DOI: 10.14744/ejmi.2021.12734
EJMI 2021;5(1):107–112

Research Article

Pre-Treatment Lymphopenia and NLR May Have Prognostic Value in Turkish High-Grade Glial Tumor Patients

Ali Murat Sedef,[1] Zuleyha Calikusu,[2] Aykut Bahceci,[3] Serkan Gokcay,[1] Ahmet Taner Sumbul[4]

[1]Department of Medical Oncology, Sanliurfa Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey
[2]Department of Medical Oncology, Acıbadem Mehmet Ali Aydinlar University, Adana, Turkey
[3]Department of Medical Oncology, Ersin Arslan Training and Research Hospital, Gaziantep, Turkey
[4]Department of Medical Oncology, Baskent University Faculy of Medicine, Adana, Turkey

Abstract

Objectives: We aimed to determine the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocytopenia in Turkish high-grade glial tumor patients.

Methods: This study was designed as a hospital-based retrospective observational case series study. A total of 111 patients with recurrent glioblastoma multiforme (GBM) at four different oncology centers in Turkey between 2009 and 2017 have included to our study.

Results: All of the patients (n=111) had recurrent disease. Sixty-nine (62.2%) patients died and overall survival (OS) was estimated 28 months. Cutoff NLR value is found as 3.06. The OS of patients who had low NLR was statistically significantly longer than the patients who had high NLR (30 months vs. 23 months, p=0.008). The OS of patients with lymphocytopenia was statistically significantly worse than the other group (24 months vs. 30 months, p=0.04). Progression-free survival was estimated 8 months. Median PFS was statistically better in GBM than the astrocytoma (8 months vs. 4 months, p=0.03).

Conclusion: In our study, we showed that high NLR and lymphocytopenia may also have prognostic value in recurrent Turkish high-grade glial tumor patients and the present findings confirm that these markers may be used to predict the mortality risks for these patients.

Keywords: NLR, recurrent glial tumor, PLR

Cite This Article: *Sedef AM, Calikusu Z, Bahceci A, Gokcay S, Sumbul AT. Pre-Treatment Lymphopenia and NLR May Have Prognostic Value in Turkish High-Grade Glial Tumor Patients. EJMI 2021;5(1):107–112.*

High-grade gliomas are malignant brain tumors that are divided into anaplastic gliomas (anaplastic astrocytoma and anaplastic oligodendroglioma) and glioblastoma. Modern classification of gliomas is based on the World Health Organization classification of central nervous system tumors. High-grade gliomas are malignant, often rapidly progressive brain tumors. Patients with high-grade glioma present with neurologic signs and symptoms that vary according to the location of the tumor within the brain. Standard therapy is the combination of temozolomide with concomitant chemoradiotherapy and adjuvant temozolomide after maximal surgical resection.[1,2] Despite these treatments, median overall survival (OS) and 2-year survival rates were 14.6 months and 26.5%, respectively, and the prognosis is very poor.[3] Treatment options for recurrent disease are limited. New targets are being identified such as

Address for correspondence: Ali Murat Sedef, MD. Sanliurfa Mehmet Akif İnan Egitim ve Arastirma Hastanesi, Tıbbi Onkoloji Klinigi, Sanliurfa, Turkey
Phone: +90 507 701 92 97 **E-mail:** alimuratsedef@gmail.com

Submitted Date: April 20, 2020 **Accepted Date:** March 02, 2021 **Available Online Date:** April 01, 2021

the anti-VEGF monoclonal antibody bevacizumab has produced dramatic radiologic responses and prolonged PFS. [4,5] The most commonly used treatment regimen is known as irinotecan-bevacizumab. Important factors affecting outcome and survival in high-grade glioma are age, performance status, histologic type and grade, and increasingly well-characterized molecular factors, including O6-methylguanine-DNA methyltransferase promoter methylation, 1p/19q-codeletion (primarily in oligodendroglial tumors), and mutations in isocitrate dehydrogenase Type 1 or Type 2. However, these molecular tests are not feasible and cost effective for all cancer centers. Therefore, more easily applicable prognostic markers are needed for high-grade glial tumors before starting therapy.

There are limited studies in the literature showing the prognostic significance of systemic inflammation biomarkers for glioblastoma multiforme (GBM) patients. Our aim in this study was to evaluate the prognostic significance of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocytopenia in Turkish high-grade glial tumor patients.

Methods

We designed this study to evaluate the prognostic role of systemic inflammation biomarkers in recurrent high-grade glial tumor patients. This study was a hospital-based retrospective observational case series study. One hundred and eleven patients were included in the study from Sanliurfa Mehmet Akif Inan Training and Research Hospital, Acıbadem Mehmet Ali Aydinlar University, Gaziantep Ersin Arslan Training and Research Hospital, and Baskent University Departments of Medical Oncology between the years of 2009 and 2017. The systemic inflammation biomarkers of the patients at the diagnosis were recorded. Cutoff NLR and PLR values are calculated with ROC analysis. The NLR and PLR values were divided into two separate groups: High NLR (>3.06, n=56) versus low NLR (≤3.06, n=55) and high PLR (>163, n=54) versus low PLR (≤163, n=57). Kaplan-Meier survival analyses and Cox proportional hazard models were used to examine the effects of NLR and PLR on OS.

Ethical Approval

Ethical approval was not required based on the law and the national ethical guidelines of our country and written informed consent was not required for individual patient because of retrospective nature. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical Analysis

All results were presented as the rate for categorical values or mean and median for continuous variables. Clinical and statistical significant correlation between continuous variables was calculated by Spearman's rank correlation test, Spearman's correlation coefficient (rs) and P value (two tailed) were noted. OS was defined by the time from the date of death and last control minus the 1st day of the chemotherapy. Survival curves were estimated according to the Kaplan-Meier method, and log-rank tests were used for univariate statistical comparisons. Adjusted hazard ratio and 95% confidence interval (CI) were used for estimation. Receiver operating characteristic curve analysis was performed to determine the NLR cutoff. All statistical data were analyzed using the SPSS version 17.0, and $p<0.05$ was considered statistically significant.

Results

Study Patients

Patient and tumor characteristics are shown in Table 1. The median age of the patients was 50 (range 18-83) years and 70 (63.1%) patients were male. All of the patients (n:111) had recurrent disease. Majority of patients had European Cooperative Oncology Group (ECOG) performance score 0 and 1 (n=63, 56.8% and n=45, 40.5%, respectively), small percentage of patients (n=3, 2.7 %) had ECOG performance score 2. Histologically, patients were divided into two groups as GBM and astrocytoma (n=85, 76.6% and n=26, 23.4%, respectively). The most common site of tumor localization was the frontal lobe (n=25, 22.5%). All patients received temozolomide as adjuvant treatment. All patients received irinotecan-bevacizumab treatment for recurrent disease. The number of cycles of the patient with the longest duration of treatment was 83. Twenty (18%) patients underwent surgery for recurrent disease and 24 (21.6%) patients received radiotherapy for recurrent disease.

Treatment and Outcomes

The median follow-up time was 23 months and 69 (62.2%) patients died and OS was estimated 28 months (23.2-32.8, 95% CI) (Fig. 1). All patients recurred after adjuvant treatment and median recurrence-free survival was 10 months (8.5-11.5, 95% CI). All patients received irinotecan-bevacizumab combination regimen and 74 (66.7%) patients were progressed with this treatment. Progression-free survival (PFS) was estimated 8 months (6.3-9.7, 95% CI) (Fig. 2). Complete response was obtained in 11 (10%) patients after irinotecan-bevacizumab treatment. Treatment outcomes are shown in Table 2.

Table 1. Patient and tumor characteristics

Characteristics	n (%)
Median age	50 (18-83) years old
Gender	
Men	70 (63.1)
Women	41 (36.9)
European Cooperative Oncology Group	
0	63 (56.8)
1	45 (40.5)
2	3 (2.7)
Histology	
GBM	85 (76.6)
Astrocytoma	26 (23.4)
Localization	
Frontal lobe	25 (22.5)
Temporal lobe	22 (19.8)
Parietal lobe	12 (10.8)
Frontoparietal lobe	12 (10.8)
Frontotemporal lobe	12 (10.8)
Others	28 (25.3)
NLR	
≥3.06	56 (50.5)
<3.06	55 (49.5)
PLR	
≥163	54 (48.6)
<163	57 (51.4)
Lymphocytopenia	
Yes	53 (47.7)
No	58 (52.3)

GBM: Glioblastoma multiforme; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 2. Treatment and outcomes

Characteristics	n (%)
Recurrent surgery	
Yes	20 (18)
No	91 (82)
Reradiotherapy	
Yes	24 (21.6)
No	87 (78.4)
Response to "İri-Beva"	
Stable disease	20 (18.2)
Partial response	65 (59.1)
Complete response	11 (10)
No response	14 (12.7)
Progression with "İri-Beva"	
Yes	74 (66.7)
No	37 (33.3)
Final status	
Died	69 (62.2)
Alive	42 (37.8)

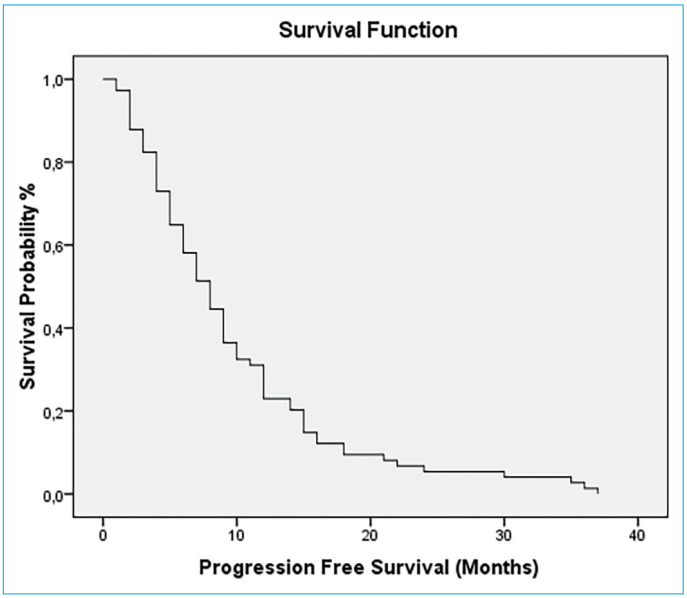

Figure 2. Progression-free survival (PFS) was estimated 8 months (6.3-9.7, 95% CI).

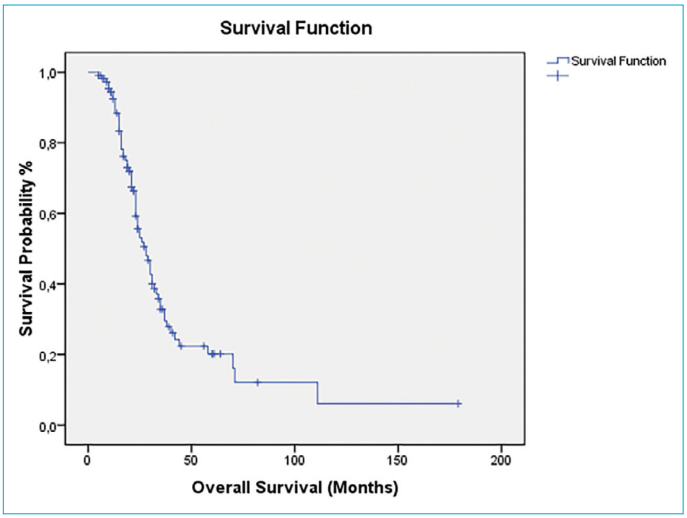

Figure 1. OS was estimated 28 months (23.2-32.8.95% CI).

The association of systemic inflammatory markers with PFS and OS is shown in Table 3. PFS in the high NLR (>3.06) group was worse than the low NLR (<3.06) group, but there was no statistical significance (6 months vs. 9 months, p=0.10). Similarly, there was no statistically significant difference for PFS between high PLR (>163) and low PLR (<163) groups (8 months vs. 7 months, p=0.69). Median PFS was statistically better in GBM than the astrocytoma (8 months vs. 4 months, p=0.03) (Fig. 3). There was no statistically significant relationship between the presence of lymphocytopenia and PFS (7 months vs. 8 months, p=0.35).

The OS of patients who had low NLR was statistically significantly longer than the patients who had high NLR (30

Table 3. Relationship between systemic inflammatory response markers with survival analysis

Variables	Median OS		Median PFS	
	Months	p	Months	p
NLR				
High (≥3.06)	23	0.008[a]	6	0.10
Low (<3.06)	30		9	
PLR				
High (≥139.8)	24	0.30	8	0.69
Low (<139.8)	28		7	
Lymphocytopenia				
Yes	24	0.04[a]	7	0.35
No	30		8	

[a]Statistically significant. OS: Overall survival; PFS: Progression-free survival; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

months vs. 23 months, p=0.008) (Fig. 4). The median OS of the patients who had lymphocytopenia was statistically significantly lower than the other patients (24 months vs. 30 months, p=0.04) (Fig. 5). There was no statistically significant difference for OS between high PLR (>163) and low PLR (<163) groups (24 months vs. 28 months, p=0.30). There was no statistically significant difference for OS between diagnosis that GBM and astrocytoma (27 months vs. 34 months, p=0.06). In addition, tumor localization was not a prognostic factor in our study. Individual survival analyzes were performed for each lobe, but no statistically significant relationship was found.

Relationship between systemic inflammatory response markers with disease features and treatment outcomes is summarized in Table 4. There was no correlation between treatment responses and NLR, PLR, and lymphocytopenia.

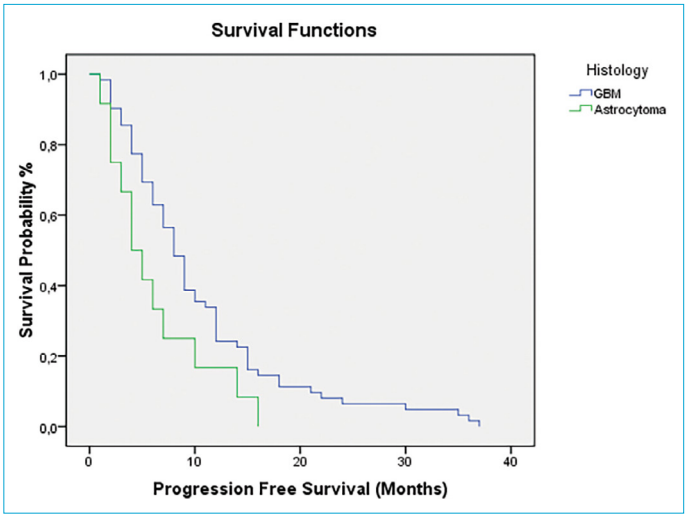

Figure 3. Median PFS was statistically better in GBM than the astrocytoma (8 months vs. 4 months, p=0.03).

According to median OS duration after irinotecan, the patients were divided into two groups, short and long living patients. There was no statistically significant correlation between tumor histological type (GBM vs. astrocytoma) and NLR, PLR, and lymphocytopenia.

Discussion

In our study, OS and PSF were estimated 28 months and 8 months, respectively. OS was worse in the patients who had lymphocytopenia and high NLR. Our study showed the prognostic significance of NLR and lymphocytopenia in Turkish high-grade glial tumor patients.

NLR, PLR, and lymphocyte are easily measurable and re-

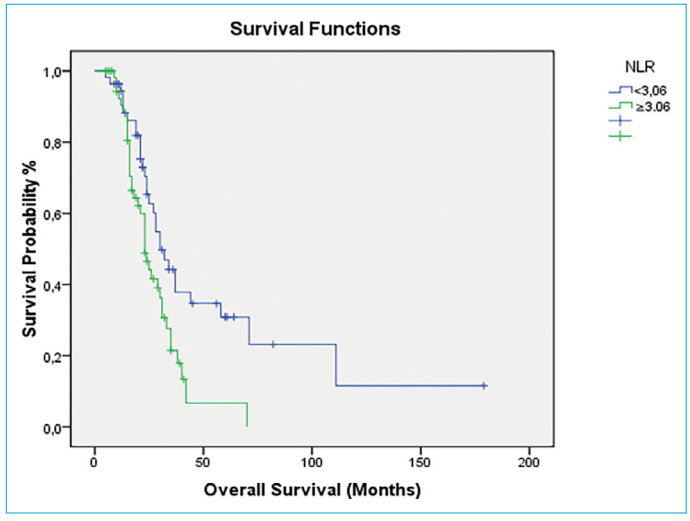

Figure 4. The OS of patients who had low NLR was statistically significantly longer than the patients who had high NLR (30 months vs. 23 months, p=0.008).

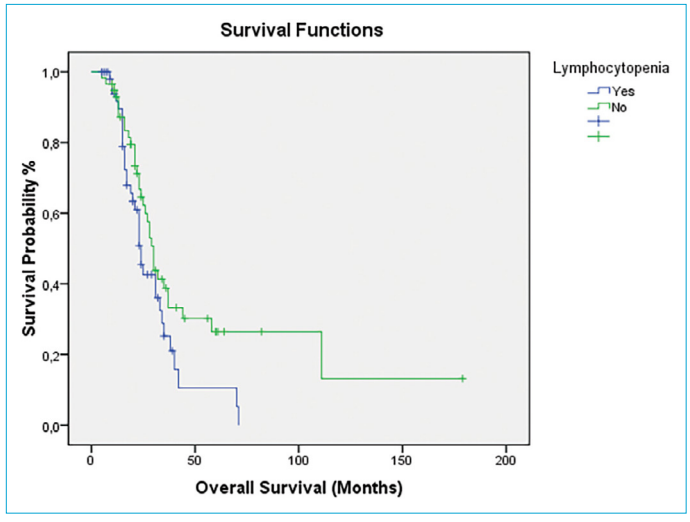

Figure 5. The median OS of the patients who had lymphocytopenia was statistically significantly lower than the other patients (24 months vs. 30 months, p=0.04).

Table 4. Relationship between systemic inflammatory response markers with disease features and treatment outcomes

Factor	NLR			PLR			Lymphocytopenia		
	High	Low	p	High	Low	p	High	Low	p
Response to treatment									
Yes[1]	46	51	0.09	46	51	0.49	44	53	0.18
No	10	4		8	6		9	5	
Complete response									
Yes	3	7	0.18	4	6	0.58	4	6	0.62
No	52	48		49	51		48	52	
Median OS									
<12 m	36	30	0.29	31	35	0.60	33	33	0.56
≥12 m	20	25		23	22		20	25	
Histology									
GBM	44	41	0.61	44	41	0.23	41	44	0.85
Astrocytoma	12	14		10	16		12	14	

[a]Statistically significant. [1]: Stable disease+partial response+complete response. OS: Overall survival; GBM: Glioblastoma multiforme; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

peatable parameters. Several studies demonstrate an association between a higher systemic inflammatory markers and a worse prognosis in many malignancies.[6] However, prognostic value of these markers in high-grade glial tumors is still not clear. Wang et al.[7] found that NLR and PLR were prognostic significance in 141 GBM patients. Similarly, Bambury et al.[8] showed that prognostic significance of NLR in 137 GBM patients. The findings of the trial of Kaya et al.[9] confirm that NLR can be used as a prognostic factor in 90 patients with glioblastoma in Turkey. Han et al.[10] demonstrated the prognostic significance of NLR in 152 GBM patients. In contrast to these positive studies, Lopes et al.[11] could not show the correlation between a higher NRL and worse survival in 139 GBM patients. In our study, we showed that NLR and lymphocytopenia are associated with poor prognosis in patients with high-grade glial tumors.

In a review of eight clinical trials with 225 recurrent malignant gliomas, the 6-month survival was 15% versus 31% for GBM versus anaplastic astrocytoma.[12] There was no statistically significant difference for OS between diagnoses that GBM and astrocytoma in our study. There were several studies in literature that about tumor localization. However, prognostic significance of tumor localization is not clear. In our study, we did not show the prognostic significance of tumor localization in GBM patients.

Limitations of our study are being a retrospective study, conducted in relatively small population groups and not being consideration with other molecular and clinical prognostic factors.

Conclusion

We showed that high NLR and lymphocytopenia may also have prognostic value in recurrent Turkish high-grade glial tumor patients and the present findings confirm that these markers may be used to predict the mortality risks for in patients with high-grade glial tumors.

Disclosures

Ethics Committee Approval: Ethical approval was not required based on the law and the national ethical guidelines of our country and written informed consent was not required for individual patient because of retrosprective nature. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Authorship Contributions: Concept – A.M.S., A.T.S.; Design – A.M.S., A.T.S.; Supervision – A.T.S.; Materials – A.M.S., Z.Ç., A.B., S.G., A.T.S.; Data collection &/or processing – A.M.S., Z.Ç., A.B., S.G., A.T.S.; Analysis and/or interpretation – A.M.S., A.T.S.; Literature search – A.M.S., Z.Ç., A.B., S.G., A.T.S.; Writing – A.M.S., A.T.S; Critical review – A.T.S.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
2. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ,

Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459–66.
3. Wu W, Lamborn KR, Buckner JC, Novotny PJ, Chang SM, O'Fallon JR, et al. Joint NCCTG and NABTC prognostic factors analysis for high-grade recurrent glioma. Neuro Oncol 2010;12:164–72.
4. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Dowell JM, Reardon DA, Quinn JA, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 2007;13:1253–9.
5. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009;27:740–5.
6. Del Prete A, Allavena P, Santoro G, Fumarulo R, Corsi M, Mantovani A. Molecular pathways in cancer-related inflammation. Biochem Med (Zagreb) 2011;21:264–75.
7. Wang PF, Song HW, Cai HQ, Kong LW, Yao K, Jiang T, et al. Preoperative inflammation markers and IDH mutation status predict glioblastoma patient survival. Oncotarget 2017;8:50117–23.
8. Bambury RM, Teo MY, Power DG, Yusuf A, Murray S, Battley JE, et al. The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. J Neurooncol 2013;114:149–54.
9. Kaya V, Yıldırım M, Yazıcı G, Yalçın AY, Orhan N, Güzel A. Prognostic significance of indicators of systemic inflammatory responses in glioblastoma patients. Asian Pac J Cancer Prev 2017;18:3287–91.
10. Han S, Liu Y, Li Q, Li Z, Hou H, Wu A. Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. BMC Cancer 2015;15:617.
11. Lopes M, Carvalho B, Vaz R, Linhares P. Influence of neutrophil-lymphocyte ratio in prognosis of glioblastoma multiforme. J Neurooncol 2018;136:173–80.
12. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 1999;17:2572–8.