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Growth Rate of Metastatic Non-seminomatous Germ Cell Testicular Tumours

S.M. Crawford

DR PRICE and her colleagues [1, 2] calculate marker production doubling time (MPDT) of testicular germ cell tumours (GCT) and hence by implication the doubling time of the marker-producing clone. They show that patients who failed chemotherapy have tumours with short MPDT. An important point in the argument for the application of this technique is that they found a disparity between MPDT and serum tumour marker doubling time (SMDT). This discrepancy raises the question, why calculate MPDT rather than simply measure the tumour markers?

An important variable in their equation is the clearance rate for the marker, which is a function of the half-life of the tumour marker. Price *et al.* assume that the half-life of alpha-fetoprotein (AFP) is 5 days. In our patients [3] with stage I GCT, the range of half-life of AFP was 2.0–15.1 days in patients who did not relapse (S.M.C., unpublished). This defeats the object of making conclusions that include this variable if a major source of variation is dismissed by assumption. However, in practice, the effect of the variation is minimal as the following example shows.

Given the minimum acceptable frequency for tumour marker measurements in the workup phase is weekly [4], a patient with a SMDT of 20 days may have the following sequence of values: day 1, 100; day 8, 127; day 15, 162. With an assumed half-life of 5, MPDT is 19.78 days. However, if the half-life is 3 days, MPDT is 19.87. Thus variation in clearance of AFP makes only a small contribution to variation in the observed SMDT. The need for calculation of MPDT is therefore unclear.

Another point that Price *et al.* make is that their calculation averages two periods of tumour marker increase. This procedure probably introduces the variation between MPDT and SMDT which they describe. Any biochemical mesurement has errors within its assay. In the Charing Cross Hospital assay for AFP, the within-assay coefficient of variation is 5% and the between-assay coefficient is 8% (H. Mitchell). If we increase the day 8 value in the example by 5% to 133 and use a half-life of 5 days, MPDT now becomes 30.34. The explanation is the fact that MPDT is not derived from an average of marker production over a large number of observations, but from the logarithm of the ratio between marker production quantity on 2 days (equation A8). This means that only three observations are used ($C[t_1]$, $C[t_2]$, $C[t_3]$) and the calculation is especially vulnerable to variation in the measurement of $C[t_2]$ because of its incorporation into the calculation twice. If $C[t_2]$ is higher than expected, then $Q(t_2, t_1)$ is increased and $Q(t_3, t_2)$ is reduced; and $[Q(t_3, t_2)] \div [Q(t_2, t_1)]$ is even more reduced.

These examples show that the question of whether calculations of MPDT have any prognostic advantage over calculation SMDT remains unanswered, at least for AFP. It would be useful if Price *et al.* could make the comparison from their data [2].

Variations in MPDT and especially in discrepancies between MPTD and SMDT are unlikely to convey more information about the status of the patient with an AFP-producing germ cell tumour; the best way of analysing the marker data is the simplest, namely to observe the slope of the graph of log [AFP] against time. This can effectively average the doubling time over a large series of observations, avoiding the artefactual effect of assay variation.

1. Price P, Hogan SJ, Horwich A. The growth rate of metastatic non-seminomatous germ cell testicular tumours measured by marker production doubling time - I: Theoretic basis and practical application. *Eur J Cancer* 1990, **26**, 450–453.
2. Price P, Hogan SJ, Bliss JM, Horwich A. The growth rate of metastatic non-seminomatous germ cell testicular tumours measured by marker production doubling time - II. Prognostic significance in patients treated by chemotherapy. *Eur J Cancer* 1990, **26**, 453–457.
3. Crawford SM, Rustin GJS, Begent RHJ, Newlands ES, Bagshawe KD. Safety of surveillance in the management of Stage I anaplastic germ cell tumours of the testis. *Br J Urol* 1988, **61**, 250–253.
4. Seckl JM, Rustin GJS, Bagshawe KD. Frequency of serum tumour marker monitoring in patients with non-seminomatous germ cell tumours. *Br J Cancer* 1990, **61**, 916–918.

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Growth Rate of Metastatic Non-seminomatous Germ Cell Testicular Tumours—a Reply

P. Price, S.J. Hogan and A. Horwich

DR CRAWFORD asks why calculate marker production doubling time (MPDT) rather than measuring the serum tumour marker doubling time (SMDT)?

Firstly, MPDT provides quantifiable information about the change in number of marker-producing cells with time and is thus a measure of the growth rate of the marker-producing cells. SMDT simply describes the change in serum marker level with time and the rate of such a rise has no direct biological meaning. It is because there is a consistent disparity between MPDT and SMDT [1] that MPDT should be measured.

Secondly, the variation in clearance of the marker is not "dismissed by assumption". The clearance is taken into account

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when calculating the tumour marker production per day (TMP) for a given period (ref. 1, equations A1 and A4). The MPDT measures the rate of change of TMP (ref. 1, A2) and thus the individual variation in clearance is taken into account. The effect of such variation appears minimal only because in equation A4 [1] the function $T_{1/2}$ is logged. Individual values of clearance will affect an absolute value of TMP at any one time point, but as long as clearance is consistent in time in an individual, this will not affect the rate of change of TMP. This does not mean that clearance is a constant variable and that SMDT can be taken as a value of MPDT. This would be mathematically incorrect.

Thirdly, Crawford uses a worked example to demonstrate how errors in serum marker level can produce larger discrepancies in MPDT than in SMDT. However, the accuracy of the two estimations in his example are not comparable. Calculation of SMDT in this instance uses three time points, and so rate of change is little dependent on variation in the middle value. Calculation of MPDT in this instance uses values of TMP at only two time points. The larger the number of serum marker levels that are available, the more accurate individual values of either SMDT or MPDT will be. Crawford may be suggesting that MPDT can only be calculated from three serum marker levels at time t_1, t_2, and t_3. This is incorrect. TMP and MPDT can be calculated up to time t_x where x is the last measured serum marker level.

Crawford asks if SMDT carried prognostic information in our patients. The prechemotherapy SMDT was completely unrelated to prognosis in our group of patients. We are unaware of any publication suggesting the rate of increase in serum marker level (SMDT) is prognostically important in germ cell tumours. The absolute level of serum marker level prechemotherapy is known to provide prognostic information as it is a guide to the bulk of the tumour. However, the rate of increase in serum level has no direct biological meaning. We found that the prechemotherapy growth rate, as measured by the MPDT, to be prognostically significant in the group of patients treated with a 3-weekly course of BEP chemotherapy [2]. SMDT does not measure growth rate.

Finally, Crawford refers to unpublished data suggesting that there is a wide range of half-lives of AFP. Our observations do not support this [3]. In a group of 20 stage 1 patients, the plasma half-life was 3.5–8 days, median 5.25 days, with 85% of patients having a half-life of between 4–6.25 days.

Calculation of TMP and MPDT provides for the first time quantifiable information about tumour cell growth and regression *in vivo*. It can be used to measure the growth of marker producing cells pretreatment, and can quantify regression post-treatment. Interestingly, the detection of any tumour marker production post-treatment may in fact help in those cases alluded to by Crawford, where individual variation in marker half-life may obscure the picture.

1. Price P, Hogan SJ, Horwich A. The growth rate of metastatic non-seminomatous germ cell testicular tumours measured by marker production doubling time I. Theoretical basis and practical application. *Eur J Cancer* 1990, **26**, 450–453.
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3. Price P. (MD thesis). Cambridge, Cambridge University, 1990.