Changes of Serum Thymidine Kinase in Children with Acute Leukemia

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Abstract. Background: Thymidine kinase (TK) is involved in nucleic acid synthesis and is therefore considered to be an important proliferation tumor marker. Our main goal was to determine the significance of elevated TK levels as a relapse marker during follow-up with child patients suffering from acute leukemia. Patients and Methods: TK serum levels in 38 children with acute leukemia (34 lymphoblastic, 4 myeloblastic) were determined using radio-receptor analysis (RRA, Immunotech, Prague, USA). All patients included in this study had had TK examined before the start of the treatment and at least twice during the follow-up. Results: Our results showed that TK serum levels at the time of diagnosis were extremely high (78-5826 U/l, median value 403 U/l, normal <8 U/l), while in remission TK serum levels were much lower (5-80 U/l, median value 31 U/l). During relapse of acute leukemia (5 cases), TK levels increased considerably to measurements between 120-800 U/l (median value 324 U/l). The study showed that the elevation of TK serum levels during follow-up was a helpful marker for the recognition of an early stage of relapse and in some cases occurred as early as one month before the appearance of clinical signs. Sensitivity in this case was 87% and thus TK serum levels seem to be a very good parameter during follow-up because of acceptable sensitivity, low cost (4 $/sample) and the elimination of a requirement for screening of bone marrow samples. Conclusion: While TK serum levels were helpful in predicting relapse during follow-up, it is necessary to note that they did not correlate with prognosis in our group of patients during the time of the initial diagnosis of acute leukemia.

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maximum) were calculated for the whole group of patients, as well as for individual subgroups. Profiles of specificities and corresponding sensitivities for individual referential groups are illustrated with receiver operating characteristics (ROC) curves in accordance with EGTM recommendations (21). The comparison of variables in given groups and subgroups, considering the distribution of the variables, was performed by non-parametric tests (Kruskal-Wallis test or two-sample Wilcoxon test). The relations between the parameters were computed using Spearman’s correlation coefficient.

The measured TK levels were compared with other parameters that are usually tested in patients with hemoblastosis and are considered to be markers of cell proliferation (lactate dehydrogenase, erythrocyte sedimentation, β-2 microglobulin, ferritin) (5). The TK levels were compared with the clinical status of the patients and the afore-mentioned parameters. Children who underwent the complete therapy during the observed time, and who had no other somatic problems after finishing the treatment, were included in the study for follow-up.

Results

The basic characteristics of the patients who participated in this study are shown in Table I, followed by figures containing the summaries of the measurements. The levels of TK before the start of the treatment, during remission, and during relapse are shown in Figure 1. The diagnosis values are extremely high (normal is up to 8 U/l), remission values are much lower, and there is a significant increase \((p<0.001)\) in the TK levels about 1 month before relapse that almost reaches the values measured during the diagnosis and before the beginning of the treatment. Figure 2 shows the same for the levels of β-2 microglobulin. Note that during relapse, there is also a significant increase \((p<0.041)\) of the levels of β-2 microglobulin compared to remission status. The levels of ferritin during diagnosis, remission and relapse are shown in Figure 3. Note that there is no significant change of levels of ferritin during relapse compared to remission status. The erythrocyte sedimentation rates at diagnosis, during remission and during relapse are shown in Figure 4. There is a statistically significant increase \((p<0.001)\) in the erythrocyte sedimentation rate during relapse compared to remission status. A comparison of ROC characteristics for investigated parameters is shown in Figure 5. The best profile was achieved using TK.

Table I. Basic characteristics of the study group.

<table>
<thead>
<tr>
<th>Number of children</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>α 28 (♀) 10</td>
</tr>
<tr>
<td>Type of leukemia</td>
<td>34 x ALL (4 x AML)</td>
</tr>
<tr>
<td>Length of observation</td>
<td>46.7 months</td>
</tr>
<tr>
<td>Number of relapses in group</td>
<td>5 (all in bone marrow) (4 x first relapse) (1 x second relapse)</td>
</tr>
</tbody>
</table>

Figure 1. Box and whisker plots of levels of thymidine kinase at diagnosis, during remission and during acute leukemia relapse.

Figure 2. Box and whisker plots of levels of β-2 microglobulin at diagnosis, during remission and during relapse.
Discussion

Based on our results and the published literature, we conclude that TK is a very good parameter for monitoring the progress of basic hemato-oncological disease after the end of the intensive part of the therapy (11-17). Out of all of the parameters that we investigated (TK, lactate dehydrogenase, erythrocyte sedimentation, β-2 microglobulin, ferritin), TK seems to be the most suitable for long-term monitoring and follow-up. However, we were not able to demonstrate the prognostic capabilities of TK levels or other parameters determined at diagnosis with clinical continuation of the disease (18, 19). A group of our patients who experienced a relapse did not show significant differences in the levels of the monitored parameters (at the time of diagnosis) as compared to patients without a relapse. We conclude from our results that despite the fact that the level of TK reflects the activity of the leukemic process, entry levels of TK are not suitable for stratification of child patients with acute leukemia into risk categories (20). Because there is very little published literature dealing with tumor markers for acute hemoblastosis in children and because of the promising results of our studies, we plan to continue our research with a primary focus on TK and possibly other proliferative molecules.

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References


