Efficacy of metronomic vinorelbine in elderly patients with advanced non-small-cell lung cancer and poor performance status

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ABSTRACT

Background Metronomic chemotherapy—administration of low-dose chemotherapy—allows for a prolonged treatment duration and minimizes toxicity for unfit patients diagnosed with advanced non-small-cell lung cancer (NSCLC).

Methods Oral metronomic vinorelbine at 30 mg thrice weekly was given to 35 chemotherapy-naïve patients who were elderly and vulnerable to toxicity and who had been diagnosed with advanced NSCLC.

Results Median age in this male-predominant cohort (29:6) was 76 years (range: 65–86 years). Histology was squamous cell carcinoma in 21 patients and adenocarcinoma in 14. There were no complete responses and 9 partial responses, for an overall response rate of 26%. Stable disease was seen in 15 patients (43%), and 11 patients (31%) had progressive disease. The 1-year survival rate was 34%, and the 2-year survival rate was 8%. The survival analysis showed a median progression-free survival duration of 4 months (range: 2–15 months) and an overall survival duration of 7 months (range: 3–24 months).

Conclusions Metronomic vinorelbine had an acceptable efficacy and safety profile in elderly patients with multiple comorbidities who had been diagnosed with advanced NSCLC. Metronomic vinorelbine could be a treatment option for elderly patients with poor performance status who are unfit for platinum-based chemotherapy and intravenous single-agent chemotherapy, and who are not candidates for combination modalities.

Key Words Metronomic vinorelbine, non-small-cell lung cancer, poor performance status

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in developing countries. It is the most common cancer in men and the 5th most common cancer in women in Turkey, with 81% of cases being diagnosed as stage III or IV.

Treatment for NSCLC depends on the tumour cell type, disease stage, molecular results, performance status (PS), comorbid illness, and overall social life of the patient. Most patients in developed countries are more than 65 years of age at the time of their NSCLC diagnosis. Medical oncologists might hesitate to start cytotoxic chemotherapy, especially when the patient has a poor PS with comorbid illness, is prejudiced against treatment choices, resides in a rural area, receives insufficient health care (especially in less-developed countries), and presents contraindications to multimodal treatments. In all of those cases, metronomic chemotherapy could be an appropriate option, as determined on a case-to-case basis. Metronomic chemotherapy, which is the consistent administration of low-dose chemotherapy, allows for a prolonged treatment duration and might minimize toxicity.

In the present study, we investigated the efficacy of oral metronomic vinorelbine in elderly patients with poor PS who were diagnosed with advanced NSCLC.
METHODS

Eligibility Criteria
Starting after December 2013, patients 65 years of age and older who were diagnosed with
adenocarcinoma or squamous cell carcinoma) in stage III or IV (according to
the 7th edition of the American Joint Committee on Cancer
staging manual), with measurable disease (based on the
Response Evaluation Criteria in Solid Tumors, version 1.1)
were eligible for the study. Other inclusion criteria were
an Eastern Cooperative Oncology Group (ECOG) of 2;
life expectancy of more than 3 months; ineligibility for
chemoradiation or surgery for stage III disease; EGFR and
ALK wild-type status, or status unknown because of an
insufficient pathology sample; unsuitability for systemic
intravenous chemotherapy (based on physician decision)
because of at least 1 serious comorbidity (such as hyperten-
sion, heart failure, chronic obstructive pulmonary disease,
cerebrovascular disease, valvular heart disease, diabetes
mellitus, or uncontrolled arrhythmia with 1 medication or
with hospitalization and treatment using an intravenous
antiarhythmic drug); need for caregiver support; and
refusal of intravenous chemotherapy. The exclusion crite-
ria were an ECOG of 0 or 1, inadequate hepatic or renal
function, insufficient bone marrow reserve, a history of
chemotherapy, and concomitant malignancies.

All patients provided informed consent before receiv-
ing treatment. Our retrospective study was approved by
the local ethics committee, and the procedures applied
accorded with the Helsinki Declaration. Staging was
performed using imaging by computed tomography or
positron-emission tomography. The baseline evaluation
included physical examination, ps determination, labora-
tory and radiologic evaluation, and a medical history. All
data were analyzed retrospectively. Toxicity was evaluated
according to the U.S. National Cancer Institute’s Common
Terminology Criteria for Adverse Events, version 4.0.

Study Design and Treatment
Oral vinorelbine was started at a dose of 30 mg (1 capsule)
thrice weekly (every Monday, Wednesday, and Friday) until
disease progression or grade 4 toxicity. The vinorelbine cap-
sules were to be taken after a meal, without chewing, and
primary antiemetic prophylaxis with a serotonin receptor
antagonist was recommended.

The dose was to be reduced to 20 mg thrice weekly
up on the occurrence of a first grade 3 or 4 toxicity or upon
persistent grade 2 toxicity with reduced quality of life. If
the grade 3 or 4 toxicity continued, treatment was to be
stopped; if the toxicity abated to grade 2, the dose was to
be reduced to 20 mg twice weekly (every Monday and Friday),
and then permanently stopped if necessary.

The patients received palliative treatment as needed.
“One-step dose reduction” meant dose reduction after the
1st month of treatment. Patients who received assistance
for more than half their activities of daily living during the
daytime were considered to have caregiver support.

All patients were evaluated during the first 7–10 days
after starting vinorelbine and then monthly thereafter.
Each follow-up visit included a complete blood count and
liver and kidney function tests based on blood samples. If a
patient had a specific complaint, the appropriate test—such
as echocardiography, hormone test, or radiologic exam—
was ordered. All patients were followed by computed tomo-
ography to determine tumour response every 3 months
in year 1 and every 4–6 months thereafter.

Statistical Analyses
All statistical analyses were performed using the IBM SPSS
Statistics software application (version 22.0: IBM, Armonk,
NY, USA). Continuous data are summarized as medians,
with minimum and maximum values; categorical data are
expressed as frequencies and percentages. Confidence
intervals were calculated at the 95% level. Time-dependent
values were analyzed by the Kaplan–Meier method. Un-
paired t tests were used for data with a normal distribution,
and the Mann–Whitney U-test was used for data with a
non-normal distribution. Correlations were determined
using the Spearman rho. Overall survival was analyzed by
the Kaplan–Meier method and Cox regression analysis. All
p values are two-tailed.

Primary efficacy was defined as either a complete
(CR) or a partial response (PR); the overall response rate
was defined as the disease control rate [CR plus PR plus
stable disease (SD)]. Survival curves for progression-free
survival (PFS) and overall survival (OS) were constructed by
the Kaplan–Meier method, and log rank tests were used to
evaluate the differences between groups. Cox proportional
hazards models (univariate and multivariate) were used to
evaluate variables that are potentially prognostic for PFS,
including sex, age, PS, histologic subtype, T stage, N stage,
clinical stage, and treatment method. Safety and toxic-
ity analyses were performed for patients who received at
least 1 dose of the study treatment. Values of p < 0.05 were
considered statistically significant.

RESULTS

Patient Characteristics
The study included 35 patients with a median age of 76
years (range: 65–86 years) and a male predominance of
29.6. Table 1 shows the baseline characteristics of the study
population. Histology was squamous cell carcinoma in 21
patients and adenocarcinoma in the remaining 14. None of
the adenocarcinoma patients had a known EGFR or ALK
status, and all patients had an ECOG of 2 with a median
of 2 comorbid illnesses (range: 1–5 comorbid illnesses).
The most common of the comorbid illnesses were chronic
obstructive pulmonary disease [which was diagnosed in
26 patients (74%), 5 of whom used oxygen therapy] and
hypertension [which was present in 20 patients (57%), most
of whom used combination therapy]. Heart failure was diag-
nosed in 10 patients (29%), 3 of whom had an ejection frac-
tion of less than 35%; and diabetes mellitus was present in
7 patients (20%), all of whom were receiving insulin therapy.
In addition, 5 patients (14%) had undergone coronary artery
bypass graft, all of whom had an ejection fraction less than
50%, with 3 patients having an ejection fraction less than
35%. A cerebrovascular event with sequelae had occurred
in 5 patients (14%) who therefore required caregiver sup-
port, and 4 patients (11%) had cardiac arrhythmia. In this
cohort, 15 patients (43%) required caregiver support from
family members; 1 patient lived in a nursing home. Brain metastases had occurred in 2 patients, who were treated with whole-brain radiation before the study chemotherapy.

**TABLE I** Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>35</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>76</td>
</tr>
<tr>
<td>Range</td>
<td>65–86</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>29</td>
</tr>
<tr>
<td>Women</td>
<td>6</td>
</tr>
<tr>
<td>ECOG PS (n)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>Stage (n)</td>
<td></td>
</tr>
<tr>
<td>III/IVB</td>
<td>14</td>
</tr>
<tr>
<td>IV</td>
<td>21</td>
</tr>
<tr>
<td>Histology [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Smoking status (n)</td>
<td></td>
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<tr>
<td>Never-smoker</td>
<td>2</td>
</tr>
<tr>
<td>Past smoker</td>
<td>29</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4</td>
</tr>
<tr>
<td>Metastatic site [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (28)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Brain</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Mean laboratory values</td>
<td></td>
</tr>
<tr>
<td>AST (IU/μL)</td>
<td>18.9±10</td>
</tr>
<tr>
<td>ALT (IU/μL)</td>
<td>16±13</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9±0.6</td>
</tr>
<tr>
<td>Platelet count (&gt;1000/mL)</td>
<td>299±145</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.1±1.9</td>
</tr>
<tr>
<td>White blood cells (/mL)</td>
<td>9300±3800</td>
</tr>
<tr>
<td>Body mass index</td>
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</tr>
<tr>
<td>Median</td>
<td>21</td>
</tr>
<tr>
<td>Range</td>
<td>17–26</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
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</tr>
<tr>
<td>Median</td>
<td>1.5</td>
</tr>
<tr>
<td>Range</td>
<td>1.25–1.8</td>
</tr>
<tr>
<td>Comorbidities [n (%)]</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 (11)</td>
</tr>
<tr>
<td>2</td>
<td>15 (43)</td>
</tr>
<tr>
<td>3</td>
<td>10 (29)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>6 (17)</td>
</tr>
</tbody>
</table>

ECOG PS = Eastern Cooperative Oncology Group performance status; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

**Treatment**

Median follow-up in the group was 7 months (range: 3–24 months). All patients received at least 1 cycle of vinorelbine (360 mg during 1 month), and the median dose during the study period was 1440 mg (range: 360 mg–5400 mg). In this cohort, 87% of patients received vinorelbine without a dose reduction; in 13%, dose reduction was used. Only 1 patient did not receive subsequent cycles of vinorelbine, having refused the treatment.

Two patients of advanced age with heart failure started on 30 mg vinorelbine thrice weekly; however, after the 1st vinorelbine tablet was given, the dose was reduced to 20 mg thrice weekly. In those 2 patients, ejection fraction remained stable at 30%. Clinically, however, the patients had mild edema and physical activity restrictions; thus, their heart failure medications had to be adjusted. A one-step dose reduction to 20 mg thrice weekly occurred in 5 patients (because of fatigue in 3 patients and neutropenia in the other 2). In 2 patients, a two-step dose reduction to 20 mg twice weekly was required because of grade 2 diarrhea and thrombocytopenia. After the dose reductions, the patients did not complain of any further significant toxicity. High treatment compliance was observed in the study population.

**Efficacy**

At the time of the final analyses, 22 of the 35 patients had died. All patients were evaluable for both efficacy and safety. The group experienced 9 prs and no crs, for an overall response rate of 26%, with 15 patients having sd (43%), and 11 patients (31%) having progressive disease. The 1- and 2-year survival rates were 34% and 8% respectively. The survival analysis showed a median pfs of 4 months (range: 2–15 months) and a median os of 7 months (range: 3–24 months; Table ii, Figure 1). Only 2 patients were able to receive weekly paclitaxel as second-line chemotherapy. The pfs and os analyses showed no significant differences by histologic subtype (squamous cell carcinoma and adenocarcinoma).

**Toxicity and Quality of Life**

No deaths related to treatment toxicity occurred, and only 1 patient had grade 3 fatigue and diarrhea that required hospitalization. Grades 3 and 4 toxicities were rare, especially in patients with severe heart failure (ejection fraction less than 35%) and in immobile patients with cerebrovascular events. No incidences of febrile neutropenia, transfusion-requiring anemia, or thrombocytopenia occurred.

Regardless of severity, the main toxicities observed were neutropenia (22% of patients), anemia (14%), and fatigue (17%). Among the gastrointestinal toxicities observed were nausea (14%), diarrhea (8%), constipation (8%), and vomiting (4%); however, most events were assessed as grade 1 or 2. Just 1 patient was admitted to hospital for a gastrointestinal toxicity.

**DISCUSSION**

In the present study, we showed that a metronomic 30 mg dose of vinorelbine given thrice weekly until disease progression is a safe and effective treatment regimen for elderly patients.
patients with advanced NSCLC who are not candidates for systemic intravenous chemotherapy or multimodal approaches. The median PFS was 4 months (range: 2–15 months), and the median OS was 7 months (range: 3–24 months). The 1- and 2-year survival rates were 34% and 8% respectively.

Single-agent chemotherapy should be the first-line treatment for selected populations, especially elderly and frail patients. Platinum derivatives could also be options; however, comorbidities and organ function can be a barrier to the latter choice. Thus, metronomic therapies have recently attracted interest. Vinorelbine was developed as an intravenous drug, although it is currently available in an oral formulation. It has a relatively safe profile and can be used both as monotherapy and as part of combination regimens.

Increasingly, the research involving vinorelbine has focused on elderly and unfit patients diagnosed with NSCLC. Earlier studies used vinorelbine mostly in combination chemotherapy. In a phase II trial in locally advanced NSCLC, 54 patients were treated with chemoradiation that included oral vinorelbine plus cisplatin; the investigators found a 54% response rate with a PFS of 12.5 months and an OS of 23.4 months. A similar regimen in another phase II trial showed a 65% response rate. Lastly, vinorelbine as a single agent with radiation therapy was well tolerated, and the response rate was approximately 60%. In combination trials in NSCLC, an acceptable safety and efficacy profile was observed with vinorelbine plus platinum-based chemotherapy, as well as with oral or intravenous formulations of vinorelbine alone, compared with platinum plus taxanes.

In our clinical practice, many of the patients diagnosed with NSCLC are of older age or have poor PS, potentially needing caregiver support or having multiple comorbidities. In addition, they can have social problems, which, together with their poor PS, make the selection of the optimal treatment choice challenging. Those patients should therefore be evaluated in terms of the risk–benefit ratio of treatment. Many prefer oral rather than intravenous treatment.

![TABLE II](image)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (33)</td>
</tr>
<tr>
<td>Survival [n (%)]</td>
<td></td>
</tr>
<tr>
<td>1-Year</td>
<td>12 (34)</td>
</tr>
<tr>
<td>2-Year</td>
<td>3 (9)</td>
</tr>
<tr>
<td>PFS duration (months)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>2–15</td>
</tr>
<tr>
<td>OS duration (months)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
</tr>
<tr>
<td>Range</td>
<td>3–24</td>
</tr>
<tr>
<td>Dose reduction rate (%)</td>
<td>13</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; OS = overall survival; Gr = grade.

![FIGURE 1](image)

FIGURE 1 Kaplan–Meier plots of (A) progression-free survival (PFS) and (B) overall survival (OS) in the patient cohort. Cum = cumulative.
in that study, compared with all the patients in the present work, had an ECOG PS of 2. Thus, we can speculate that metronomic vinorelbine has an efficacy comparable with that for intravenous vinorelbine. Other data also support that hypothesis. In a phase II trial, Jassem et al.\textsuperscript{17} compared oral with intravenous vinorelbine in 115 patients diagnosed with stage IIB or IV NSCLC. The efficacies of the two dosage forms were similar; the objective response rates were, respectively, 12% and 11%; and the OS durations were 9.3 and 7.9 months.

A phase I trial investigated the oral vinorelbine dose in patients with advanced NSCLC. Oral doses of vinorelbine up to 30 mg daily do not have dose-limiting toxicity, and 50 mg daily is the maximum tolerated dose\textsuperscript{18}. In a phase II study, 46 heavily pretreated NSCLC patients received 50 mg oral metronomic vinorelbine thrice weekly. Median OS was 9.4 months, and the 1-year survival rate was 30.1%. Grade 3 or 4 neutropenia was observed in 23.9% of cases, and febrile neutropenia in 10.9% of patients. Grade 3 fatigue was the most common severe nonhematologic toxicity (10.9%)\textsuperscript{19}. Given those findings, we hesitated to give a dose of 50 mg thrice weekly to our elderly patients with a poor PS.

In an Asian phase II trial, chemotherapy-naïve patients 70 years of age and older with advanced NSCLC were randomized to receive either oral erlotinib 150 mg daily or oral vinorelbine 60 mg/m\textsuperscript{2} on days 1 and 8 every 3 weeks. Erlotinib was found to be superior to vinorelbine in terms of objective response rate and PSs, but the difference in OS was not statically significant (median survival duration: 11.6 months vs. 9.3 months respectively)\textsuperscript{20}.

Thus far, three studies in groups similar to our study population have been published. Two of those studies used (non-metronomic) oral vinorelbine, and one applied metronomic oral vinorelbine\textsuperscript{14,21,22}. Kosmidis et al.\textsuperscript{22} compared two single agents, paclitaxel (intravenous) and vinorelbine (oral), in NSCLC patients with an ECOG PS of 2. The drug doses were 60 mg/m\textsuperscript{2} vinorelbine given orally on days 1, 8, and 15 every 4 weeks and 90 mg/m\textsuperscript{2} paclitaxel given intravenously for 1 hour on days 1, 8, and 15 every 4 weeks. No significant difference in the objective response rate (CR + PR) was found between the two groups (20% and 31% respectively), and the survival analyses also showed no significant differences. The OS was 2.1 months for patients in the vinorelbine group and 2.6 months for those in the paclitaxel group ($p = 0.49$). The OS durations were 3.1 months and 5.1 months respectively ($p = 0.95$)\textsuperscript{22}. The OS duration in that trial was lower than in the present work (3.1 months vs. 7 months), although both studies included only patients with an ECOG PS of 2.

There could be reasons for some of the differential findings in the two studies. The trial by Kosmidis et al. had more patients with stage IV disease (86% vs. 60%), and the study population included patients who had previously received radiation therapy (28%), which might have resulted in higher toxicity. Further, the patients in the Kosmidis et al. study experienced more grades 3 and 4 toxicity, especially hematologic toxicity. That toxicity profile was not significantly different from the profile in the paclitaxel group; overall, however, toxicities were more common in their cohort than in ours. Metronomic oral vinorelbine might result in fewer toxicities than oral vinorelbine: we gave nearly 60 mg/m\textsuperscript{2} vinorelbine as a metronomic regimen (30 mg on days 1, 3, and 5 weekly); the previous studies gave oral vinorelbine at 60 mg/m\textsuperscript{2} once weekly.

Camerini et al. published two reports on this topic, showing survival results similar to those observed in the present work. The first trial\textsuperscript{23} investigated the efficacy of single-agent oral vinorelbine (60 mg/m\textsuperscript{2} on days 1–8 every 3 weeks) in 43 elderly patients with poor PS diagnosed with advanced NSCLC. The overall clinical response to oral vinorelbine (CR + PR + SD) was about 50%. The median OS was 4.0 months (range: 2–22 months), and the median OS was 8.0 months (range: 3–35 months). In that study, 46% of patients had previously received chemotherapy; thus, grades 1 and 2 and nonhematologic toxicities were especially common (range: 10%–48%). The more recent study\textsuperscript{14} investigated the role of oral metronomic vinorelbine as a single agent in the first-line treatment of elderly patients with advanced NSCLC. That study included 43 chemotherapy-naïve elderly patients (70 or more years of age), with a PS of 0–2 in stages IIB–IV NSCLC. The objective response rate was 18.6%, with 7 PRs and 1 CR. Of the 43 patients, 17 had SD lasting more than 12 weeks, and the clinical response rate was 58%. The median OS in the study was 5 months (range: 2–21 months), and the median OS was 9 months (range: 3–29 months). In addition, the 1- and 2-year survival rates were 37.2% and 9.3% respectively\textsuperscript{14}.

Our study population included only patients with an ECOG PS of 2 and multiple comorbidities; however, we found survival and efficacy rates comparable to those in the Camerini et al. trials\textsuperscript{14,21}. The lower toxicity and improved safety profile were also similar. Metronomic vinorelbine might therefore be a better choice than non-metronomic protocols of oral vinorelbine, a possibility supported by the findings of Camerini and colleagues. The nonhematologic toxicity profile of metronomic vinorelbine was better than that in the first trial by Camerini et al.\textsuperscript{21}.

In addition to directly killing tumour cells, metronomic chemotherapy is now known to have other antitumour effects, such as reduction of T-regulatory cells and prevention of immune escape. Continuous administration of the drug in low doses also lessens tumour angiogenesis and inhibits circulating endothelial progenitor cells\textsuperscript{23}. Thus, metronomic chemotherapy could be a good choice in certain cancer types and in selected patients, as well as in some combination or maintenance therapies.

A major limitation of our research is its retrospective design, although the analyses included real data on the metronomic schedule of elderly patients with poor PS. We chose a dose of 30 mg thrice weekly because, compared with previous studies, our study population included patients with a poorer PS and multiple comorbidities, most of whom refused intravenous chemotherapy.

CONCLUSIONS

The present study showed that metronomic vinorelbine had an acceptable efficacy and safety profile in elderly patients with multiple comorbidities who had been diagnosed with advanced NSCLC. Consistent with earlier studies, our results indicate that metronomic vinorelbine could represent a treatment option for elderly patients with poor PS who are...
not candidates for systemic intravenous chemotherapy or combination modalities.

ACKNOWLEDGMENTS

We thank the investigators and staff of the Young Medical Oncologists Group of the Turkish Medical Oncology Society for their dedicated efforts.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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