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CA-125 in Ovarian Cancer: Relation Between Half-life, Doubling Time and Survival

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In a retrospective study of 35 patients with stage III-IV ovarian cancer, the probability to reach a complete (CR) or partial remission (PR) was studied by comparing the initial level, half-life and normalisation time of CA-125 during chemotherapy. In 15 CR patients, pretreatment CA-125 level was lower (70 U/l, range 16–1500 U/l) than in 20 PR patients (800 U/l, range 60–9000 U/l). The median normalisation time (NT) was 6 weeks in CR (range 0.7–5.5 months) and 4 months in PR patients (range 1.2-9 months). Marker half-life was 12 days for the CR group (range 4.5–30 days) and 21 days for the PR group (range 5.5–39 days). Remission duration ($r = 0.56$) and log cell kill ($r = 0.72$) were correlated with survival. Combining initial tumour diameter, marker level and NT predicted CR in 87.5% and PR in 86%. Estimating log cell kill by combining marker half-life and doubling time gives more insight into tumour cell kinetics and individual survival.
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INTRODUCTION

OVARIAN CANCER has been called a silent killer, because its late detection leads to a dismal prognosis in the majority of patients. By an aggressive surgical approach and the use of intensive cytostatic treatment, a remission can be reached in most patients, but only the achievement of a complete remission carries a chance for survival. A complete remission can only be established by performing a second look laparotomy, because small tumour residuals are hardly detectable by conventional diagnostic means such as ultrasound or computed tomography. The development and use of the tumour marker CA-125 have enabled a correct prediction of tumour response by serial measurement of its serum levels [1–3]. A rise of the marker heralds a tumour relapse [4]. For the detection of small tumour residuals after cytostatic treatment and especially to demonstrate a complete remission, the approximately 50% sensitivity of the marker is still insufficient [2, 5–9].

In a retrospective study we compared the ability of a number of marker parameters to predict a complete (CR) or partial remission (PR) and survival. In detail, we studied (1) the ability to predict CR or PR by the height of the initial marker level, its half-life during chemotherapy or the time needed for normalisation of the marker in responding patients; and (2) the relation between the estimated log cell kill or the marker doubling time and survival in patients with a tumour relapse.

PATIENTS AND METHODS

45 consecutive patients with advanced ovarian cancer, FIGO stage 3 or 4, were all treated with standard combination chemotherapy (CAP-5) [9]. This comprised cyclophosphamide 500 mg/m^2 and doxorubicin 35 mg/m^2 on day 1, and cisplatin 20 mg/m^2 day 1–5, every 4 weeks. All patients underwent maximal debulking surgery before cytostatic treatment. Marker levels were measured weekly from the date of surgery, and monthly during subsequent chemotherapy, at every cycle of chemotherapy.

Complete or partial remissions were established by a second look laparotomy after six cycles of chemotherapy. Thereafter, a 6-weekly control schedule was followed. In case of a relapse, most patients were treated with intravenous single-agent cyclophosphamide.

CA-125 was measured by Abbott IRMA. The upper limit of normal is 35 U/l and the sensitivity was 0.5-1 U/l. For all patients we determined the initial marker levels before laparotomy. The marker half-life ($t_{\frac{1}{2}}$) was measured by extrapolation of several measurements and expressed in days. For every patient we measured the time necessary for the normalisation of marker levels, and after tumour relapse, its rate of increase, expressed as the doubling time (t_2). By extrapolating both the downward half life and upward doubling curve to the intersection point (C) below base line, we estimated the 2-log kill, taking the difference between the initial level (I) and this point C (Fig. 1). For practial reasons, we did not differentiate between the effect of debulking surgery and of chemotherapy on marker half-life. Part of the initial marker decrease thus will be the result of tumour removal, depending on the ratio of the amount of tumour removed and tumour remaining, which will be different in every case.

RESULTS

The serum level of CA-125 could be determined before laparotomy, during subsequent chemotherapy, remission and relapse, in 20 patients with a PR and in 15 patients with a histological CR. 6 patients, who did not exhibit measurable levels at presentation, and 4 who had tumour progression from the start of chemotherapy were excluded from study. In the CR group, 12 patients had residual tumour deposits smaller than 2 cm, and 3 patients had larger amounts of tumour at the start of chemotherapy. In the PR group, 17 patients had residuals over 2 cm and 3 had smaller ones.

Figure 2 shows the initial marker levels before laparotomy in

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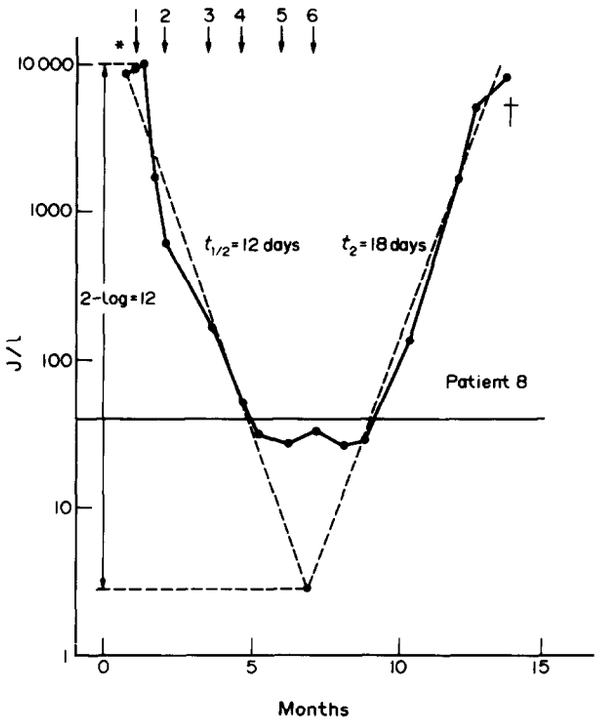

Fig. 1. Extrapolation of serum half-life and doubling time in 1 patient, demonstrating log kill by 2-log (initial level minus intersection point of dotted lines, C). * indicates laparotomy, arrows 1–6 = chemotherapy cycles with CAP-5, † = patient died.

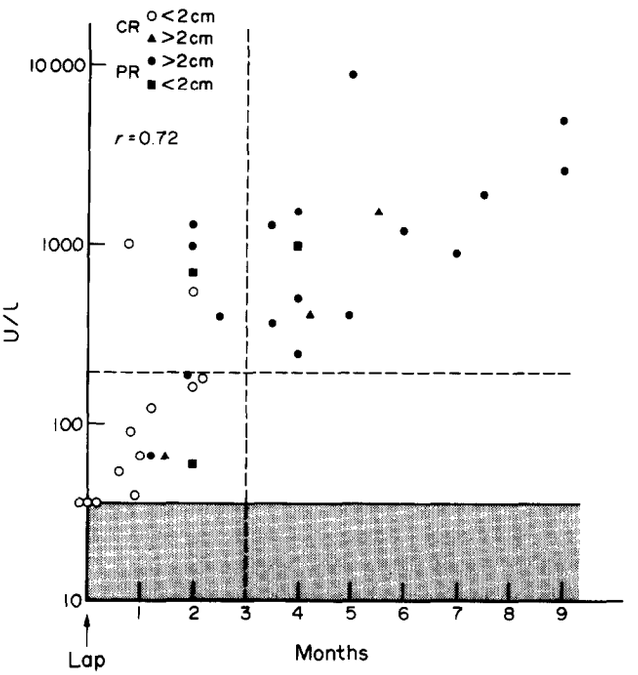

Fig. 2. Relation between initial marker level at laparotomy (Lap) and time necessary for normalisation; dotted lines representing best cut-off values to differentiate histopathological complete remission (CR) and partial remission (PR). Area beneath solid line = normal range of CA-125.

CR and PR patients, for patients wth small and larger residuals. The median level in patients reaching CR was 70 (range 16–1500 U/l), in patients with a PR 800 (range 60–9000 U/l), but there was a considerable overlap. No patient in the CR group had an initial level over 1500 U/l, and a level over 200 U/l seems to give the best separation between complete and partial responders, as only 4/15 patients with CR had initial levels above this value and 3/20 patients with PR had lower ones.

The time necessary to reach a normal level was different for the CR and PR group (Fig. 2). In CR patients a median time of 6 weeks after laparotomy was needed for marker normalisation (range 0.7–5.5 months), and 13/15 patients had normal values within 3 months. Patients with a partial response needed a median of 4 months for the normalisation of the market (range 1.2–9.0 months), implicating that more than three cytotoxic cycles were needed in half of them. Taking into account the diameter of tumour residuals after debulking surgery, residual tumour under 2 cm resulted in CR in 9/12 (75%) and normalisation within 3 months in 10/17 CR (59%). 7 of the 8 patients (87.5%) fulfilling all three criteria (level below 200 U/l, residuals <2 cm and normal within 3 months) achieved CR, and 12 of 14 patients having none of them reached only PR (86%).

For the CR group the median $t_{\frac{1}{2}}$ was 12 days (range 4.5–30 days) and for patients reaching PR 21 days (range 5.5–39 days), $P<0.05$.However, the overlap between the two groups is considerable.

In the PR group, we found a close correlation between the initial and terminal marker levels at the time of death, $r = 0.78$, $P < 0.001$. There was no relation between the half-life and doubling time (t_2) in most patients, $t_{\frac{1}{2}}$ lying between 5–29 days, and t_2 between 9 and 28 days. 4 patients had exceptionally long doubling times of 50, 71, 80 and 90 days, respectively, compared with their initial half-lives, because the tail of the curve levelled off, according to a Gompertzian model [10], which precluded a correct extrapolation for the estimated log cell kill.

The rate of tumour growth, expressed as the marker doubling time (t_2), did not correlate with patient survival, which appeared to lie between 10–20 months from laparotomy in patients with a tumour relapse. When the individual $t_{\frac{1}{2}}$ and t_2 were extrapolated to estimate the log cell kill, there was a significant correlation with overall survival, excluding the 4 patients with Gompertzian growth curves ($r = 0.72$) (Fig. 3). The remission duration, measured as the time with normal marker levels, was also correlated with patient survival ($r = 0.56, P < 0.05$).

DISCUSSION

As far as the initial marker level, normalisation time or marker half-life during treatment are concerned, no single or combined parameter can predict a complete remission. Combination of three favourable criteria (small residuals, a low initial level and short normalisation time) could predict CR in 87% of cases, while three negative items resulted in PR in 86%. Marker half-life did not have additional predictive power as it overlapped. Some other studies found that a marker half-life of 20 days gave the best separation between CR and PR patients [11, 12]. Others showed that normalisation within two [13] or three [14] chemotherapy cycles could predict CR.

In our previous paper and in the literature no close correlation has been found between the initial marker level and tumour stage or the amount of residual tumour after debulking [14, 15]. This finding indicates the varying proportion of cells producing or releasing CA-125 in every tumour, as confirmed by the different marker concentrations in tumour tissue measured by

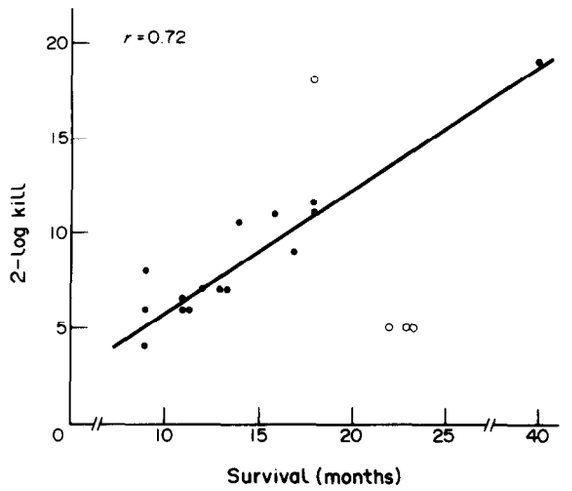

Fig. 3. Relation between estimated log kill and survival in patients with linear doubling (●) and with Gompertzian growth (○).

semiquantitative immunofluorescence [16]. Furthermore, the presence of the antigen within the cell and its release into the circulation may be two independent phenomena, as reflected by our finding of high CA-125 levels within cyst fluid, combined with normal serum levels in benign ovarian tumours [17]. The CA-125 level must, however, give some indication of the number of malignant cells present, as its level was inversely correlated with the chance to reach a complete remission.

The large overlap in half-life values between the CR and PR patients is somewhat surprising. In this study 1 CR patient even had a half-life exceeding 30 days, which is exceptionally long. The shortest half-life found in CR patients was 4 days, which approaches the natural $t_{\frac{1}{2}}$. Because the half-lives found in CR and PR patients are so similar, the initial levels will correspond with the time necessary for their disappearance. The marker disappearance curve is composed of the surgical removal of the tumour and further tumour reduction by cytostatic treatment. For practical purposes we did not try to distinguish between two factors, as cytostatic treatment was usually instituted as soon as possible after surgery.

Surprisingly, the tumour (or marker) doubling time did not reflect patient survival very well, probably because the major part of the survival period is determined by the duration of the remission period.

The extrapolated log cell kill, which is determined by $t_{\frac{1}{2}}$ and t_2 together, appeared to correlate very well with the overall survival. As expected, the remission duration, i.e. the time the marker stayed normal, was also correlated with survival, but to a lesser extent. The log cell kill varied from 4 to 18, meaning as many marker "halvings" by treatment. Assuming 1 cm^3 of tumour to contain about $10^9 = 2^{30}$ cells, representing 30 successive cell divisions, it is clear that a lower log kill will not eradicate all tumour cells.

For the follow-up of patients in remission, the determination of the levels of CA-125 is certainly of value, as sequentially rising levels are conclusive evidence of a tumour relapse and may permit earlier and possibly more effective second-line treatment. The progression rate or tumour doubling time has no great prognostic impact. A decline of the rate of increase, however, indicates an effect of subsequent second line cytostatic treatment.

In conclusion, the determination of marker levels may have prognostic value; it gives some insight in tumour kinetics during chemotherapy and can indicate tumour relapse earlier than other clinical means of diagnosis.

Based on the most critical time points found in this study, repeat measurements every 3 months should be sufficient for practical purposes, and in keeping with budgetary considerations.

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