CA125 in ovarian cancer

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Determination of CA125 from venous blood was done in 58 cases of control and benign ovarian tumour, 26 cases of common epithelial ovarian cancer and 16 cases of other female genital tract cancers. Serial determination of CA125 for follow-up was done in 8 cases. The Elisa method from a ready-made Kit of Fuji-Rebio-ince, Japan was used. The cut off value was 35 IU (by using 95% CI and comparison of sensitivity, specificity, positive and negative predictive value of CA125 at different levels). Sensitivity of 69.2%, specificity of 72.4%, positive predictive value of 58.2% and negative predictive value of 84.9% were obtained at this cut off point. According to the histologic type of ovarian cancer, the level of CA125 above 35 IU was seen in 87.5% of serous carcinoma, 75% of clearcell carcinoma and endometrioid carcinoma, 50% of mucinous carcinoma and undifferentiated carcinoma and 62.5% of other female genital tract cancers. For tumour volume (by looking at stages of ovarian cancer) the level of CA125 above the cut off value was seen in 50% of stage I and 77.7% of stages III and IV. This tumour marker was more useful for ruling out cancer than early detection or detection of tumour volume. For follow up, 6 cases with complete clinical response showed the level of CA125 below cut off value, and 2 cases with no change or progressive disease had CA125 above the cut off value. From this study the tumour marker should be used mainly for follow-up of ovarian cancers.

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คณะกรรมการฯ ได้ศึกษาถึงวัตถุ CA125 ในผลการตรวจของร่างกาย 58 ราย ผู้ป่วยที่ป่วยโรคมะเร็งของร่างกาย 26 ราย และผู้ป่วยที่ป่วยโรคมะเร็งของอวัยวะเพศหญิงอีก 16 ราย และได้ทำการ Serial determination ในการศึกษาผลผู้ป่วยที่ป่วยโรคมะเร็งของร่างกายใช้ถิง 8 ราย ใช้ venous blood ทางการ Elisa method จาก Kit ของ Fuji-Rebio-ince, Japan. Cut off value (จากการใช้ confidence interval และจากการเปรียบเทียบค่าต่าง ๆ โดยภาษา sensitivity, specificity, positive และ negative predictive value) คือ 35 IU ในขณะที่ cut of value ค่าที่จะได้เป็น sensitivity 69.2%, specificity 72.4%, positive predictive value 58.2%, negative predictive value 84.9% ถ้าจำแนกตาม Histologic type ของมะเร็งรั้วพบว่า serous carcinoma ให้ผลค่าคิง 87.8% clearcell carcinoma 82 endometrioid carcinoma ให้ 75% mucinous carcinoma และ undifferentiated carcinoma 50% มะเร็งของวัสดุเสียบผู้หญิงอีก ให้ผลค่า 62.5% ถ้าจำแนกตาม Stage พบว่า Stage I ให้ผลค่า 50% Stage II & IV 77.7% จะเห็นว่า Tumor marker นี้มีผลในการ rule out cancer จากความจะใช้เป็น early detection หรือหา tumor volume และจากการติดตามผู้ป่วยที่ได้ clinical complete response ให้ผลค่าคิง 6 ราย โดยค่าคำว่า cut of value และผู้ป่วยที่ no change หรือ progressive disease ให้ค่าคำว่า cut off value ที่ 2 ราย จากการศึกษากรณีได้ไข่ที่เกิดขึ้น คาดว่าจะใช้ CA125 ในการติดตามผู้ป่วยโรคมะเร็งของร่างกาย
Table 2. Sensitivity, specificity and predictive value of different levels of CA125.

<table>
<thead>
<tr>
<th>CA125 IU/ml</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive Positive (%)</th>
<th>Value Negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>76.9</td>
<td>70.6</td>
<td>54.0</td>
<td>70.6</td>
</tr>
<tr>
<td>30</td>
<td>69.2</td>
<td>72.4</td>
<td>52.9</td>
<td>84.0</td>
</tr>
<tr>
<td>35</td>
<td>69.2</td>
<td>77.4</td>
<td>58.2</td>
<td>84.9</td>
</tr>
<tr>
<td>40</td>
<td>65.3</td>
<td>79.3</td>
<td>43.5</td>
<td>83.6</td>
</tr>
</tbody>
</table>

* Others (Other genital tract cancers) consisted of
  - Non epithelial CA. OVARY 6 cases.
  - Borderlined CA.OVARY 3 cases.
  - CA.CORPUS and sarcoma 4 cases.
  - CA.VULVA, CA.TUBE, CA.COLO 3 cases.

Figure 1. Level of CA125.
Ovarian cancer used to be the third most common gynecological cancer. It is now the second most common gynecological cancer. Ovarian cancer is the leading cause of death from gynecological cancer. The prognosis for ovarian cancer (in terms of 5 year survival) has not improved over the past three decades. The reason for this poor prognosis is due to delayed diagnosis even with the modern development of sophisticated diagnostic instruments such as computerized tomography and magnetic resonance imaging. Recently tumour markers for ovarian cancer have been introduced for clinical evaluation such as HCG, and α Fetoprotin for germ cell tumour of the ovary. For common epithelial tumours, CA125 is one of the tumour markers which seems to be promising. The objectives for this study are:

- to find a cut off value of CA125 for Thai patients.
- to evaluate CA125 in the early diagnosis of ovarian cancer.
- to find the usefulness of CA125 in monitoring ovarian cancer.

Materials and Methods:

For the period of 10 months (from August 1987-June 1988) the study was conducted at the department of Obstetrics Gynecology, Chulalongkorn Hospital.

5 ml of venous blood were drawn from the patients as follow:

- Non malignant ovarian tumour or normal subjects: 58
- Malignant ovarian cancer: 26
- Other gynecological cancers: 16
- For follow up: 8

Total 108

Age of patients

- Control group varied from 23-52 years
- CA. OVARY group varied from 24-65 year
- Others group varied from 23-73 year

The mean age in each group was comparable.

From 5 ml of clotted venous blood, serum was obtained by process of centrifugation. Serum was kept at -20°C in the refrigerator until it was required for evaluation. Detection of CA125 was done utilizing the dliisa method and kits from FUJI-Radio-ince.

By using a pipet, 50 ml of 6 different concentrations of standard CA125 (0-480 U/ml) and specimens were dropped in each well of the tray. 150 ml of Tris-HCl buffer with pH 8.2 were added. One antibody coated bead was put into each well. The tray was tapped lightly and incubated at room temperature for 2 hours. The reaction mixture in the well was removed by suction with an aspirator. The beads were washed with 1.0 ml of saline 3 times. 200 ml of enzyme-labelled antibody were added into each well. Again the tray was tapped lightly and incubated at room temperature for a further 2 hours. The reaction mixture was removed from the wells, and the beads were once more washed with 1.0 ml of saline 4 times. The beads were then transferred from the well to the test tubes. 400 ml of developer solution was added to all the tubes. (two tubes of blank reagent included) The tubes were shaken gently and incubated at 2-10°C. for 16-20 hours then 2.0 ml of 5% oxalic acid was added to stop the reaction. Absorbance at 400 μl was measured. Standard curve was constructed and the concentration of the unknown sample was read from this curve.

Results

Because of the fluctuation in the level of CA125, as shown in Fig 1. Therefore a statistical analysis 95% CI was used to find the cut off points. (Table 1) By comparing the sensitivity, specificity and predictive value at different levels of 95% CI. CA125 at 35 IU/ml was chosen as the cut off point. (Table 2).

<table>
<thead>
<tr>
<th>CA125 (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
</tbody>
</table>

Table 1. 95% CI in control and CA ovarian cancer.
Looking at the stages of ovarian cancer as tumour burden, because of the small number of patients (Table 3) the difference between CA125 + in stages I & III is not enough to say that CA125 is a useful marker to detect tumour burden. The percentage of positively level in stage I and III is not statistically different.

Table 3. CA125 and stages of ovarian cancer.

<table>
<thead>
<tr>
<th>Stage</th>
<th>No.of +</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4/8</td>
<td>50.0</td>
</tr>
<tr>
<td>III</td>
<td>14/18</td>
<td>77.7</td>
</tr>
</tbody>
</table>

CA125 correlates with serous, clear cell & endometrioid cancers. For mucinous & undifferentiated types, the correlation is less reliable.

Following chemotherapy the level of CA125 dropped sharply in the group sensitive for CA125, while for mucinous tumours, the level of CA125 plateaued even with clinical response. (Fig. 2)

Table 4. CA125 on cell types of ovarian cancer.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>No.of +</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>7/8</td>
<td>87.5</td>
</tr>
<tr>
<td>Clear cell</td>
<td>3/4</td>
<td>75.0</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>3/4</td>
<td>75.0</td>
</tr>
<tr>
<td>Mucinous</td>
<td>4/8</td>
<td>50.0</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>1/2</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Figure 2. Level of CA125 during follow up.
Discussion

At the level of CA125 35IU/ml (similar level as some reports) specificity is higher than sensitivity and negative predictive value is higher than positive predictive value which means that this tumour marker is more useful for the exclusion of the disease rather than for detecting the disease. It's usefulness for early detection of ovarian cancer is therefore, questionable.

The margin of difference for positive CA125 in stage I & III is narrow so it is hard to be convinced that this tumour marker can be used to determine tumour burden as previously reported.

CA125 may be a good marker in follow-up period because of the sharp drop of the level in response to chemotherapy. All 8 cases followed up showed no recurrences.

The usefulness of CA125 may be supported if during a long term follow up period, the level of CA125 became raised in association with tumour recurrence. Other reports(5-8) of follow-up cases showed the level of CA125 rising 1-3 months prior to clinical recurrences.

Conclusion

CA125 at 35 IU/ml seems to be appropriate as a cut off point for ovarian cancer in the group of Thai patient studied. From this study the trend to use this tumour marker is for follow up rather than for tumour detection.

Acknowledgement:

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References
