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Antiangiogenic Molecules Suppressed Meningioma-Induced Neovascularization: A Corneal Angiogenesis Study

Necati TATARLI[1], Davut CEYLAN[2], M. Deniz OKSAL[3], Timucin AVSAR[4], Turker KILIC[5]

[1]University of Health Sciences, Dr. Lutfi Kırdar Kartal Training and Research Hospital, Department of Neurosurgery, Istanbul, Turkey
[2]Sakarya University, Sakarya Training and Research Hospital, Department of Neurosurgery, Sakarya, Turkey
[3]Bahcesehir University, Health Sciences Institute, Neuroscience Program, Istanbul, Turkey
[4]Bahcesehir University, School of Medicine, Department of Medical Biology, Istanbul, Turkey
[5]Bahcesehir University, School of Medicine, Department of Neurosurgery, Istanbul, Turkey

Corresponding author: Necati TATARLI ✉ necatitatarli@yahoo.com

ABSTRACT

AIM: To investigate the angiogenic effects of bevacizumab and imatinib on different meningioma tissue grades.

MATERIAL and METHODS: In this study, in silico analysis of angiogenesis-related gene expression was carried out using previously reported datasets. Messenger ribonucleic acid expressions of VEGFA, VEGFB, PDGFRA, and PDGFRB genes were obtained from two different meningioma transcriptome datasets. The effect of antiangiogenic drugs, bevacizumab and imatinib, on meningioma-induced vascularization was assessed by using rat corneal angiogenesis assay (CAA).

RESULTS: Bevacizumab and imatinib both significantly reduced meningioma-induced neovascularization in the CAA model.

CONCLUSION: The angiogenic characteristics of meningiomas may be suppressed by using antiangiogenic drugs to prevent neovascularization, thus improving prognosis.

KEYWORDS: Meningioma, Angiogenesis, Imatinib, Bevacizumab, Cornea angiogenesis model

ABBREVIATIONS: CAA: Corneal angiogenesis assay, **EGF:** Epithelial growth factor, **PDGF:** Platelet-derived growth factor, **PFS value:** Progression free survival, **mRNA:** Messenger ribonucleic acid, **VEGF:** Vascular endothelial growth factor, **WHO:** World Health Organization

INTRODUCTION

Meningiomas, which constitute 25%–30% of all primary central nervous system tumors, are typically benign in nature although some forms can exhibit aggressive progression (3,5,15,16,18,24). These lesions originate from arachnoid cells which occur in about 90% of the intracranial space (3,14). The World Health Organization (WHO) uses a histological classification system to group meningiomas into grades I (typical meningioma); II (atypical meningioma); and III (malignant meningioma) (3,5,18). Typical meningiomas are the most frequently observed, while the incidence of atypical and malignant meningioma ranges between15%–20% (3). Although surgical resection is the preferred method of treatment (3,15,18), radiotherapy and radiosurgery with systematic drug treatment can be used in situations where resection is unsafe, remnants of tumor tissue have been observed in the area after surgery, or disease recurrence occurs (3,15,18). Previous studies have investigated various drugs including hydroxyurea, irinotecan, temozolomide, interferon alfa, mifepristone, octreotide analog, megestrol acetate, bevacizumab, sunitinib, vatalanib, imatinib,

Necati TATARLI : 0000-0002-4106-6351
Davut CEYLAN : 0000-0002-2056-2786
M. Deniz OKSAL : 0000-0002-1256-3826
Timucin AVSAR : 0000-0001-8841-4811
Turker KILIC : 0000-0001-5982-9700

erlotinib, and gefitinib, although none of these have been recommended for the treatment of meningiomas (3,14,15,18).

Angiogenesis is a common characteristic of malignant and atypical meningiomas, with the concentration of angiogenic molecules (e.g., vascular endothelial growth factor [VEGF], platelet-derived growth factors [PDGF], and epithelial growth factors [EGF]) significantly increasing in these tumor forms. Molecules designed to inhibit the VEGF, PDGF, and EGF pathways, which act as important control mechanisms for angiogenesis, are currently being tested for treatment of various cancers and meningiomas. Bevacizumab (Avastin®, Genentech/Roche Holding AG, Basel, Switzerland), designed to inhibit the VEGF pathway, is a monoclonal antibody capable of binding to isoforms of the VEGFA protein (6,8,12,18). Grimm et al. observed that bevacizumab successfully stabilized resistant meningiomas (15), while another study showed that its use decreased peritumoral edema in anaplastic meningiomas to a greater extent when compared to the pre-therapeutic period (5). Imatinib, a 2-phenylaminopyrimidine class molecule that inhibits tyrosine kinases (e.g., PDGFR) (9), was first developed as a specific inhibitor for Bcr-Abl tyrosine kinase in chronic myelogenous leukemia (26). A phase II study investigating the use of a combination of imatinib and hydroxyurea in recurrent meningiomas reported a significant increase in progression free survival (PFS) value in the group receiving hydroxyurea only (hydroxyurea group: 0%; hydroxyurea and imatinib group: 75%) (15).

This study aims to investigate the angiogenic effects of bevacizumab and imatinib on different meningioma tissue grades using corneal angiogenesis assay (CAA), with the goal of developing therapeutic methods that can prevent tumor growth and spread by reducing the angiogenesis of meningiomas with high angiogenic activity.

MATERIAL and METHODS

In Silico Analysis of Angiogenesis-Associated Genes

Data on messenger ribonucleic acid (mRNA) expression (cancer vs. normal; expression by grades) in the Watson Brain (sample population: 18) and Lee Brain 2 datasets (sample population: 68) of *VEGFA*, *VEGFB*, *PDGFRA*, and *PDGFRB* genes, which play an important role in meningioma angiogenesis, were collected using ONCOMINE, a microarray analysis software and web-based data processing platform (17,19,25). Pathological status based on WHO grades and relevant gene parameters were selected within the specified datasets in the ONCOMINE platform. Relevant gene expressions of the patient populations were collected by selecting cancer type and WHO grade criteria. GraphPad Prism 8.0.2 software (GraphPad Software, San Diego, CA, USA) was used for data visualization and statistical analysis (19). Gene expression levels were obtained by calculating the median values of the relevant gene-related readings in the microarray system and then normalizing them with log 2. These values were expressed as log2 median-centered intensity in the graphs.

Cornea Angiogenesis Assay

Ten meningioma samples were randomly selected from each of the WHO grades I, II, and III meningiomas between 2010 and 2015, obtained from surgical interventions performed at the Marmara University Department of Neurosurgery and the Marmara University Institute of Neurological Sciences (Istanbul, Turkey). Tissue samples obtained from patients were stored in liquid nitrogen immediately after surgery for use in cornea angiogenesis assay. Informed consent for all tissue samples used in this study was obtained from the patients or their legal representatives. None of the patients received any other treatment prior to surgery, and patients with multiple meningiomas or recurrent tumors were excluded from this study.

The animal studies were approved by the Institutional Animal Care and Use Committee of Yeditepe University School of Medicine (Istanbul, Turkey; date:14July 2010, No.:125). This study used male Sprague–Dawley rats weighing 300–400 gms. Rat CAA is a method that has been optimized and frequently used in the laboratory (1,9,10,11,13,23,24,26). Tissue samples stored in a liquid nitrogen tank were brought to room temperature 4–5 hours prior to cornea implantation. Thereafter, the tissue samples were washed using dimethyl sulfoxide and cut into pieces approximately 2–3 mm in diameter under the microscope. The rats were anesthetized using ketamine administered intraperitoneally under aseptic conditions, and the whole operation was performed under a microscope. The rat corneas were anesthetized using 0.5% proparacaine applied topically, and each sphere was gently proptosed. Under the surgical microscope, 4 mm paracentral intrastromal keratotomy was performed at a right angle to the limbus with the help of an arachnoid knife. An equal amount of meningioma tissue was implanted into the micropocket created between the two epithelial tissues using a microhook. The day of implantation was consideredas day 0.

Each experimental group (imatinib, bevacizumab, and control) included 10 rats (60 corneas in total) that received bevacizumab (18 mg/mL) and imatinib (10 mg/kg) intraperitoneally. No medication was given to the control group. An antibiotic agent (200 mL of 0.1 mg/mL gentamicin) was applied topically once a day for 30 days after implantation. The formation and progression of angiogenesis was monitored using a microscope (Carl Zeiss Co., Oberkochen, Germany), and photographs were taken every 5 days with a camera connected to the microscope (Sony, Park Ridge, NJ, USA). Rats were excluded from the experiment and replaced (above-mentioned steps were repeated with a similar tissue sample) if they exhibited any signs of ocular infection (discharge and/or redness around the eyes) at any stage of the experiment.

Angiogenesis assessment was performed by someone who was blinded to the study, and scoring of vascularization near the micropocket was carried out using the following system: grade 0- no evidence of angiogenesis (no visible vascularization); grade 1- low angiogenic activity (less than three visible vessels); grade 2- moderate angiogenic activity (three to eight vessels visible); and grade 3- high angiogenic activity (more than eight vessels visible).

Data Analysis

Data visualization and analysis was carried out using the GraphPad Prism 8.0.2 software (GraphPad Software, San Diego, CA, USA). Student's *t*-test was used to analyze in silico data, and a p-value of <0.05 was considered statistically significant. General linear model univariate analysis of variance was used to evaluate the neoangiogenesis characteristics of the groups, and Tukey's and Newman–Keuls tests were used for post-hoc comparisons. The data were expressed as means and standard deviations, and a p-value of <0.05 was considered statistically significant.

RESULTS

VEGFA and VEGFB Evaluation in Meningioma Dataset

Evaluation of the *VEGFA* and *VEGFB* genes in the Watson Brain dataset showed a significant increase in VEGFB (Figure 1A; p-values= 0.2347 and 0.0036) and no significant differences in the mRNA expression of the *VEGFA* gene between population grades. Examination by WHO grade criteria showed no significant changes in the mRNA expressions of VEGFA in the Watson Brain and Lee Brain 2 datasets (Figure 1B, D; p-values= 0.0162, 0.0119, and 0.1866 for Watson Brain; p-value= 0.1673 and 0.1961 for Lee Brain 2). Moreover, a significant change in VEGFB was observed when comparing normal tissue–grade I and normal tissue–grade II in the Watson Brain dataset (Figure 1C). However, no such changes were observed between grades I–II and grades I–III in the Lee Brain 2 dataset (Figure 1E; p-value= 0.0162, 0.0119, and 0.1866 for Watson Brain; p-value= 0.2413 and 0.2013 for Lee Brain 2).

PDGFRA and PDGFRB Evaluation in Meningioma Dataset

Examination of the PDGFRA and PDGFRB genes using the Watson dataset showed no significant changes in mRNA expression upon comparison with normal tissue in the general

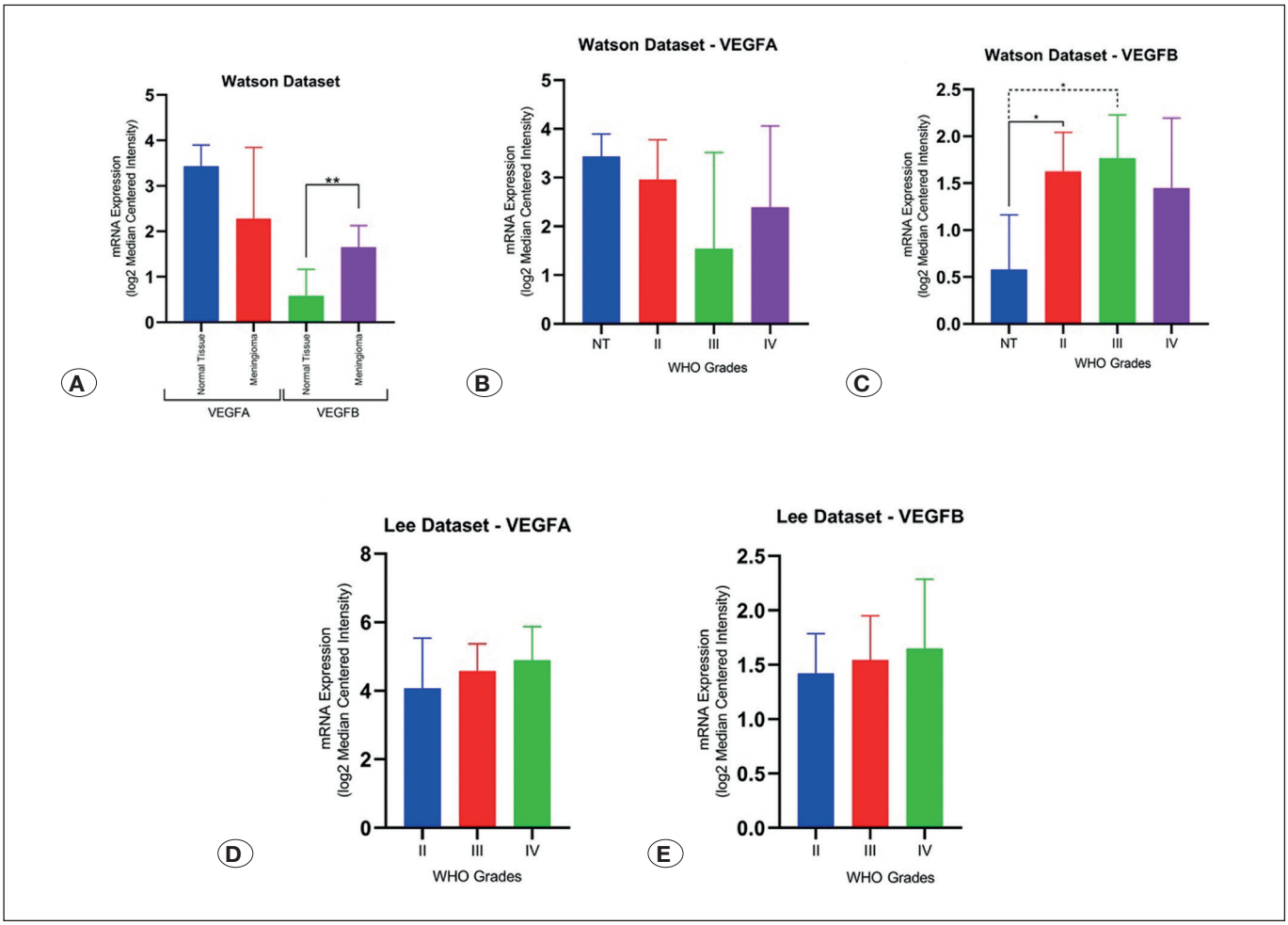

Figure 1: mRNA expressions of VEGFA and VEGFB genes in Watson Brain and Lee Brain 2 datasets. **A)** mRNA expression data provided by ONCOMINE were compared with normal tissue and meningioma grades (sample populations: 18, 65, and 68 for Watson Brain, VEGFA, and VEGFB for Lee Brain, respectively). **B)** The VEGFA mRNA levels of different pathological grade meningiomas in the Watson datasets. **C)** The VEGFB mRNA levels of different pathological grade meningiomas in the Watson datasets. **D)** The VEGFA mRNA levels of different pathological grade meningiomas in the Lee datasets. **E)** The VEGFB mRNA levels of different pathological grade meningiomas in the Lee datasets.

population (Figure 2A; p-value= 0.5713 and 0.0925). The *PDGFRA* gene exhibited no significant changes by WHO grade when compared with normal tissue (Figure 2B; p-value= 0.7539, 0.6485, and 0.1326). Similarly, the mRNA expression of the *PDGFRA* gene also exhibited no changes by grade when using the Lee Brain 2 dataset (Figure 2D; p-value= 0.6244 and 0.9367). Both the Watson Brain and Lee Brain 2 datasets showed no significant changes in the *PDGFRB* gene by WHO grades (Figure 2C, E; p-value= 0.1883, 0.1216, and 0.0507 for Watson Brain; p-value = 0.6244 and0.9367 for Lee Brain 2).

Corneal Angiogenesis Assay

Vascularization was seen to start on day 5 and was followed up until day30 as a part of the corneal angiogenesis experiments. A significant decrease in neovascularization was observed in the groups of rats receiving bevacizumab and imatinib when compared with the control group (bevacizumab group p-value= 0.0041; imatinib group p-value =0.0075; Figure 3C). However, no statistically significant decreases were observed upon comparison of the bevacizumab and imatinib groups (p-value= 0.9504).

DISCUSSION

Meningiomas are tumors with vascular potential that varies with lesion aggressiveness. Factors involved in meningioma-induced angiogenesis include VEGF, PDGF, EGF, and fibroblast growth factor. VEGF is an important regulator of angiogenesis (2,3) and its synthesis in meningioma is correlated with tumor development and peritumoral edema formation. A previous study showed that, when compared with benign meningiomas, malignant and atypical meningiomas exhibited ten- and two- fold increases in VEGF levels (14). Peritumoral edema

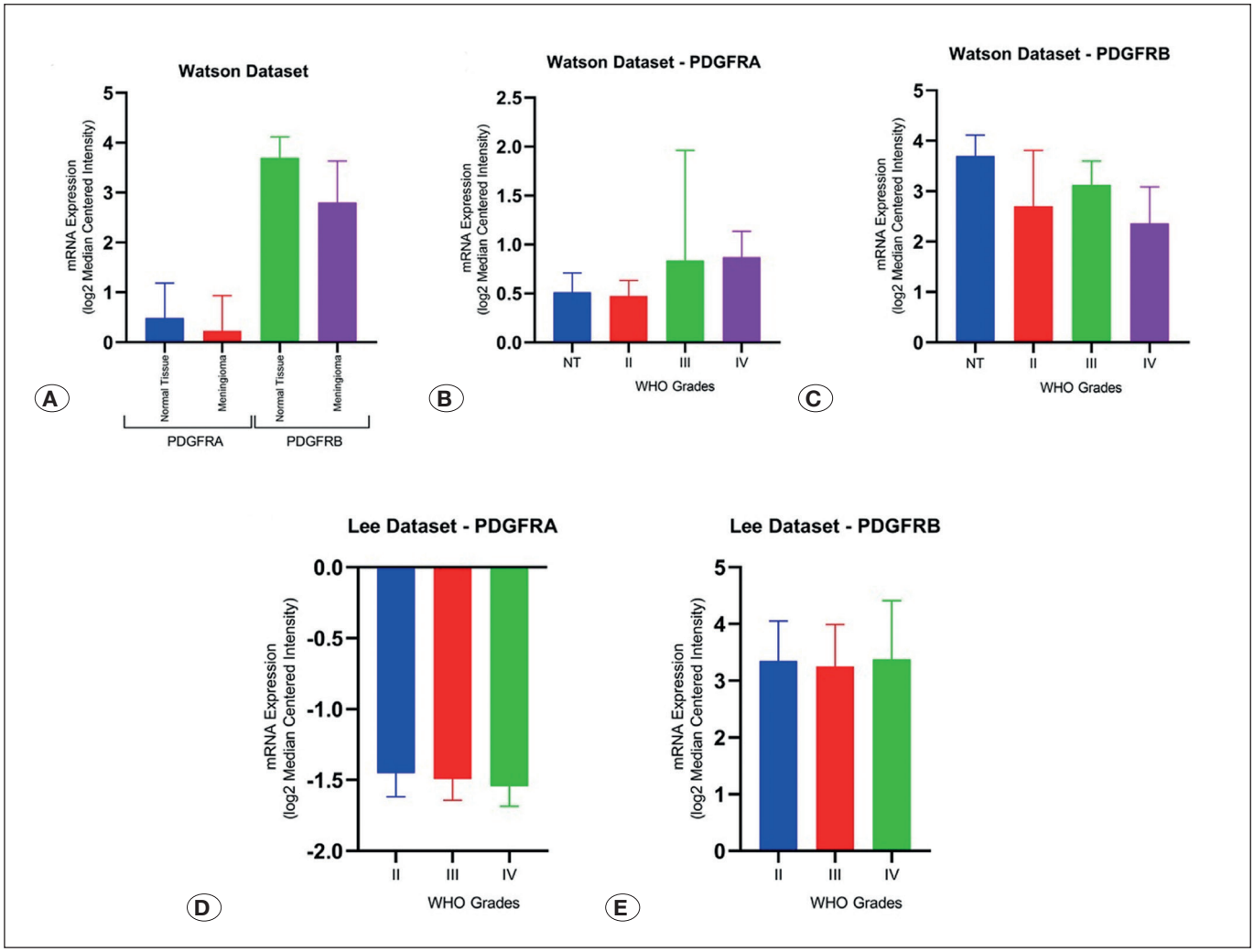

Figure 2: mRNA expressions of PDGFA and PDGFB genes in Watson Brain and Lee Brain 2 datasets. **A)** mRNA expression data provided by ONCOMINE were compared with normal tissue and meningioma grades (sample populations: 18, 65, and 68 for Watson Brain, PDGFA, and PDGFB for Lee Brain, respectively). **B)** The PDGF mRNA levels of different pathological grade meningiomas in the Watson datasets. **C)** The PDGFB mRNA levels of different pathological grade meningiomas in the Watson datasets. **D)** The PDGFA mRNA levels of different pathological grade meningiomas in the Lee datasets. **E)** The PDGFB mRNA levels of different pathological grade meningiomas in the Lee datasets.

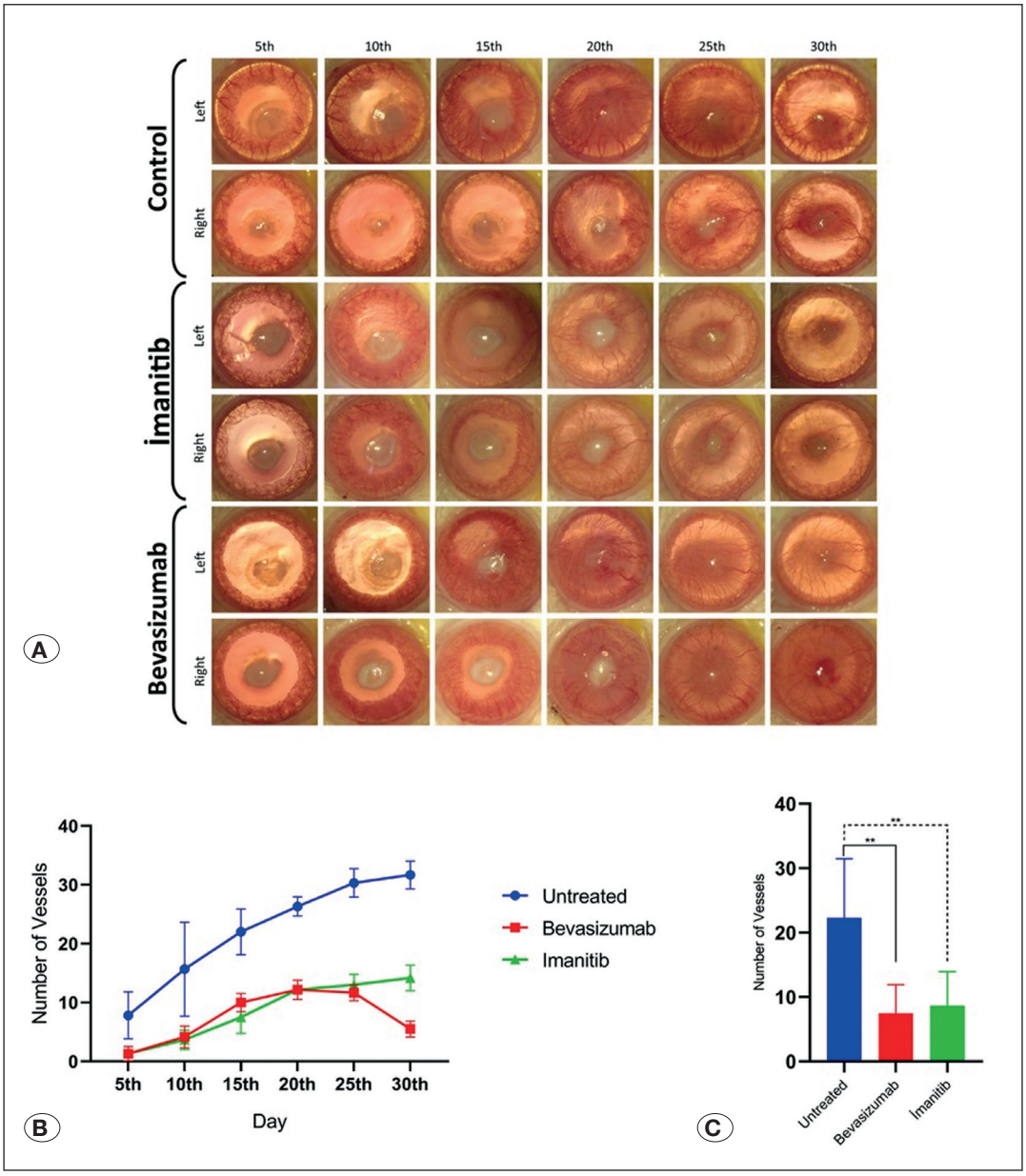

Figure 3: Corneal angiogenesis assay on rats. **A)** Vessel formation in response to meningioma tumors photographed under microscope at 4X magnification. **B)** The number of vessels at 5 days intervals of counting in all groups. The control, bevacizumab, and imatinib groups are shown in *blue*, *red,* and *green*, respectively. **C)** *Bar graph* of meningioma-induced vascularization. The average vein formation was determined.

increases with VEGF in meningiomas, triggering the hypoxia pathway and initiating a high angiogenesis rate which, in turn, affects disease malignancy and the survival rate (3). Inhibition of angiogenesis has been considered as a potential treatment option for meningiomas that are unsuitable for surgical intervention (2,4,10).

The treatment options for meningiomas vary with tumor location, spread, and WHO grade, with anti-cancer treatments being recommended in case of partial tumor removal, recurrence, or circumstances where surgical intervention is unsuitable due to tumor location. The high angiogenic potential of meningiomas and subsequent edema formation and/or tumor tissue growth can negatively affect a patient's quality of life (21). Although previous clinical studies have included systematic drug trials, none of them have been able to identify drugs suitable for supporting resection and radiotherapy for meningioma management. This study examined the antiangiogenic potential of various drugs by observing the angiogenic behavior of meningiomas using a reliable animal model. According to Staton et al., the ideal angiogenesis experiment should be robust, fast, reproducible with reliable readings, and include positive and negative controls subjected to multiparameter evaluations (22). The cornea angiogenesis assay is a dynamic and robust experimental setup developed by Gimbrone et al. where the observer can see variations in vascularization overtime (7,26). This model was optimized in the laboratory of the current study using rats and the angiogenesis behavior was observed when different tumor tissues were inoculated in various studies (1,9,10,11,13,23,24,26). This study used CAA to examine the

effects of bevacizumab and imatinib, whose antiangiogenic efficacy has been proven for other tumors, on meningioma-induced angiogenesis.

Bevacizumab Inhibits Meningioma-Induced Angiogenesis

VEGF plays an important role in the behavior of meningiomas. It contributes to tumor spread and aggression by stimulating the vascular formation mechanism and contributing to peritumoral edema formation (5). Previous gene expression and immunohistochemical staining studies among meningioma patients have shown a positive correlation between VEGF expression and tumor grades (3,20). No evidence was found to support the in silico evaluation conducted in the current study. However, this situation does not affect the VEGF role in the clinical course and drug trials that affect the VEGF pathway in meningioma patients. Phase II studies conducted by Grimm et al. showed that bevacizumab stabilized the disease course, indicated by positive PFS-6 scoring (87%, 77%, and 46% for grades I, II, and III, respectively) (3). A possible explanation for this could be that bevacizumab prevented initiation of the angiogenesis pathway by binding to VEGF secreted by the tumor tissue. These findings were confirmed by the corneal angiogenesis experiment conducted in rats treated with bevacizumab in the current study (p-value= 0.0041; Figure 3A, C).

Imatinib Inhibits Neovascularization

The PDGF pathway for angiogenesis is also of importance and contributes to the proliferation of cells. Le Ruhn et al. reported observing an increase in the PDGF ligand expression and its related receptors by meningioma grades (15). No significant changes in PDGFRA and PDGFRB expressions were observed in the grade-dependent and general meningioma cohorts included in the current in silico study (Figure 2). However, this does not provide any information on how drugs that inhibit the PDGFR pathway clinically affect meningioma treatment. A phase II study of imatinib, a PDGFR inhibitor, showed that the PFS-6 values of patients treated with imatinib were 45% and 0% for grades I and II–III, respectively, while another clinical study administering a combination of imatinib and hydroxyurea reported PFS-6 values of 61.9%, 87.5%, and 46.2% for the whole meningioma cohort, grade I, and grade II meningiomas, respectively (15). In the current study, CAA analysis showed that new vessel formation significantly decreased in rats treated with imatinib (Figure 3B, C; p-value=0.0075). Although the findings demonstrated the effects of imatinib on angiogenesis, its ineffectiveness against meningioma in clinical trials is still open to further investigation.

Imatinib and Bevacizumab Suppress Meningioma-Induced Angiogenesis in Rat Cornea Angiogenesis Model

CAA is the ideal research methodology for examination of angiogenesis efficiency. The current study inoculated rats with meningioma tissues of the same WHO grade and observed the effects of bevacizumab and imatinib on neovascularization. In the 30 days following inoculation, the corneal tissues of one group of rats were treated using imatinib (18 mg/ml) while the other group received bevacizumab (10 mg/kg) daily via intraperitoneal injections. Neovascularization evaluation included counting the microvessels reaching the micropocket from the choroid and grouping them into grades I (low angiogenic activity; less than three vessels visible), II (moderate angiogenic activity; three to eight vessels visible), and III (high angiogenic activity; more than eight vessels visible). Both drugs were seen to have a negative effect on neovascularization from day 20 onwards (Figure 3A, B). At the end of day 30, the number of vessels in the bevacizumab and imatinib groups was 5.57 and 2.24 times less than that in the control group, respectively. Bevacizumab and imatinib suppressed neoangiogenesis when compared to the control corneas that were not given any medication (Figure 3C; p-value= 0.0075 and 0.0041 for imatinib and bevacizumab, respectively). No statistically significant differences were observed between the two drug groups (p-value= 0.9504).

CONCLUSION

Drugs targeting angiogenesis, a critical phenomenon affecting meningioma management, can considerably improve the quality of life and survival of patients. The current study used CAA to investigate the effects of bevacizumab and imatinib on vascular formation induced by meningioma. The findings showed that both drugs effectively suppressed the formation of blood vessels induced by meningioma. Surgical intervention and radiosurgery are still the recommended methods of treatment for meningiomas. However, studies should be carried out on the mechanism of action of angiogenesis-targeting drugs in meningioma for a systematic treatment study suitable for the disease.

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AUTHORSHIP CONTRIBUTION

Study conception and design: NT, DC, MDO, TA, TK

Data collection: NT, DC, MDO, TA, TK

Analysis and interpretation of results: NT, DC, MDO, TA, TK

Draft manuscript preparation: NT, DC, MDO, TA, TK

Critical revision of the article: NT, DC, MDO, TA, TK

Other (study supervision, fundings, materials, etc...): NT, DC, MDO, TA, TK

All authors (NT, DC, MDO, TA, TK) reviewed the results and approved the final version of the manuscript.

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