

Response of nevus of Ota to Q-switched alexandrite laser according to treatment interval

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In order to determine the appropriate treatment interval, 267 patients who underwent 3 sessions of treatment with Q-switched alexandrite laser were divided into 4 groups according to treatment interval, and their clinical responses were compared. Among them, 187 were asked about the process of pigment fading. Moreover, light and transmission electron microscopy were performed. It was noted that the clinical response of the 5–6 month interval group was significantly better than that of the 3–4 month group, but showed no significant difference from that of the 7–8 or ≥ 9 month group. 80.21% of investigated patients stated that marked pigment fading could no longer be observed 7 months after irradiation. 4 months after irradiation, the degenerated melanosomes and cell debris were still scattered among collagen fibers, scavenged gradually by macrophage. In conclusion, an appropriate treatment interval is 5–6 months.

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Nevus of Ota is a kind of facial discoloration due to presence of melanocytes in the dermis^[1], usually inflicting psychological distress on its patients. It is predominant for female and relatively common in Asians. Previous therapeutic modalities such as dermabrasion, cryotherapy and chemical peeling have been proved unsatisfactory in eliminating pigmentation. Moreover, scar formation and dyspigmentation after these therapies were not uncommon^[2–4]. In recent years, the advent of pulsed lasers has made it possible to treat nevus of Ota without injury, and there've been reports of successful treatment with Q-switched ruby laser (QSRL) and Q-switched alexandrite laser^[5]. However, the treatment interval has not been discussed in detail, though it is an important factor influencing the effect of therapy. Accordingly, among patients of nevus of Ota treated with Q-switched alexandrite laser from 1995 to 2000, we investigated 267 cases that underwent 3 treatment sessions with similar fluence, in order to determine the appropriate treatment interval.

The materials and methods of our study were listed as follows.

1. All the patients with nevus of Ota, who underwent 3 sessions of treatment by Q-switched alexandrite laser with similar fluence from 1995 to 2000 in our department, were included in the study. Those who had received treatment other than laser therapy were excluded.

2. PLTL-1 (Candela, Wayland, MA, USA) was used for treatment: wavelength 755 nm, pulse width 100 ns, spot size 3 mm in diameter, and fluence adjustable from 4 to 8 J/cm².

3. Sequential photography was performed prior to treatment and at each subsequent visit. The result of clinical response was evaluated according to the clearing of pigmentation on a 4-point scale: excellent, good, fair and poor. "Excellent" refers to a clearance of pigmentation $\geq 75\%$, "good" to a 50%–74% clearance, "fair" to a 25%–49% clearance, and "poor" to a clearing $< 25\%$. Photographs taken before and after treatment were compared independently by 3 dermatologists who were not

informed of the clinical data concerning the patients or their treatment. The average value of their ratings was designated as the final score of clinical response. In addition, adverse effects observed at each clinical visit were recorded.

4. The appropriate treatment interval should be as short as possible, on the premise that the same clinical response was achieved. We tried to determine it from the following 3 aspects.

- 1) Comparison of clinical response: The patients were divided into 4 groups according to the average treatment interval: 3–4 months, 5–6 months, 7–8 months and over 9 months. Clinical response was compared among the 4 groups statistically by means of Chi-square test.

- 2) Observation of pigment fading: Some of the patients were asked about the process of pigment fading after treatment. The time until this process could be no longer observed was recorded.

- 3) Pathological investigation: Multiple biopsies were performed on 5 female patients. Specimens obtained 3 days to 1 year after irradiation were examined under light microscope and transmission electron microscope.

5. All the statistical analyses were performed with SPSS software.

Our study presented the following results.

1. In total, 267 patients (male 34, female 233) were included in the study, ranging from 2 to 50 (mean \pm SD 21.58 \pm 8.61) years in age. Among them, were 132 cases of type I (mild type) of nevus of Ota, 69 cases of type II (moderate type), 49 cases of type III (intensive type) and 17 cases of type IV (bilateral type).

2. Cosmetic improvement was found in all the patients. Among them, 50.94% (136/267) achieved "excellent" results, 47.56% (127/267) achieved "good" results, and only 1.5% (4/267) exhibited "fair" results. There was no scar formation or permanent dyspigmentation (i.e. hyperpigmentation or hypopigmentation). In general, clinical response was satisfactory.

3. The results of study concerning the treatment interval were as follows.

Table 1. Comparison of Clinical Response for Different Interval

Clinical Response	Treatment Interval			
	3 – 4 months	5 – 6 months	7 – 8 months	≥ 9 months
Pigment Clearance ≥ 75% (No.)	15	61	26	34
Pigment Clearance < 75% (No.)	38	48	19	26
X^2	*10.956		*0.43	*0.008
P	* < 0.01		*0.836	*0.930

*Compared with the group with 5 – 6 month interval.

1) Comparison of clinical response: For the 4 groups of different treatment intervals, the age ($F = 2.35$, $P = 0.072$, Fisher test), sex ratio ($X^2 = 1.409$, $P = 0.703$, Chi-square test), color of lesion ($X^2 = 5.108$, $P = 0.825$, Chi-square test) and average fluence ($F = 0.019$, $P = 0.996$, Fisher test) employed showed no significant difference. The mean interval between the beginning of therapy and the time of the evaluation for the 4 groups was 18.1, 19.9, 22.7 and 31.1 months, respectively. The overall clinical response of the group with 5 – 6 month interval was significantly better than that with 3 – 4 month interval, but showed no significant difference from that of the other 2 groups (see Table 1). The therapeutic outcome seemed to improve with the elongation of treatment interval until it exceeded 6 months.

2) Process of pigment fading: Altogether, we asked 187 patients, claimed that pigment faded gradually after irradiation. The time when such fading ceased varied. Among them, 80.21% stated that marked pigment fading could no longer be observed 7 months after irradiation. In most of them, this process ceased in the period between the 4th and 7th month after treatment. For a few patients, such fading continued until more than 1 year after irradiation, and the longest was 2 years.

3) Pathological investigation: With a light microscope, it was found that dermal melanocytes gradually decreased after irradiation. In contrast, melanophages significantly increased in number, especially around 4 months after treatment, and returned to normal 1 year after irradiation. With a transmission electron microscope, both destruction of dermal melanocytes and degeneration of melanosomes could be observed. Scavenged mainly by macrophages, the degenerated melanosomes and cell debris were still scattered among collagen fibers around 4 months after irradiation. 1 year after treatment, they could hardly be seen at the site.

For a Q -switched alexandrite laser with a wavelength of 755 nm, there is relatively high absorption of laser energy by melanosomes and little competitive absorption by other chromophores^[6]. Its pulse width (100 ns) is shorter than the thermal relaxation time (TRT, the time needed for the temperature to decrease by 50%) of melanosomes^[7]. Therefore, according to the principle of selective photothermolysis^[8], Q -switched alexandrite laser is able to selectively destroy dermal melanocytes without injuring the surrounding tissue.

Of all our patients, 98% achieved "excellent" or "good" results without scar formation, suggesting that Q -switched alexandrite laser is both safe and effective in treating nevus of Ota, and this is consistent with the re-

sult reported in previous studies^[5].

It has been shown that the destruction of dermal melanocytes is secondary to the destruction of melanosomes in them. Degenerated melanosomes and cell debris are scavenged mainly by macrophages. This is a gradual and time consuming process, and therefore an interval is required between the two treatment sessions. There is no doubt that treatment interval is an important factor in laser therapy of nevus of Ota, which requires multiple treatments. By ensuring adequate pigment clearance, adoption of an appropriate treatment interval that is long enough improves the result of treatment, thereby decreasing the total number of treatment sessions required for complete pigment elimination. This means lower cost, making the treatment more accessible. Such an interval will also favor complete recovery of both irradiated area and surrounding tissue. On the other hand, treatment interval too long is obviously unnecessary. According to our investigation, we consider the interval of 5 to 6 months to be appropriate for most patients. The reasons are as follows.

1) The major reason lies in different clinical responses for different treatment intervals. In our studies, the overall clinical response of patients with a treatment interval of 5 – 6 months was significantly better than that of 3 – 4 months, and those with even longer intervals failed to show further clinical improvement. Since there was no statistical difference between the studied groups in average fluence, age, sex ratio and color of lesion, this result is reliable. It can be inferred that the overall clinical response can improve with the elongation of treatment interval until 6 months, beyond which the treatment outcome remained similar. Therefore, it is advisable to adopt the interval of 5 – 6 months in most cases.

2) Pigment fading has proved to be a gradual process. According to our investigation, remarkable pigment fading ceased within 7 months after irradiation in 80% of patients, and in most of them, such fading continued until the period of 4 to 7 months after irradiation. This indicates that the process of pigment fading usually takes no more than 7 months. It is advisable to start the next session of treatment after the process of remarkable pigment lightening is completed. The interval of 5 – 6 months is necessary for adequate pigment clearance, and this is important in achieving satisfactory result.

3) According to the light microscopic and transmission electron microscopic examinations, it was noted that scavenging of degenerated melanosomes as well as cell debris was still underway around 4 months after irradiation. This finding was consistent with that from the

observation of pigment fading. If re-irradiated at this time, melanophages, which play a major role in scavenging, would undergo similar destruction to that of dermal melanocytes, since melanophages also contain numerous melanosomes that are a primary target of pulsed laser^[9]. This would interrupt the process of scavenging and be unfavorable for pigment clearance. That's why a treatment interval longer than 4 months might be necessary to allow for the completion of scavenging.

As a result, all the investigations support our preliminary conclusion that a treatment interval of 5–6 months is appropriate for most patients treated with *Q*-switched alexandrite laser. Since more precise methods to evaluate clinical response lack at present, further study on more cases is required. For patients whose pigment fading is noted for more than 1 year after irradiation, elongation of the interval might be necessary.

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