KLINIKINIAI TYRIMAI

Predicting outcome of treatment with radiotherapy in endocrine ophthalmopathy

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Key words: endocrine ophthalmopathy; radiotherapy; antibodies to thyrotropin receptors; C-reactive protein.

Summary. Objective. To evaluate if the concentration of C-reactive protein and the level of antibodies to thyrotropin receptors might predict the outcome of retrobulbar irradiation in patients with endocrine ophthalmopathy.

Material and methods. Patients with moderate endocrine ophthalmopathy received orbital radiotherapy. The overall severity of endocrine ophthalmopathy was assessed using the total eye score based on the NOSPECS classification before the treatment and 6 months later. Treatment outcome was evaluated using major and minor criteria recommended by L. Bartalena 6 months after the treatment. Patients who improved in at least one major or in two or more minor criteria were considered responders. Patients in whom no changes occurred or who responded in only one minor criterion or eye status worsened were classified as nonresponders. The active disease was considered present in a patient who responded successfully to retrobulbar irradiation, and the active one when a patient did not respond.

Results. The level of antibodies to thyrotropin receptors in responders was 24.0 IU/L (range 2.0–405.0 IU/L) and in nonresponders 23.0 IU/L (range 2.0–405.0 IU/L); P=0.72. C-reactive protein levels in responders and nonresponders were 0.1 mg/L (range 0.1–3.1 mg/L) and 0.1 mg/L (range 0.1–1.5 mg/L), respectively; P=0.92. Although responders and nonresponders differed by proptosis, the severity of endocrine ophthalmopathy, and clinical activity score, but according to the binary logistic regression model, only the clinical activity score could give additional information on the prediction of the treatment outcome. If clinical activity score increased by 1, odds ratio for successful treatment outcome increased 2.4 times.

Conclusions. 1) At the baseline of radiotherapy, the level of antibodies to thyrotropin receptors and concentration of C-reactive protein in responders did not differ from nonresponders; 2) Responders did not differ from nonresponders to radiotherapy by age, gender, duration of endocrine ophthalmopathy and thyroid disease; 3) The pretreatment clinical activity score, total eye score, proptosis of the responders were higher.

Introduction
Endocrine ophthalmopathy (EO) is an autoimmune disease characterized by enlarged volume of the retrobulbar tissue and extraocular muscles. Clinical manifestations of EO include exophthalmos, strabismus, eyelid swelling, etc. (1). The underlying pathophysiology involves lymphocytic infiltration of the extraocular muscles (predominantly by T cells) and fibroblast proliferation with the production of glycosaminoglycans, resulting in interstitial edema. The treatment of this disorder is aimed at reducing the local immune response. Approximately only 60–70% of patients respond to immunosuppressive treatment (1, 2). Supposedly, the activity of the disease (active or inactive) has impact on the effectiveness of the treatment. The idea of different stages in the course of the eye disease is largely derived from the observation made by I. B. Hales and F. F. Rundle (3). They observed that the natural course comprises an initial, dynamic phase followed by a static “burn out” phase.
in which the ocular findings do not change, but alterations such as proptosis and motility restrictions remain. The duration of the active phase is variable and ranges from several months to a few years (2, 4). The given treatment might be effective at the dynamic stage, but ineffective during the static phase. During the active phase, immune reactions take place in the orbits while during the inactive phase fibrosis is a predominant process (2, 4). The severity of EO may be the same at both the phases of activity (4, 5). There is no doubt that at the beginning of the disease, when the condition of the eyes is severe and progressive, the disease is active, and this necessitates immunosuppressive treatment.

The determination of the phase of the disease should serve as an indicator for treatment: immunosuppression in case of an active disease, and corrective surgery for the inactive phase of disease. The correct choice should lead to a satisfactory level: the response rate to immunosuppression might rise and reach 100% (4). No benefit would be noticed if immunosuppression is given when the inactive stage has been already reached. If surgery is applied in active phase, later on the condition of the eyes may even worsen (4). If the immunosuppressive treatment is prescribed in cases when the disease is already inactive, the treatment will be ineffective, and the patient will be exposed to an unnecessary risk. Management of the disease according to disease activity has the advantage as immunosuppression will be administered only to patients who are likely to respond, and patients with inactive disease might be referred directly for surgery (1, 4, 6).

Thus, a dilemma arises for doctors: how to treat the patient with still severe EO if the patient has been ill for more than 1 year and has already been treated with one of the immunosuppressive treatment modalities – to give additional immunosuppressive treatment or to perform reconstructive surgery? A correct method for the distinguishing these phases would save time, money, and an unnecessary risk. Possibility to distinguish these phases is very important not only in choosing EO treatment modalities, but also in cases of radioiodine treatment of hyperthyroidism, i.e., in choosing whether to administer or not the preventive treatment with glucocorticoids before radioiodine treatment (1, 6).

The determination of the stage of the disease is complicated. The “golden standard” for assessment of the disease activity should be biopsies of the retrobulbar tissues, but they are seldom feasible. The duration of the disease and other clinical signs in many cases are not informative enough. The “surrogate standard” – treatment outcome – is used for determining the informative value of the parameters of disease activity. A variety of methods for distinguishing these phases have been suggested, including the assessments of T2 relaxation time by magnetic resonance imaging (7) and extraocular muscle reflectivity using ultrasound (8), orbital scintigraphy using octreotide (9), and the determination of urinary glycosaminoglycan levels (10). Unfortunately, none of these methods has sufficient power to be useful in clinical practice. Additionally, some of them are expensive and related to exposure to radiation.

Our pilot study was aimed at the estimation of the concentration of C-reactive protein (CRP) and level of antibodies to thyrotropin (TSH) receptors as parameters of disease activity. CRP concentration is a parameter of disease activity in other autoimmune diseases such as rheumatoid arthritis (11). The level of antibodies to TSH receptors as parameter of disease activity has been already examined in one study (12). We applied the logistic regression model for obtaining additional information using the level of antibodies to TSH receptors and CPR concentration, clinical activity score (CAS), and the duration of the disease as parameters of disease activity. Active disease was considered present in a patient who successfully responded to retrobulbar irradiation, and the inactive one when a patient did not respond.

The aim of the study was to evaluate if the concentration of C-reactive protein and the level of antibodies to TSH receptors might predict the outcome of retrobulbar irradiation in patients with endocrine ophthalmopathy.

**Material and methods**

A prospective study of 25 patients with moderately severe EO was performed at the Department of Endocrinology of Kaunas University of Medicine Hospital. The study was approved by the local Medical Ethics Committee.

Inclusion criteria were as follows: age of 35–75 years, consent to take part in the study, diagnosed Graves’ disease (GD) (normal thyroid function achieved before and during the study), and diagnosed EO of moderate severity. All patients had been treated for their eye disease with oral prednisone for more than 6 months before the study; the patients had no diabetes mellitus, pregnancy, or surgery for EO performed previously; no immunosuppressive treatment or treatment with steroids was prescribed 6 months before study and during it.

All patients received orbital irradiation (2 Gy,
total dose of 20 Gy). The overall severity of endocrine ophthalmopathy was qualitatively evaluated by ophthalmologist before treatment and 6 months later using the total eye score based on the NOSPECTS classification. Treatment outcome was assessed using major and minor criteria (recommended by L. Bartalena (13)) 6 months later. Patients who improved in at least one major or in two or more minor criteria were considered responders. Patients in whom no changes occurred or who responded in only one minor criterion or eye status worsened were classified as nonresponders. It was considered that the responders are in the active and nonresponders are in the inactive phase of the disease. Later on, various activity parameters of endocrine ophthalmopathy were linked with the response to the treatment. The informative value of these parameters predicting the treatment outcome was evaluated.

The study included 20 females and 5 males; the mean age of patients was 54.0±9.2 years. The median duration of endocrine ophthalmopathy was 21.0 months (minimal duration 10 months, maximal 216 months); the median duration of Graves’ disease was 24.0 months (minimal 10 months, maximal 296 months).

The condition of soft tissue of the eyes (lid swelling and redness) was evaluated according to the color profile and frontal facial photographs. The pictures were blindly evaluated by an ophthalmologist. Proptosis was measured with a Hertel exophthalmometer. The eye muscle damage was evaluated according to NOSPEC classification (14). The Snellen chart was used to measure visual acuity. The assessment of the severity of the eye disease was performed using the NOSPEC classification by calculating total eye score (TES) (15). The clinical activity score (CAS) based on the classical signs of the inflammation (pain, redness, swelling, etc.) was calculated according to M. Mourits classification (16).

Venous blood was taken for the assessment of serum TSH and free thyroxine (FT\textsubscript{4}) concentration; blood analysis was performed using commercial kits obtained from IMMUNOTECH (Prague, Czech Republic) with sensitivity of 0.025 mIU/L for TSH and 0.4 pmol/L for FT\textsubscript{4}. Intra-assay variation ranged from 4% to 8%, and inter-assay variation – from 3% to 11%. The normal range of TSH concentration was from 0.17 mIU/L to 4.0 mIU/L; of FT\textsubscript{4} concentration, from 11.5 pmol/L to 23.0 pmol/L. Venous blood was also taken for the assessment of the level of antibodies to TSH receptors as thyrotropin-binding inhibitory immunoglobulin (TBII) in serum; the analysis was performed using commercial kits obtained from IMMUNOTECH (by RIA, Prague, Czech Republic) with the sensitivity of 0.1 IU/L. The upper limit of normal TBII level was 14 IU/L. Intra-assay variations ranged from 3% to 8%, and inter-assay variations – from 3% to 9%.

C-reactive protein was detected by photometric turbidimetric quantitative test using “HUMAN” kit according to manufacturer’s recommendations with sensitivity of 0.01 mg/L. The concentration lower than 8 mg/L was considered normal. Intra-assay variation was between 2% and 8%, and inter-assay variation between 5% and 10%.

Statistical analysis. The results are expressed as mean±SD or as median (range). The comparison between groups was performed using the unpaired t test for parametric data or the Mann–Whitney U test for nonparametric data. The paired test was used for comparisons within a group. The Kruskal–Wallis test was used for comparison among more than two groups. Comparisons between groups concerning categorical variables were performed using the two-tailed χ\textsuperscript{2} analysis. A probability level of P<0.05 was taken as significant. Using a two-by-two table, sensitivity and specificity was calculated for various activity parameters proposed. The binary logistic regression models were created with the purpose to detect significant signs for predicting the treatment outcome. The outcome was dependent variable, and such signs as CAS, duration of the disease, sex, and others were independent ones. The critical value for CAS and the duration of EO were the indices with the greatest specificity and sensitivity.

Results

There were 15 (60.0%) patients assigned to the group of responders and 10 (40.0%) patients to the group of nonresponders. Two groups did not differ by the patients’ age, gender, the duration of EO and GD, or the frequency and duration of cigarette smoking (Table 1).

The greatest proptosis and the severity, as total eye score (TES), and activity, as CAS of the disease, were found in patients who responded to radiotherapy (Table 1).

There were more smokers in nonresponse group compare with response group (difference is not statistically significant).

CPR concentration was 0.1 mg/L (range 0.1–3.1 mg/L) and TBII level was 22.0 IU/L (range 2.0–405.0 IU/L) in the whole study group at the beginning of the study. Median baseline CPR concentration and TBII level did not differ between responders and nonresponders (Table 2).

The percentage of patients with the level of
Table 1. The characteristics of patients who responded and those who did not respond to treatment at the beginning of the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n=15)</th>
<th>Nonresponders (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>54.0 (38–75)</td>
<td>50.5 (42–74)</td>
<td>0.74</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>2 (13.3)</td>
<td>3 (30.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Duration of endocrine ophthalmopathy, median (range), months</td>
<td>20.0 (10–214)</td>
<td>21.5 (10–216)</td>
<td>0.87</td>
</tr>
<tr>
<td>Duration of Graves’ disease, median (range), months</td>
<td>24 (12–78)</td>
<td>24 (10–396)</td>
<td>0.86</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>6 (40.0)</td>
<td>7 (70.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Duration of endocrine ophthalmopathy, median (range), years</td>
<td>22 (20–30)</td>
<td>18 (9–30)</td>
<td>0.23</td>
</tr>
<tr>
<td>Proptosis, mean±SD, mm</td>
<td>22.6±2.4</td>
<td>20.2±1.8</td>
<td>0.04*</td>
</tr>
<tr>
<td>Total eye score, median (range)</td>
<td>15.0 (9–32)</td>
<td>12.5 (7–24)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Clinical activity score, mean±SD</td>
<td>3.7±1.3</td>
<td>2.1±1.3</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

* The differences are statistically significant. SD – standard deviation.

Table 2. The results of laboratory assays of responders and nonresponders before the treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n=15)</th>
<th>Nonresponders (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of C-reactive protein, mg/L</td>
<td>0.1 (0.1–3.1)</td>
<td>0.1 (0.1–1.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Concentration of antibodies to TSH receptors, IU/L</td>
<td>24.0 (2.0–405.0)</td>
<td>23.0 (2.0–405.0)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

TSH – thyroid-stimulating hormone. The data are presented as median and range. The groups were compared using the Kruskal–Wallis test.

antibodies to TSH receptors more than 14 IU/L did not significantly differ between groups (60.0% vs. 62.0%; P=0.72) Thus, positive prognostic and negative prognostic values (44.0%) were low. The sensitivity and specificity were low as well – 66.6% and 40.0%, respectively.

We analyzed if there were any differences (in clinical signs or CRP concentration and level of antibodies to TSH receptors) among patients with different treatment outcomes (Table 3).

There was a trend towards more favorable treatment outcome in cases of greater CAS, although the difference between the groups was not significant (P=0.17; Fig.).

Binary logistic regression analysis was performed with the purpose to detect factors that might predict treatment outcome.

All signs that could be informative for the prediction of the treatment outcome were included in these models (Table 4).

Only CAS was included in the optimal logistic regression model using the procedure of model construction “Forward LR” (Table 5). Other parameters such as EO duration, age, smoking, or TBI1 level and CRP concentration were not included into the optimal model.

If CAS increased by 1, odds ratio for successful treatment increased 2.4 times (Table 5). This model described the treatment outcome correctly in 68.0% of cases.

The value of CAS equal to 4 was taken as a critical. If CAS was equal to or more than 4, odds ratio for successful treatment was 10.2 (Table 5). According to this model, it is possible to predict the treatment outcome correctly in 72.0% of cases. For example, if CAS is 3, then the probability for successful treatment outcome is 66.0%; if CAS is 5, then the probability is 82.0%.

Discussion

It is not easy to find methods for assessing the EO activity phase. Histological examination is the golden standard for the determination of the disease activity.

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Table 3. The clinical signs and results of laboratory assays of patients with different treatment outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment outcome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>very good (n=9)</td>
<td>good (n=6)</td>
</tr>
<tr>
<td>Clinical signs EO duration</td>
<td>24 (10–214)</td>
<td>18 (12–36)</td>
</tr>
<tr>
<td>Results of laboratory assays</td>
<td>Concentration of CRP, mg/L</td>
<td>0.1 (0.1–3.1)</td>
</tr>
<tr>
<td></td>
<td>Concentration of TBII, IU/L</td>
<td>9.3 (2.0–405.0)</td>
</tr>
</tbody>
</table>

CAS – clinical activity score; EO – endocrine ophthalmopathy; TBII – thyrotropin-binding inhibitory immunoglobulin; CRP – C-reactive protein.
The data are presented as median and range. The groups were compared using the Kruskal–Wallis test.

Fig. Median values of clinical activity score in patients with different treatment outcome

Table 4. The informative value of indicators for predicting the treatment outcome in logistic regression model

<table>
<thead>
<tr>
<th>Characteristic (factor)</th>
<th>Exp (B)</th>
<th>Standard error</th>
<th>P</th>
<th>Exp (B) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1</td>
<td>0.16</td>
<td>0.34</td>
<td>0.8–1.6</td>
</tr>
<tr>
<td>Sex</td>
<td>0.3</td>
<td>2.2</td>
<td>0.66</td>
<td>0.01–33.0</td>
</tr>
<tr>
<td>Duration of EO</td>
<td>0.9</td>
<td>0.02</td>
<td>0.47</td>
<td>0.9–1.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>50.6</td>
<td>3.2</td>
<td>0.22</td>
<td>0.08–2883.0</td>
</tr>
<tr>
<td>Propotosis</td>
<td>4.0</td>
<td>0.95</td>
<td>0.14</td>
<td>0.6–26.1</td>
</tr>
<tr>
<td>TES</td>
<td>0.8</td>
<td>0.19</td>
<td>0.49</td>
<td>0.5–1.2</td>
</tr>
<tr>
<td>CAS</td>
<td>5.2</td>
<td>1.2</td>
<td>0.17</td>
<td>0.4–56.0</td>
</tr>
<tr>
<td>Concentration of TBII</td>
<td>1.0</td>
<td>0.01</td>
<td>0.16</td>
<td>0.9–1.0</td>
</tr>
<tr>
<td>Concentration of CRP</td>
<td>12.5</td>
<td>2.3</td>
<td>0.28</td>
<td>0.1–1347.0</td>
</tr>
<tr>
<td>Constant</td>
<td>28.8</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TES – total eye score; CAS – clinical activity score; EO – endocrine ophthalmopathy; TBII – thyrotropin-binding inhibitory immunoglobulin; CRP – C-reactive protein; CI – confidence interval; Exp (B) – Exp: the base of the natural logarithms, B: coefficient estimated from data.
Biopsy of extraocular muscles or retrobulbar tissue is a complicated and risky procedure, and thus usually it is not used in clinical practice and trials. Besides, even in biopsy, the mistakes may occur while taking the material for the examination (4). For this reason, indirect methods are usually applied. This means that the activity parameter is analyzed in association with the treatment effectiveness. If the parameter can help to predict the effectiveness of the treatment, it is considered useful. Our study was a pilot study for evaluation of the informative value of CPR concentration as a parameter of disease activity and a predictor of treatment outcome. The concentration of CRP is widely used as an indicator of disease activity also in other autoimmune disorders such as rheumatoid arthritis.

The production of C-reactive protein is induced by interleukin-1 and interleukin-6, produced by active lymphocytes during the active phase of an autoimmune disease (17). It is known that the concentration of C-reactive protein during acute inflammation can increase more than hundreds of times for a longer period, whereas the concentration of other acute inflammation proteins such as interleukin-6 decreases very soon (17, 18). The fact that the concentration of C-reactive protein decreases more slowly than the concentration of interleukin-6 (17) lets us expect that the concentration of CRP may give even more information on the activity of the disease than the concentration of interleukin-6.

Thus, our hypothesis was that CRP concentration might give information for detection of the active phase of the disease, especially considering the fact that some studies have shown the concentration of interleukin-6 to be helpful in differentiating the phases of the disease (18, 19). In our study, the concentration of C-reactive protein in all cases was within normal limits. There was no difference in CPR concentration between the responders and nonresponders before the treatment. Unfortunately, this concentration not only did not help to predict the outcome of the treatment, but it was not even increased in any of the patients. This may be explained in several ways. First, it may be that the volume of the infiltrated retrobulbar tissues was too small to influence significantly the level of CRP in the systemic venous blood. Second, all studied patients previously had been treated with glucocorticoids. It is possible that the treatment with glucocorticoids decreased the concentration of C-reactive protein before our evaluation.

It is generally accepted that the TSH receptor is an autoantigen against which the immune response is directed in Graves’ hyperthyroidism and EO (1, 20) as it was found in both the thyroid and the orbital tissues. Dutch scientists reported a significant correlation between the level of antibodies to TSH receptors and the activity and severity of the disease (12).

Our results have shown that the level of antibodies to TSH receptors before the treatment did not help to differentiate the future responders from nonresponders. No clear tendency was observed in the groups of patients with different treatment outcome. These findings correspond to those of other researchers who did not reveal any correlation between the level of the same antibodies (determined in the same way as in our study) and clinical signs of EO (20, 21). M. Gerding (12) stated that the level of antibodies to TSH receptors directly correlates with clinical features and CAS. The reason why this concentration was not informative and the results were variable may be explained in several ways:

1. It is possible that antibodies to TSH receptors play an important role only at the beginning of the autoimmune process in the orbits, but later other mechanisms such as production of antibodies to the extraocular muscles, release of cytokines from the lymphocytes, or synthesis of glycosaminoglycans have a greater influence and become more important in the development of the active process and severity of EO.

2. It may be that not only thyroid function, but also thyroid size has an influence on the level of antibodies to TSH receptors. There are data indicating that antibodies are produced not only in the lymph

Table 5. The logistic regression model for the prediction of the outcome of retrobulbar irradiation with the help of clinical activity score

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Exp (B)</th>
<th>Standard error</th>
<th>P</th>
<th>Exp (B) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>2.4</td>
<td>0.4</td>
<td>0.02</td>
<td>1.1–5.4</td>
</tr>
<tr>
<td>CAS ≥4</td>
<td>10.2</td>
<td>1.1</td>
<td>0.04</td>
<td>1.0–102.7</td>
</tr>
</tbody>
</table>

CAS – clinical activity score; CI – confidence interval; Exp (B) – Exp: the base of the natural logarithms, B: coefficient estimated from data.

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nodes, but also in the thyroid gland (1). All our patients had normal thyroid function, but the thyroid size was not measured in our study. Therefore, we cannot exclude that the thyroid size influenced the level of antibodies to TSH receptors in our study.

3. Previous treatment of thyrotoxicosis could influence the level of antibodies. In cases of thyroid surgery or treatment with radioactive iodide, the pool of the TSH receptors is eliminated. If the remission of thyrotoxicosis is achieved with antithyroid drugs, the immunomodulatory effects of the drugs may influence the level of the antibodies to TSH.

4. One more reason for the absence of difference between groups, compared to the results provided by M. Gerdin (12), could be the specificity of first-generation kit used in our study (with porcine TSH receptors as an antigen), while the aforementioned investigator used a second-generation kit. The sensitivity and the specificity of second-generation kits are much higher than the first generation ones, because recombinant human thyrotropin is used in second-generation kits (22).

In our study, age, gender, duration of the disease, or smoking habits of patients in whom the treatment was effective did not differ from those who did not respond to the treatment (Table 1). Other researchers did not find such differences between the responders and nonresponders either (23), although J. Kriss (24) indicated that the desired effect of retrobulbar irradiation in elderly people, especially males, was lower than in the younger individuals. T. Hurblt with colleagues (25) noticed that the treatment was more effective in patients with a shorter duration of the illness.

Our study has shown that the responders were ill with more severe EO than the nonresponders. Before the treatment, the responders had eyelid proptosis greater than the nonresponders. In the literature, there is no uniform opinion concerning the dependence of the treatment efficacy on severity (mild, moderate, or severe) of EO. Some authors reported a better response in patients with fewer eye lesions. These authors did not find how clinical signs could be used for the prognostication of the treatment effect. In a randomized trial, Dutch scientists did not notice any beneficial effect when retrobulbar irradiation was administered in the treatment of mild EO (26).

Some authors suggest using the “wait and see” method as a parameter of disease activity. However, for this purpose, objective methods for evaluation of the clinical signs are needed, though in clinical practice such methods are rarely used. Moreover, the patients in such cases have to wait, and the disease may become more severe (12). In general, almost all authors agree that it is impossible to predict the treatment outcome based on clinical signs (4, 26).

In our study, CAS was significantly greater in the group of the responders than nonresponders. In addition, a trend towards a higher effectiveness of the treatment was noticed in cases with greater CAS before the treatment.

CAS reflects the main signs of inflammation. M. Mourits et al. reported that CAS could provide information about the phase of the disease and predict the outcome of the treatment (16). This simple method allows a sufficiently good prognostication of the treatment outcome.

Smoking frequency of responders did not differ from nonresponders, but nonsmokers were more likely to show a positive treatment outcome than smokers. The difference was not statistically significant, perhaps due to the insufficient number of cases. The duration of smoking did not differ between both the groups. There are also data in the literature that smoking not only increases the risk of EO, but also decreases the effectiveness of radiotherapy (6, 13, 14, 27).

Though the responders differed from nonresponders by proptosis, the severity of EO, and CAS, only the CAS was included in a logistic regression model. If CAS increased by 1, the odds ratio for the successful treatment outcome increased 2.4 times. Using the critical CAS value of 4, odds ratio increased more than 10 times if the patients’ CAS was greater than 4.

Thus, the evaluation of the clinical activity score (easy to be used by an ophthalmologist and an endocrinologist) is the best basis for decision-making concerning the choice of treatment. Other parameters do not provide additional information for the prognostication of the treatment outcome. Further studies are needed for the evaluation of new methods or combinations of them while determining the phase of EO and prognosticating the outcome of immunosuppressive treatment taking also into consideration the supposition that genetic factors may influence the treatment outcome too.

Conclusions

1. At the baseline of radiotherapy, the level of antibodies to thyrotropin receptors and the concentration of C-reactive protein in the responders did not differ from the nonresponders.

2. The responders to radiotherapy did not differ from nonresponders by age, gender, or the duration of endocrine ophthalmopathy and thyroid disease.

3. The pretreatment clinical activity score, total eye score, and proptosis in the responders were significantly higher than nonresponders.
Endokrininės oftalmopatijos gydymo jonizuojančiają spinduliuotę efekto prognozavimo tyrimas

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Kauno medicinos universiteto Endokrinologijos institutas, 1Endokrinologijos klinika, 2Akių ligų klinika

Raktąžodžiai: endokrininė oftalmopatija, jonizuojančioji spinduliuotė, antikūnai prieš tiretropinio hormono receptorijų, C reaktyvusis baltymas.

Santrauka. Tyrimo tikslas. Įvertinti, ar galima, remiantis C reaktyviojo bažnytimo ir antikūnų prieš tiretropinio hormono receptorijų koncentracija, prognozuoti jonizuojančiosios spinduliuotės veiksmingumą gydant ligonius, sergančius endokrinine oftalmopatija.


Rezultatai. Asmenims, kuriems gydymas buvo veiksmingas, antikūnų prieš tiretropinį hormoną koncentracija buvo 24,0 IU/l (ribos 2,0–405,0 IU/l), o tiems, kuriems gydymas buvo neveiksmingas – 0,1 mg/l (ribos 0,1–3,1 mg/l, o tiems, kam gydymo poveikis buvo neveiksmingas – 0,1 mg/l (ribos 0,1–1,5 mg/l); p=0,72. C reaktyviojo bažnytimo koncentracijos mediana asmenims, kuriems gydymas buvo veiksmingas – 0,1 mg/l (ribos 0,1–3,1 mg/l, o tiems, kam gydymo poveikis buvo neveiksmingas – 0,1 mg/l (ribos 0,1–1,5 mg/l); p=0,92. Nors išverstakamos, endokrininės oftalmopatijos sunkumas skyrėsi tiems, kam gydymas buvo veiksmingas ir tiems, kam nebuvo gydymo poveikio, tačiau, naudojant dvinarės logistinės regresijos modelį, tik ligos aktyvumo indeksas suteikė papildomos informacijos prognozuojant gydymo veiksmingumą. Jei ligos aktyvumo indeksas padidėja vienetu, šansų santykis, kad gydymas bus veiksmingas, padidėja 2,4 karto.

Išvados. 1) Antikūnų prieš tiretropinį hormono receptorijų koncentracija ir C reaktyviojo bažnytimo koncentracija prieš gydymą nesiskyrė tiems, kuriems Apticojusioji spinduliuotė buvo veiksminga ir tiems, kuriems nebuvo gydymo poveikio; 2) asmenims, kuriems gydymas buvo veiksmingas, nesiskyrė nuo tų, kuriems jonizuojančioji spinduliuotė buvo neveiksminga pagal amžių, lytį, endokrininės oftalmopatijos ir skydeliaus ligos trukmė; 3) prieš gydymą ligos aktyvumo indeksas, bendras oftalmopatijos indeksas, išverstakomas buvo didesni asmenims, kuriems jonizuojančioji spinduliuotė buvo veiksminga.

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