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Growth Rate of Metastatic Non-seminomatous Germ Cell Testicular Tumours

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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patients [3] with stage I GCT, the range of half-life of AFP was 2.0–15.1 days in patients who did not relapse (S.M.C., unpublished).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.

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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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