Distribution of recurrence time intervals after anti-vascular endothelial growth factor therapy for myopic choroidal neovascularization

Myopic choroidal neovascularization (mCNV) is one of the most sight-threatening complications of pathological myopia. Currently, anti−vascular endothelial growth factor (VEGF) therapy is a standard treatment strategy for mCNV.[1] Once the CNV activity was ceased after initiating the therapy, patients were followed up every month and were generally treated as soon as recurrence was observed (pro re nata; PRN protocol). The continuous visits for examination pose a burden for patients and health care providers. Although the average number of treatments per year declined remarkably after 1 year,[2] it is difficult to apply these data directly to care protocol. In particular, the change in the recurrence risk should be investigated. Herein, we investigated the recurrence interval of mCNV after anti-VEGF therapy and assessed the existence and location of possible change points.

Methods

This retrospective study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Tokyo. The medical data of 50 eyes of 47 patients diagnosed with mCNV between August 2012 and August 2016 were retrospectively reviewed. Patients underwent ophthalmologic examinations, including best-corrected visual acuity measurement, fundus examination, and optical coherence tomography (OCT) at baseline. Patients were given anti-VEGF therapy and followed-up with PRN regimen based on the description in a previous study.[1] Recurrence was defined as the relapse of subretinal hemorrhage and/or fluid on fundus examination and/or OCT. The major outcome was the recurrence-free period. As part of the survival analysis, cumulative incidence probability was estimated using the Weibull model, which is frequently used for a parametric model of survival distribution, with or without change points.

Results

The baseline characteristics are the drugs used in this study are shown in Table 1 and Table 2. During the follow-up (38.8 ± 31.5 months), the recurrence rate was 18.3% at 6 months, 22.6% at 1 year, and 29.4% at 2 years after the treatment. The recurrence rate in the early period was underestimated by the Weibull distribution without any change point (Fig. 1). We then located a change point in this model. Based on the corrected Akaike information criterion (AICc) value, we found that the Weibull model with 1 change point at 10 months was optimal and better fitted than that without any change point (AICc = 181.3 and 182.1, respectively) (Fig. 1). In the patients who had not recurred until 10 months, the conditional recurrence rate at an additional 6 months was 4%.

Discussion

The parametric Weibull model was originally used for the estimation of product failure rate.[3] In medicine or biosciences, some researchers have estimated the mortality using this model.[4,5] A Weibull model with a change point was better fitted than a simple Weibull model without any change point. Parametric models with change points, including the Weibull model, can be potentially ideal to mathematically identify the possible failure process. We found that the estimated recurrence risk changed at 10 months after initiating the therapy, implying that there may be 2 phases of recurrence, the early phase with high recurrence rate and the late phase with lower recurrence rate. In a previous report, the change in mortality rate in HIV-infected patients after antiretroviral therapy was estimated using the Weibull model with change points.[6] Such objective estimates could help refining care protocol such as the interval of visits, counseling, and outreach, which have been empirically determined.

The limitation of the study was its retrospective nature with a relatively small sample size. Therefore, prospective study is required to convince our finding more. Second, because of limited sample size, we focused on characterizing the distribution of recurrence-free period in general and did not identify factors correlated with recurrence-free period. A further study will be needed to investigate them with larger number of patients. Third, not all patients underwent fluorescein angiography, because some of them who have been diagnosed with mCNV on the basis of clinical findings needed an emergent treatment without further angiography or did not consent to the examination. Therefore, we could not evaluate active vascular leakage on angiography before

Table 1—Baseline demographic and clinical characteristics

Number of eyes	50
Mean age ± SD (min to max), y	58.7 ± 15.3 (29 to 86)
Sex, n (%)	
Male	18 (36)
Female	32 (64)
Eye with mCNV, n (%)	
Right	28 (56)
Left	22 (44)
Mean BCVA, logMAR ± SD (min to max)	0.461 ± 0.486 (−0.176 to 1.699)
Mean refraction sphere, D ± SD (max to min)	−9.10 ± 5.22 (−18 to 0.5)
mCNV location, n (%)	
Subfoveal	35 (70)
Juxtafoveal	15 (30)

mCNV, myopic choroidal neovascularization; BCVA, best-corrected visual acuity.

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Table 2—Drugs used and treatments to achieve resolution of mCNV activity during the observation in this study

Drug, n (%)	
Bevacizumab	17 (33)
Ranibizumab	27 (54)
Aflibercept	6 (12)
Number of treatments to achieve resolution of mCNV activity, n ± SD	1.18 ± 0.44
Bevacizumab	1.56 ± 0.96
Ranibizumab	1.74 ± 1.30
Aflibercept	1.57 ± 1.47
Duration to achieve resolution of mCNV activity, months ± SD	1.64 ± 1.19
Bevacizumab	1.12 ± 0.33
Ranibizumab	1.15 ± 0.37
Aflibercept	1.50 ± 0.84
Time to recurrence, months ± SD	24.0 ± 28.8
Bevacizumab	46.7 ± 35.4
Ranibizumab	16.7 ± 17.0
Aflibercept	7.0 ± 5.4

mCNV, myopic choroidal neovascularization.

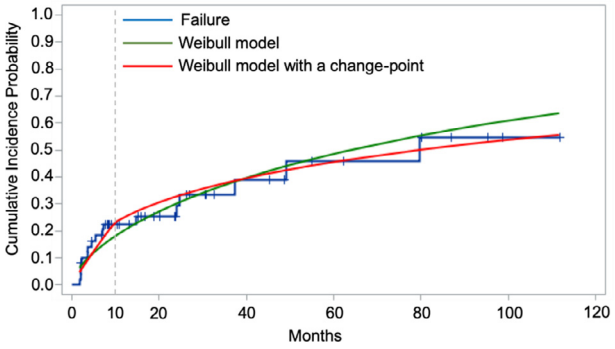

Fig. 1—Cumulative hazard curve. A Weibull model with one change point at 10 months was better fitted than a simple Weibull model.

the treatment. Fourth, we could not determine what affects the pathogenesis of mCNV recurrence. However, our mathematical model supported the existence of time-dependent factors influencing the recurrence. It can be helpful for physicians to provide a more efficient anti-VEGF treatment strategy for mCNV.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.