Delayed cytogenetic response with prolonged interferon-\(\alpha\) treatment in chronic myeloid leukemia patients: quantification of BCR-ABL transcript by competitive reverse transcription-polymerase chain reaction

Interferon-\(\alpha\) (IFN) induces a major reduction of the Philadelphia chromosome (Ph) positive clone in about 40% of patients with chronic myelogenous leukemia (CML) in chronic phase (CP) and in a substantial minority a complete cytogenetic response (CCyR), predicting a favorable outcome.\(^1,2\) Most of the major CyR are obtained within one year from starting therapy; we present data concerning patients in whom late major and complete CyR were achieved after prolonged treatment with IFN.

Twenty-two CML patients in CP diagnosed between September 1986 to December 1993 (9M/13F; median age 51 years, range 30-69) were treated with IFN. They had received minimal or no treatment before IFN. The percentage of Ph negative metaphases (at least 25 metaphases examined if possible, but fewer in the case of insufficient metaphases as often happens in IFN-treated CML patients) was used to classify the response as major (67-99%) or complete (100%).\(^2\) Any major CyR obtained more than 14 months after starting IFN therapy was considered a delayed response. The detection of BCR/ABL transcript by reverse transcription polymerase chain reaction (RT-PCR) and competitive RT-PCR was performed as described elsewhere.\(^3,4\) The 22 patients treated with IFN had an estimated median survival of 114 months (range 14–168) and at 5 years the overall survival probability was 61% (95% CI, 41% to 82%). Fifteen of the 22 IFN-treated patients did not have a cytogenetic response. Twelve patients (11 cytogenetically non-responders) died of blastic crisis after a median of 41 months (range 14–131). One patient (#7) had a major CyR after 26 months, maintained it for 37 months and then became resistant and died. Ten of the IFN-treated patients are still alive in CP (median observation time 115 months; range 92–168); 4 of them are cytogenetically non-responders and alive after 93, 100, 120 and 130 months (Sokal’s score: \(^1\) 1.16, 0.79, 0.69, 0.93), the other 6 patients reached a CCyR. Seven patients (32%) (Table 1) reached the major and/or complete CyR, achieved as a delayed response (> 14 months) in six cases in which the IFN treatment has been prolonged at the maximum tolerated doses even in the absence of major CyR in the first 14 months of IFN therapy. It should be noted that the maximum tolerated doses in five cases corresponded to a low daily dosage\(^7\) when the major CyR was obtained. The response achieved by patient #2 is one of the most delayed described to date.\(^8\) Only one of the 7 patients (#5) reached an early CCyR after 10 months of IFN therapy. The 6 Ph negative patients proved BCR-ABL positive by PCR assay.\(^9,10\) During the molecular follow-up two patients (#1 and #5) became PCR negative (Figure 1) 122 months after beginning IFN therapy (74 months after Ph negativity) and after 36 months of IFN therapy (25 months after Ph negativity), respectively. Patient #1 is still PCR negative, patient #5 was intermittently PCR pos-

Table 1. Findings at diagnosis, dosage and duration of IFN therapy and time to reach major and/or complete cytogenetic response in CML patients.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>BCR/ABL L type</th>
<th>Age (years)</th>
<th>Sokal's score</th>
<th>IFN dosage (months)</th>
<th>Follow-up (months)</th>
<th>Cytogenetic response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major Complete</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>b2a2</td>
<td>46</td>
<td>0.62</td>
<td>9MU/die (9) 12MU/die (11) 9MU/die (146+)</td>
<td>168 16 48</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>b3a2</td>
<td>56</td>
<td>0.72</td>
<td>9MU/die (9) 3MU/die (138+)</td>
<td>151 61 97</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>b2a2</td>
<td>49</td>
<td>0.83</td>
<td>3MU/die (5) 9MU/die (11) 4.5MU/die (102+)</td>
<td>120 22 57</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>b3a2</td>
<td>30</td>
<td>0.50</td>
<td>3MU/die (109+)</td>
<td>110 36 60</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>b3a2</td>
<td>47</td>
<td>0.69</td>
<td>6MU/die (1) 1.5 MU/die (84+)</td>
<td>94 10</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>b2a2</td>
<td>50</td>
<td>0.65</td>
<td>9MU/die (15) 1.5 MU/die (69+)</td>
<td>92 49 59</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>b3a2</td>
<td>60</td>
<td>1.03</td>
<td>9MU/die (4) 4.5MU/die (13) 3MU/die (74)</td>
<td>118* 26</td>
<td></td>
</tr>
</tbody>
</table>

Pt, patient; M, male; F, female; MU/die, MegaUnits (10⁶) per day. *This patient died. The discrepancy between the follow-up and the sum of periods of IFN therapy is due to delay of IFN therapy or to discontinuation of therapy because of intervening side effects.
itive/negative maintaining a low ratio % and then reverted again to PCR negativity. Five of the 6 Ph negative patients were also studied with competitive PCR evidencing a decreasing trend in the BCR-ABL/c-abl ratios % (Figure 1). A ratio % close to 1 or higher occurred, in the majority of cases, in patients who actually had a low number of metaphases and in whom it was not, therefore, possible to evaluate cytogenetics. Patient #4 had a high ratio % although cytogenetically he had 5 Ph negative metaphases out of 5. The ratio %, however, decreased when the patient had 13 Ph positive metaphases out of 29 and the same ratio % was maintained with 2 Ph positive metaphases out of 15.

In conclusion, our series seems to suggest that it could be useful to continue IFN therapy even when a cytogenetic response is not obtained quickly and/or the IFN dose has to be reduced because of side effects. Quantitative PCR shows that, with IFN treatment at the maximum tolerated dose, the level of residual disease, even after many months of CCyR, tends to decrease over time although, of course, more patients are needed to confirm these findings. Patients might become PCR negative or reach a stable plateau at a very low level of residual disease at which relapse is unlikely, as evidenced by the transplant experience. Competitive PCR in our patients seems to give a better quantitative representation of residual disease when there are too few metaphases for significant evaluation, as often happens in IFN-treated patients.

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