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Combination of 6-thioguanine, capecitabine, and celecoxib with temozolomide or lomustine for recurrent high-grade glioma

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Abstract

We evaluated the efficacy of temozolomide (TMZ) or lomustine (CCNU) in combination with 6-thioguanine, capecitabine, and celecoxib for the treatment of recurrent high-grade glioma. Forty-three patients with recurrent glioblastoma and 31 patients with recurrent anaplastic glioma (AG) were enrolled in this open-label, non-comparative study. Patients previously treated with TMZ received CCNU while all others received TMZ; all patients received 6-thioguanine, capecitabine, and celecoxib. Endpoints were 12-month progression-free survival (PFS) for patients with AG, 6-month PFS for patients with glioblastoma, duration of PFS, and MRI-based objective response rates. Results from the TMZ and CCNU treatment arms were combined in the final analysis because there was no statistically significant difference between them. Thirty-eight patients with glioblastoma were treated with the lomustine-based regimen, and five received the TMZ-based regimen. For the 43 glioblastoma patients, the objective response rate was 12 and 33% had stable disease; the 6-month PFS was 14% and median overall survival 32 weeks. For the 31 AG patients, the combined objective response rate was 26 and 42% had stable disease; the 12 month PFS was 44%. Treatment was reasonably well tolerated with hematological toxicity common and more frequent with CCNU than TMZ. The combination therapy with 6-thioguanine, capecitabine and celecoxib plus CCNU or TMZ does not appear to be more effective than other alkylating agent schedules for patients with recurrent glioblastoma. The combination, however, is promising for patients with recurrent high-grade AG.

Keywords

6-Thioguanine; Capecitabine; Celecoxib; Temozolomide; Lomustine; Glioblastoma; Anaplastic glioma

Introduction

It is estimated that approximately 20,500 patients were diagnosed with glioma in the United States in 2007. [1]. Glioblastoma, the most common and aggressive glioma accounts for 50% and anaplastic gliomas (AG) 19% of all neuroepithelial central nervous system tumors [1]. Optimal treatment with surgery, radiation, and chemotherapy remains largely palliative, with a median survival of 14–15 months for glioblastoma [2]. Patients with anaplastic gliomas [3] have a moderately better prognosis, with a median survival of 2–5 years [4–6]. Typically, the rate of 6-month progression-free survival (PFS-6) is 21% for patients with recurrent glioblastoma after treatment with temozolomide [7]. Patients with AG had a PFS-6 of 46% following initial treatment with temozolomide in one study [8]; the PFS-6 in other studies of patients with AG have ranged from 37 to 41% [9]. After primary therapy with radiotherapy and temozolomide followed by adjuvant temozolomide, there exists no established salvage therapy for patients with high-grade glioma, although the FDA approved antiangiogenic therapy with bevacizumab for recurrent glioblastoma because of promising response rates and increased median PFS [10].

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Temozolomide is an orally administered alkylating agent with excellent bioavailability that has demonstrated activity in patients with AG as well as those with glioblastoma [8]. In 2005, a randomized phase III trial showed increased median survival from 12.1 months to 14.6 months with the concomitant and adjuvant use of temozolomide in patients with glioblastoma [2]. A recent long-term follow-up of these patients showed a 5-year survival rate of 10% for glioma patients receiving radiotherapy with concomitant and adjuvant temozolomide versus 2% for those receiving radiation therapy alone [11].

Lomustine (CCNU) is another alkylating agent that has been effective both as a single agent and in combination with procarbazine and vincristine in the treatment of low- and high-grade gliomas [3, 12] (see Goerne et al. [13] for a detailed review).

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Capecitabine is a prodrug of 5-fluorouracil (5-FU). In phase II studies, 5-FU combined with carmustine or lomustine showed promising activity against recurrent malignant gliomas [3, 12]. Capecitabine offers good oral bioavailability, which facilitates oral dosing.

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6-Thioguanine (6-TG) is a purine analog that can Épotentiate the cytotoxicity of nitrosoureas to tumor cells when administered in doses that produce little cytotoxicity as a single agent [14, 15]. It is thought that the alkylation of the sulfhydryl group of the thioguanine that is substituted into the DNA leads to more DNA crosslinks and potentiated cytotoxicity of nitrosoureas [15]. A clinical trial combining 6-TG with carmustine as adjuvant therapy for glioblastoma and AG tumors reported improved PFS as well as overall survival than other studies done at the time [16]. 6-TG has also been used in combinations with procarbazine, lomustine, and hydroxyurea for high-grade gliomas in adults and children and showed promising response rates and durable responses [17]. The addition of 6-TG to temozolomide has not been studied in clinical trials with glioma patients, but based on earlier studies of 6-TG in combination with the alkylating agents lomustine and carmustine, we expect its safety to be similar and toxicity mainly hematologic.

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Celecoxib is a nonsteroidal selective cyclooxygenase-2 (COX-2) inhibitor that has been widely used for its anti-inflammatory, analgesic, and antipyretic activities. High-grade gliomas have been shown to have upregulated cyclooxygenase activity, and upregulation appears to be inversely related to patient survival and directly related to MIB-1 expression [18, 19]. Preclinical studies have shown that COX-2 inhibition can induce apoptosis, potentiate chemotherapy cytotoxicity, antagonize angiogenesis, and impair cell migration [20–26]. The combination of COX-2 inhibitors and 5-FU resulted in additive to synergistic effects against a variety of adenocarcinoma cell lines [27–30].

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On the basis of the studies listed above, we hypothesized that a combination of 6-thioguanine, capecitabine, and celecoxib with temozolomide or lomustine would yield in longer PFS and overall survival in patients with recurrent malignant glioma than the current standard of care. We initiated a protocol to administer 6-TG on a dose-intense schedule before the administration of temozolomide or lomustine (depending on the prior chemotherapy received by the patient) in an attempt to potentiate the cytotoxic effects of the alkylating agent. We followed this regimen with capecitabine and celecoxib to maximize anti-tumor interactions with COX-2 inhibition. In developing this strategy, we expected that

the dose-limiting toxicities of temozolomide and lomustine would not overlap with those of 6-TG, capecitabine, and celecoxib but would increase efficacy.

Patients and methods

Eligibility criteria

Thirty-one patients with AG and 44 patients with glioblastoma were prospectively entered on institutional review board-approved protocol 2003-0600 between October 2003 and June 2009 at the University of Texas M. D. Anderson Cancer Center. Informed consent was obtained prior to enrollment.

The specific patient eligibility criteria were:

- Age 18 years or older.
- Histologic confirmation of a supratentorial AG [anaplastic oligodendroglioma (AO), anaplastic mixed oligoastrocytoma (AOA), or anaplastic astrocytoma (AA)] or glioblastoma. One patient with gliosarcoma was enrolled into the glioblastoma stratum. All pathological specimens from the latest pre-protocol surgeries were reviewed by a neuropathologist at M. D. Anderson and were used for study registration.
- Unequivocal evidence of tumor recurrence or progression by magnetic resonance imaging (MRI) within 14 days prior to enrollment or documented recurrence by tumor resection.
- Prior radiation therapy, chemotherapy or both.
- Stable dosing of corticosteroids or no corticosteroids for 7 days before the baseline MRI.
- Karnofsky performance status ≥ 60 .
- Absolute neutrophil count $\geq 1,500/\text{mm}^3$ and platelet count $\geq 100,000/\text{mm}^3$.
- Adequate hepatic and renal function, defined as total bilirubin ≤ 1.5 mg/dL, alanine aminotransferase and alkaline phosphatase < 2 times the upper limit of normal, and creatinine < 1.5 times the institutional normal.
- A status of having recovered from the toxic effects of prior therapy and being at least 4 weeks removed from temozolomide, 2 weeks from vincristine, 6 weeks from a nitrosourea, 3 weeks from procarbazine, and 1 week from noncytotoxic agents.

Patients who had undergone prior treatment with capecitabine, 5-FU or a combination of temozolomide with lomustine or carmustine were not eligible to participate in this study.

Study treatment

This was an open-label study with two treatment arms. Patients who had not received prior treatment with temozolomide were entered into Arm 1 and were treated with the following regimen:

- 6-Thioguanine: 3 days every 28-day cycle on days 1–3, orally every 6 h for a total of 12 doses at 80 mg/m²/dose.
- Temozolomide: 5 days every 28-day cycle on days 4–8, orally at bedtime at 150 mg/m²/dose.
- Capecitabine: 14 days every 28-day cycle on days 14–27, orally every 12 h at 825 mg/m²/dose.
- Celecoxib: 14 days every 28-day cycle on days 14–27, orally every 12 h at 400 mg/dose.

Patients who had previously received temozolomide but had not received lomustine or carmustine were entered into Arm 2 and were treated with the following regimen:

- 6-Thioguanine: 3 days every 42-day cycle on days 1–3, orally every 6 h for a total of 12 doses at 80 mg/m²/dose.
- Lomustine: 1 day every 42-day cycle on day 4, orally at bedtime at 100 mg/m²/dose.
- Capecitabine: 14 days every 42-day cycle on days 11–24, orally every 12 h at 825 mg/m²/dose.
- Celecoxib: 14 days every 42-day cycle on days 11–24, orally every 12 h at 400 mg/dose.

Treatment evaluation

Brain imaging with MRI was performed prior to study registration and subsequently at day 56 for patients in Arm 1 and between days 42 and 49 for patients in Arm 2. For patients with measurable disease, the MacDonald criteria were used for response assessment [31]. A complete response (CR) was defined by the complete disappearance of all measurable and evaluable disease with no evidence of new lesions or non-evaluable disease. Partial response (PR) was defined by a 50% decrease of the sum of the products of the perpendicular diameters of all measurable lesions, no progression of evaluable disease, and no new lesions. Progressive disease (PD) was defined by a 25% increase of all measurable lesions or clear worsening of any evaluable disease. If imaging showed the appearance of any new lesions or if patients failed to return for evaluation because of death or cancer-related deterioration, they were counted as having PD. Patients with imaging findings not meeting criteria for CR, PR, or PD for at least 12 weeks were considered to have stable disease (SD). Toxicity was monitored and graded according to the NCI CTC version 2.0.

Statistical considerations

The primary objective of this study was to determine the extent to which the two treatment regimens would be able to delay tumor progression in patients with recurrent or progressive glioblastoma or AG. To that end, we chose as primary endpoints 12-month progression-free survival (PFS-12) for the AG stratum and PFS-6 for the glioblastoma stratum and the duration of PFS for both groups. Secondary endpoints were response rates (CR, PR, PD, and SD) associated with treatment regimen for both groups.

Event times were examined using Kaplan–Meier estimates. Univariate Cox proportional hazards regression models were used to estimate any impact of age at diagnosis, Karnofsky performance status, clinical response (CR, PR, SD vs. PD), treatment regimen (lomustine vs. temozolomide) and tumor histology (GB or AG) on overall survival and PFS. As these models did not reveal any significant differences between the treatment regimen in Arm 1 and Arm 2, the outcomes for patients in the two histological strata were evaluated separately, but both treatment groups were combined in the Kaplan–Meier estimates for OS and PFS.

Based on an expected PFS-12 of 40% in the group of AG, we used a one-sided, one-sample binomial test with a two-stage design. The first stage included 20 patients and was expanded to 40 patients after the minimum of four successes (alive and progression free at 12 months) was met (alpha 8%; beta 10%). The same model was applied to the glioblastoma group and a PFS-6 of 20% was assumed. As more than four patients out of 20 were alive and progression free at six months, the sample size was extended to a total of 40 patients (alpha 8%; beta 10%).

Results

Patient characteristics

Table 1 shows the patient characteristics. Forty-three patients with glioblastoma and one with gliosarcoma were screened for the glioblastoma treatment groups; however, one patient could not enroll because of increased liver enzymes. Thus, 43 patients were enrolled, treated, and evaluated for response. The AG stratum was closed before reaching the predetermined amount of patients because of slow patient accrual. In 5.5 years, only 31 patients were enrolled; all were evaluable for response and toxicity. One patient had not undergone any chemotherapy prior to enrollment, but had disease progression documented by MRI and repeat resection. The patient's pathology did not reveal any signs of treatment effect but only GB recurrence. The AG stratum included 20 patients with anaplastic astrocytoma, nine patients with anaplastic oligodendroglioma, and two patients with anaplastic oligoastrocytoma (AOA). Four patients (two AA, one AO and one AOA) had not undergone prior chemotherapy but radiation treatment only and were enrolled into the TMZ cohort.

Treatment Outcomes

At the time of last follow-up, the PFS-6 for patients with glioblastoma was 14% (95% CI, 7–29%) (See Table 2, Fig. 1). Combining the data from Arms 1 and 2 revealed that 12% of the glioblastoma patients responded (1 CR and 4 PR) and 33% (14) had SD. Median OS was 32 weeks (95% CI, 25.6–39.0 weeks). All but one patient with glioblastoma had died. The surviving patient had received the lomustine-based regimen for 24 weeks and had no changes detected on MRI before discontinuing the protocol because of drug toxicity. Univariate Cox proportional hazards models were unable to show that age, Karnofsky performance status, or chemotherapy regimen significantly affected PFS or OS (Table 3). Not surprisingly, the reported tumor response ($P = 0.04$) did correlate with the overall outcome.

Anaplastic Glioma response

The PFS-12 in the stratum of AG patients was 44% (95% CI 29–67%) (Table 2, Fig. 2). Median PFS was 25 weeks (95% CI 18–224 weeks), and median OS was 54 weeks (95% CI 32–202 weeks) (Fig. 2). When the data for Arms 1 and 2 were combined for the AG stratum, 26% of the patients showed an objective response (1 CR, 7 PR), and 42% (13) had SD (Table 2). Ten patients (32%), six with AA and four with AO were alive at the time of last follow up. Three of these patients were treated on Arm 1, while seven received the lomustine-based treatment on Arm 2 of the protocol. Two of the patients had a PR (both treated with lomustine), six had SD and two had PD.

Two patients (1 deceased, 1 alive) stopped treatment because of a lack of insurance or refusal to continue on the protocol. The univariate Cox proportional hazards model indicated a significant effect of age at diagnosis on OS time ($P=0.03$), while there was no correlation between age and PFS time ($P=0.16$). For the AG group, we also evaluated AO + AOA versus AA as well as AO versus AA + AOA with respect to PFS and overall survival (OS). Neither of grouping of AG histologies showed a statistical difference in PFS ($P=0.13$ and 0.16). While the median PFS for AO was 106 weeks and that for AA + AOA 21 weeks, the two curves intersected at 220 weeks, indicating similar OS based on tumor histology. In addition, Karnofsky performance status, treatment regimen and clinical response had no significant effect on OS or PFS (Table 3).

Toxicity

Therapy was reasonably well tolerated by patients in both treatment arms. There were no treatment-related deaths in either arm of this study. Adverse events (grade 3 and 4) are shown in Table 4. Of all patients, 17–18% had grade 3 hematological toxicity and 6% had grade 4 hematological toxicity. Overall, the temozolomide-based chemotherapy was better tolerated than the lomustine-based treatment. Of the 13 patients receiving the temozolomide-based regimen, only one patient required a dose reduction of temozolomide and capecitabine prompted by neutropenia. One other patient receiving temozolomide required a one-time dose reduction of capecitabine and celecoxib because of gastrointestinal symptoms. The use of the nonsteroidal selective COX-2 inhibitor celecoxib was not associated with any significant cardiovascular toxicities in this particular vulnerable patient population. No grade 3 or grade 4 cardiovascular toxicities were observed in this study.

Most dose reductions in the lomustine arm were due to hematological toxicities. Five patients required a one-time dose reduction and two patients required a two-time dose reduction of lomustine. Thirteen percent of the patients on the lomustine-based regimen had grade 3 fatigue. Four patients discontinued treatment because of toxicity (one from Arm 1, three from Arm 2).

Discussion

The combination of 6-thioguanine, capecitabine, and celecoxib plus lomustine or temozolomide does not suggest any marked improvement in PFS or OS over earlier studies for recurrent glioblastoma. A meta-analysis of eight chemotherapy trials for glioblastoma

showed a PFS-6 of 15% [8]; other prospective studies using alkylating agents for recurrent glioblastoma reported PFS-6 of 21–44% with temozolomide [32, 33] and 18% with carmustine [34]. Twenty of our patients (46%) received only one full cycle of chemotherapy and stopped because of tumor progression.

While the results for glioblastoma did not show significant improvement over earlier trials, the PFS analysis for the AG group was more promising. Patients with AG had a median PFS of 25 weeks (95% CI 18–224 weeks), PFS-6 of 48%, and PFS-12 of 44%. The PFS results are very promising given the results of a retrospective study of 16 sequential or simultaneous phase II trials conducted between 1999 and 2004 that included 529 patients with AG [9]. Using the combined outcome data of these 16 studies, the impact of age, Karnofsky performance status, number of prior chemotherapies and the response to treatment on PFS were identified. The most effective therapies in this combined analysis resulted in PFS-6 in the range of 37–41% and PFS-12 in the range of 21–33%. Other earlier studies using carmustine or lomustine alone or in combination with 6-TG yielded a PFS-6 of 36% and a PFS-12 of 28% [9]. Compared with patients in these earlier studies, our patients responded well to the combination chemotherapy and experienced only the expected toxicities.

Unfortunately, the patient stratum for AG had to be closed early because of slow accrual after enrolling only 31 patients rather than the 40–80 patients originally planned. The PFS as well as the OS curves from our study are very promising and in comparison with historic controls, suggest that patients treated with these multi-agent chemotherapy regimens fared better than those treated only with an alkylating agent. Unfortunately, the number of patients was too low to reach the preset statistical certainty, although the confidence intervals for the 44% PFS-12 were reasonably tight around the median (95% CI 29–67%).

The failure to enroll the planned number of patients highlights a major problem in finding new treatments for patients with high-grade AG since the WHO classification for glioblastoma was implemented in our institution in 2000. The current criteria allow patients with vascular proliferation and without pseudopalisading necrosis to be diagnosed with glioblastoma, thereby markedly reducing the number of patients with tumors now diagnosed as AA. Our inability to accrue patients to meet our accrual goals in 5.5 years supports the need for multi-institutional or cooperative group studies for this disease.

On the basis of our results, combination therapy with 6-thioguanine, capecitabine, and celecoxib with lomustine or temozolomide cannot be recommended for the treatment of patients with recurrent glioblastoma. However, our data suggest that these regimens are promising and well tolerated for patients with high-grade AG. A multi-institutional prospective study would be needed to further define the role of this regimen in patients with AG.

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Fig. 1. Kaplan–Meier estimate of progression-free and overall survival for glioblastoma ($n = 43$). Median and 95% confidence intervals (CI) are shown on the plot

Fig. 2. Kaplan-Meier estimate of progression-free and overall survival for anaplastic glioma ($n = 31$). Median and 95% confidence intervals (CI) are shown on the plot

Table 1

Patient demographics for glioblastoma and anaplastic glioma study patients

Characteristic	Histology stratum	
	Glioblastoma <i>n</i> = 43	Anaplastic glioma <i>n</i> = 31
Sex		
Female	16	15
Male	27	16
Histology		
Glioblastoma	42	–
Gliosarcoma	1	–
AA	–	20 (65%)
AO	–	9 (29%)
AOA	–	2 (6%)
Median age, years (range)	53 (26–76)	39 (23–76)
Median KPS (range)	80 (60–100)	90 (70–100)
Median number of prior chemotherapies (range)	2 (0–5)	1 (0–3)
Chemotherapy		
Lomustine	38 (88%)	23 (74%)
Temozolomide	5 (12%)	8 (26%)

AA anaplastic astrocytoma, AO anaplastic oligodendroglioma, AOA anaplastic oligoastrocytoma, KPS Karnofsky performance status

Table 2

Collated outcomes measures for each histology stratum

Outcome measure	Histology stratum	
	Glioblastoma	Anaplastic glioma
	43	31
Alive, <i>n</i> (%)	1 (2%)	10 (32%)
AA	42 (98%)	6 (19%)
AO	–	4 (13%)
AOA	–	0 (0%)
Dead, <i>n</i> (%)	–	21 (68%)
AA	–	14 (45%)
AO	–	5 (16%)
AOA	–	2 (6%)
Best Response, <i>n</i> (%: tumor histology)		
CR	1 (2%)	1 (3%: 1AO)
PR	4 (9%)	7 (23%: 4AA, 1OA, 2AOA)
SD	14 (33%)	13 (42%: 7AA, 6OA)
PD	24 (56%)	10 (32%: 9AA, 1OA)
Progression-free survival		
Median, weeks (95% CI)	7.4 (5.8–13.5)	24.5 (18–224)
6 months	14%	48%
9 months	9%	44%
12 months	5%	44%
Overall Survival		
Median, weeks (95% CI)	32.1 (25.6–39)	53.6 (32.2–202.0)

AA anaplastic astrocytoma, AO anaplastic oligodendroglioma, AOA anaplastic oligoastrocytoma, CI confidence interval, CR complete response, PR partial response, PD progressive disease, SD stable disease

Table 3

Univariate Cox model for progression-free survival in patients with anaplastic glioma and glioblastoma

Variable	Histology stratum					
	Glioblastoma			Anaplastic glioma		
	Estimate	HR (95% CI)	P	Estimate	HR (95% CI)	P
Age at diagnosis	0.01	1.01 (0.99–1.04)	0.35	0.02	1.03 (0.99–1.06)	0.16
KPS	0.0001	1.0 (0.98–1.03)	0.99	–0.01	0.98 (0.94–1.03)	0.63
MRI response (CR, PR, or SD vs. PD)	–0.99	0.37 (0.14–0.97)	0.04	–0.40	0.67 (0.26–1.75)	0.41
Treatment regimen (lomustine vs. temozolomide)	0.45	1.56 (0.61–4.03)	0.36	0.51	1.67 (0.60–4.64)	0.33
Histology (AO + AOA vs. AA)	–	–	–	–0.73	0.48 (0.19, 1.23)	0.13
Histology (AO vs. AOA + AA)	–	–	–	0.73	2.08 (0.75, 5.74)	0.16

CI confidence interval, CR complete response, HR hazard ratio, MRI magnetic resonance imaging, KPS Karnofsky performance status, PR partial response, PD progressive disease, SD stable disease

Table 4

Adverse events per patient by treatment arm

Event	Treatment			
	Lomustine (n = 61)		Temozolomide (n = 13)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Anemia	5 (8%)	–	1 (8%)	–
Neutropenia (ANC/AGC)	9 (15%)	8 (13%)	3 (23%)	1 (8%)
Leukopenia	18 (30%)	4 (7%)	3 (23%)	0
Lymphopenia	15 (25%)	5 (8%)	3 (23%)	2 (15%)
Thrombocytopenia	8 (13%)	1 (2%)	1 (8%)	1 (8%)
Nonhematologic				
Seizure	1 (2%)	–	–	–
Mental Status	1 (2%)	–	–	–
Muscle weakness	1 (2%)	–	–	–
Neuropathy (sensory)	1 (2%)	–	–	–
Metabolic				
Alanine transaminase	1 (2%)	–	–	–
Hypoalbuminemia	1 (2%)	–	–	–
Hypokalemia	–	–	2 (15%)	–
Hyponatremia	2 (3%)	–	–	–
Hypophosphatemia	–	1 (2%)	–	–
Gastrointestinal				
Anorexia	1 (2%)	–	–	–
Colitis	–	1 (2%)	–	–
Constipation	–	1 (2%)	–	–
Dehydration	1 (2%)	–	–	–
Diarrhea	2 (3%)	–	1 (8%)	–
Pain (abdominal)	1 (2%)	–	–	–
Vomiting	3 (5%)	–	–	–
Others				
Pneumonitis	1 (2%)	–	–	–
Dyspnea	1 (2%)	1 (2%)	–	–
Fatigue	8 (13%)	1 (2%)	–	–
Sepsis	1 (2%)	–	–	–
Thrombosis/embolism	–	1 (2%)	–	–

Adverse events that occurred during the planned treatment period were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC), version 2.0

AGC absolute granulocyte count, ANC absolute neutrophil count