Are serum inhibin concentrations new markers of placental tumours in the course of chemotherapy?

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BACKGROUND: The study was conducted to evaluate whether the detection of serum molecular forms of inhibin (A and B) could be useful for the diagnosis, prognosis and follow-up of placental tumours. METHODS: A total of 17 patients with hydatidiform mole (n = 13), invasive mole (n = 1) or choriocarcinoma (n = 3) were studied; serum concentrations of inhibins A and B, human chorionic gonadotrophin (HCG) and its free β subunit (HCGβ) were measured before chemotherapy (after mole evacuation for eight patients) and also during the course of chemotherapy (for 10 patients). RESULTS: After evacuation or before chemotherapy for refractory disease, serum inhibin A and B concentrations were found to be increased in 10/17 and 4/17 patients, when HCG and HCGβ concentrations were high in all patients. In 10 patients with a follow-up during treatment, nine had a high concentration of inhibin A which correlated with those of HCG and HCGβ. Normalization of inhibin A was faster than that of HCG and HCGβ for three and six patients respectively. There was no correlation between changes of inhibin B and HCGβ concentrations. CONCLUSIONS: Our results suggest that inhibins A and B are not useful markers and that HCG determination still remains the most useful marker for diagnosis and follow-up of placental tumours.

Key words: human chorionic gonadotrophin/inhibinmarker/trophoblastic disease

Introduction

Inhibins (A and B) are heterodimeric glycoprotein hormones assembled from two subunits with a common α subunit. These hormones are mainly produced by the gonads and play a critical role in the control of gamete maturation (Webb et al., 1999). In clinical oncology, inhibins are sensitive markers in the detection and follow-up of patients with ovarian cancers, particularly those bearing granulosa cell tumours (Lappöhn et al., 1989; Healy et al., 1993; Petraglia et al., 1998; Frias et al., 1999).

Inhibins are also produced by the placenta and fetal membranes during pregnancy (Riley et al., 1996, 2000; Fowler et al., 1998; Petraglia et al., 1999). Indeed, human placentas express inhibin β- and α-subunit transcripts and proteins (Petraglia et al., 1991; McCluggage et al., 1998). Inhibins may be important regulators of fetal and placental development as well as being involved in the establishment of pregnancy (Riley et al., 1996). This probably explains why serum maternal concentrations vary according to the term of the pregnancy, declining after delivery (Wallace et al., 1997). Measurement of serum inhibin is useful in cases of various gestational pathologies, including pre-eclampsia, Down’s syndrome and molar pregnancies (Aitken et al., 1996; Muttukrishna et al., 1997). Inhibin has been also postulated to play a role in trophoblastic molar invasion and its presence in molar trophoblast cells has been reported (Minami et al., 1993; McCluggage et al., 1998; Pelkey et al., 1999; Shih and Kurman, 1999). However, controversies exist regarding the clinical interest of measuring inhibin in patients bearing trophoblastic tumours (Yohkaichiy et al., 1989; Badonnel et al., 1994). This is due to the fact that immunoassays used in these studies detect total inhibin without differentiating the two molecular forms.

Taking advantage of the recent development of specific immunoassays for inhibin A and inhibin B (Robertson et al., 1996), we investigated whether molecular forms of inhibin may represent better markers than human chorionic gonadotrophin (HCG) and its free β subunit (HCGβ) for diagnosis, prognosis and follow-up of gestational trophoblastic diseases (GTD). Indeed, if HCG and HCGβ are well-established sensitive markers of GTD (Schlaerth et al., 1981; Fan et al., 1987; Yedema et al., 1993), they have no predictive value either for prognosis or for response to chemotherapy and, moreover, their normalization after evacuation is variable over time (Bagshawe et al., 1976; Azab et al., 1988; Bidart et al., 1999).

Materials and methods

Serum collection

Serum samples were obtained from 17 patients who were referred to our institution for first or second line chemotherapy of a trophoblastic disease. The study included patients with a diagnosis of hydatidiform mole (n = 13, one with lung metastasis), invasive mole (n = 1) or
Table I. Serum inhibin A, inhibin B, human chorionic gonadotrophin (HCG) and HCGβ concentrations before chemotherapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Diagnosis</th>
<th>Previous CT</th>
<th>CT</th>
<th>Inhibin A (ng/l)</th>
<th>Inhibin B (ng/l)</th>
<th>HCG (IU/l)</th>
<th>HCGβ (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>99.7</td>
<td>&lt;10</td>
<td>41 000</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>47.6</td>
<td>&lt;10</td>
<td>14 000</td>
<td>18.3</td>
</tr>
<tr>
<td>3</td>
<td>ChorionK</td>
<td>Y (MTX+D+O/A+CDDP)</td>
<td>Hysterectomy</td>
<td>93.8</td>
<td>&lt;10</td>
<td>28 600</td>
<td>760</td>
</tr>
<tr>
<td>4</td>
<td>I mole</td>
<td>N</td>
<td>D+E</td>
<td>141.1</td>
<td>23.4</td>
<td>628 000</td>
<td>3160</td>
</tr>
<tr>
<td>5</td>
<td>H mole</td>
<td>Y (MTX)</td>
<td>D+E+CDDP</td>
<td>&lt;4</td>
<td>32.5</td>
<td>75</td>
<td>0.59</td>
</tr>
<tr>
<td>6</td>
<td>H mole</td>
<td>Y (MTX)</td>
<td>D+E</td>
<td>74.9</td>
<td>&lt;10</td>
<td>35 900</td>
<td>153</td>
</tr>
<tr>
<td>7 (brain metastases)</td>
<td>ChorionK</td>
<td>N</td>
<td>HD MTX+D+E+C+O</td>
<td>&lt;4</td>
<td>&lt;10</td>
<td>1575</td>
<td>2.7</td>
</tr>
<tr>
<td>8 (lung metastases)</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>5.2</td>
<td>&lt;10</td>
<td>281</td>
<td>4.1</td>
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<tr>
<td>9</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>8</td>
<td>60.4</td>
<td>535</td>
<td>6.3</td>
</tr>
<tr>
<td>10</td>
<td>H mole</td>
<td>Y (MTX)</td>
<td>D+E+CDDP</td>
<td>&lt;4</td>
<td>&lt;10</td>
<td>1400</td>
<td>0.29</td>
</tr>
<tr>
<td>11</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>300</td>
<td>28</td>
<td>351 500</td>
<td>4820</td>
</tr>
<tr>
<td>12</td>
<td>ChorionK</td>
<td>N</td>
<td>D+E+CDDP</td>
<td>610</td>
<td>&lt;10</td>
<td>53 200</td>
<td>2150</td>
</tr>
<tr>
<td>13</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>&lt;4</td>
<td>14</td>
<td>262</td>
<td>2.92</td>
</tr>
<tr>
<td>14</td>
<td>H mole</td>
<td>N</td>
<td>MTX</td>
<td>16</td>
<td>&lt;10</td>
<td>1339</td>
<td>6.9</td>
</tr>
<tr>
<td>15</td>
<td>H mole</td>
<td>Y (MTX)</td>
<td>D+E</td>
<td>&lt;4</td>
<td>&lt;10</td>
<td>231</td>
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</tr>
<tr>
<td>16</td>
<td>H mole</td>
<td>N</td>
<td>D+E</td>
<td>46</td>
<td>&lt;10</td>
<td>32 800</td>
<td>163</td>
</tr>
<tr>
<td>17</td>
<td>H mole</td>
<td>Y (MTX)</td>
<td>D+E</td>
<td>550</td>
<td>54</td>
<td>207 580</td>
<td>860</td>
</tr>
</tbody>
</table>

*With serum follow-up. Normal values: inhibin A <20 ng/l; inhibin B <30 ng/l; HCG <10 IU/l; HCGβ <0.1 mg/l.

CT = chemotherapy; H = hydatidiform; I = invasive; ChorionK = choriocarcinoma; MTX = methotrexate; HD MTX = high dose MTX; CDDP = cisplatin; D = dactinomycin; E = etoposide; O = oncovic; C = cyclophosphamide.

Results

Serum inhibin A, serum inhibin B, HCG and HCGβ concentrations before starting chemotherapy are presented in Table I. Initial serum inhibin A was increased in 10/17 patients, including seven hydatidiform moles, one invasive mole and two choriocarcinomas. Initial serum inhibin B was increased in 4/17 patients. None except one (hydatidiform mole) of the patients had a simultaneous increase of both inhibins A and B. In contrast, all patients presented high concentrations of both HCG and free HCGβ.

Serial measurement of the four biological parameters were repeated during the treatment and follow-up in 10 patients, including seven hydatidiform mole, with two patients resistant to methotrexate, one invasive mole and one choriocarcinoma. A complete response to chemotherapy was observed for the 17 patients. Figure 1 shows that, in 10 patients with a serum follow-up during treatment, nine had a high concentration of inhibin A and a correlation was found with the decrease of HCG and HCGβ. Normalization of inhibin A was faster than that of HCG and HCGβ for three and six patients respectively. In contrast, there was no correlation between changes of inhibin B and HCGβ serum concentrations.

Discussion

Chemotherapy has totally transformed the prognosis of GTD. Nevertheless prognosis depends on a series of factors and some patients have a high risk tumour with poor prognosis. Hormonal follow-up by serial measurements of serum HCG and/or HCGβ is reliable but has no predictive value. Furthermore, the time to obtain normalization of these markers is variable during treatment and may have an effect on the choice and/or the duration of treatment (Bidart et al., 1999). These observations emphasize the need for more appropriate markers. Among new potential markers, the inhibin family, including the various forms of inhibins and activins, has been proven to be useful for the detection and management of patients bearing granulosa cell tumours. In ovarian adenoacarcinoma, and particularly in mucinous tumours, inhibins display a good sensitivity but a weak specificity (Healy et al., 1993). The pre-operative serum inhibin A concentration is an independent prognosis parameter on the survival of post-menopausal women with epithelial ovarian
Figure 1. Serum inhibin (A and B), human chorionic gonadotrophin (HCG) and HCGβ concentrations in 10 patients (patients 1, 2, 4, 6, 9, 11, 12, 14, 16 and 17) before, during and after chemotherapy.

carcinoma (Frias et al., 1999). Several observations demonstrated that trophoblast cells secrete both inhibin A and activin A, a dimer of the β-subunit of inhibin, suggesting that those hormones may be useful in the detection and follow-up of patients with trophoblastic diseases (Petraglia et al., 1991; McCluggage et al., 1998). We recently reported that serum activin A is not a useful marker of placental tumours (Florio et al., 1998).

Our present observations demonstrate that the specific measurements of serum molecular forms of inhibins, namely inhibins A and B, do not seem to be of any clinical relevance in the biological survey of patients with GTD. Indeed, all our patients had elevated serum HCG and HCGβ concentrations, while only 15 had elevated inhibin A, including only two patients with choriocarcinoma, and seven had a moderate increase of inhibin B, indicating that inhibins A and B are not sensitive enough markers. As is the case during pregnancy, inhibin A appears to be the major circulating form (Wallace and Healy, 1996). Although no serum measurement was
performed before evacuation, all the patients included in our study had persistent or recurrent GTD. Moreover, three patients had choriocarcinoma, which is known to be a more aggressive disease.

In ten patients, serial determinations were performed during chemotherapy. Inhibin A was elevated in eight of these and a correlation was found between the kinetics of inhibin A and those of HCG and HCGβ. However, the time to normalization was similar for the three parameters, except for five patients in whom it was faster for inhibin A. No correlation between inhibin B, HCG and HCGβ was found. There was no benefit for inhibin determination before and during chemotherapy for GTD. A correlation was found between the kinetics of inhibin A and HCG during normal pregnancy: there was a peak at 9–10 weeks, coinciding with the HCG peak, and then a fall to a plateau between 15–30 weeks.

Yohkaichiya and collaborators reported the evolution of total inhibin, HCG and FSH serum concentrations before and 7–10 days after mole evacuation in six patients bearing hydatidiform mole (Yohkaichiya et al., 1989). Before evacuation, serum inhibins were higher than those observed during normal pregnancies at the same term. Three patients had elevated inhibin concentrations higher than those seen in the follicular phase of normal menstrual cycles 2 weeks after evacuation. Only the latter developed a persistent trophoblastic disease. But in one case, inhibin concentrations were at the upper limit of normality, which was then considered to be elevated. So, we may conclude that in this study, inhibin failed to detect a persistent disease (Wallace and Healy, 1996).

In conclusion, inhibin A and B do not seem to be reliable markers for persistent GTD. HCG and its free HCGβ remain the most efficient and useful tumour markers for the diagnosis and follow-up after treatment of GTD.

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References


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Placental tumour markers