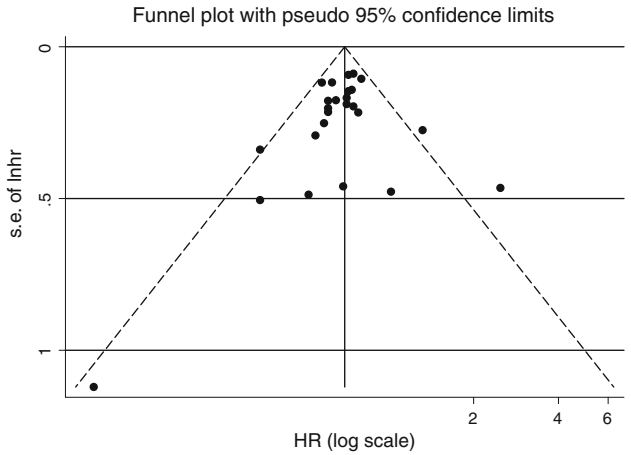

Fig. 4 Funnel plot of included studies

of the purported benefit in this meta-analysis. Ideally, an individual data-based meta-analysis might clarify this issue. Further study is warranted.

In conclusion, this meta-analysis indicated that neutropenia or leukopenia occurring during chemotherapy in patients with solid tumors or hematological malignancies is strongly associated with better prognosis. This suggests that neutropenia or leukopenia could be utilized as a surrogate marker to determine adequate antitumor doses of chemotherapeutic agents. An additional well-defined prospective trial designed to evaluate dose escalation in patients without neutropenia or leukopenia during the early course of treatment is warranted. We are currently planning a dose-escalation study of weekly paclitaxel in patients with advanced gastric cancer based on incidence of neutropenia.

Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

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