Objective assessment of tumour response to therapy based on tumour growth kinetics

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BACKGROUND: Current standards for assessment of tumour response to therapy (a) categorise therapeutic efficacy values, inappropriate for patient-specific and deterministic studies, (b) neglect the natural growth characteristics of tumours, (c) are based on tumour shrinkage, inappropriate for cytostatic therapies, and (d) do not accommodate integration of functional/biological means of therapeutic efficacy assessed with, for example, positron emission tomography or magnetic resonance imaging, with data from anatomical changes in tumour.

METHODS: A quantity for tumour response was formulated assuming that an effective treatment may decrease the cell proliferation rate (cytostatic) and/or increase the cell loss rate (cytotoxic) of the tumour. Tumour response values were analysed for 11 non-Hodgkin’s lymphoma patients treated with 131I-labelled anti-B1 antibody and 12 prostate cancer patients treated with a nutritional supplement.

RESULTS: Tumour response was found to be equal to the logarithm of the ratio of post-treatment tumour volume to the volume of corresponding untreated tumour. Neglecting the natural growth characteristics of tumours results in underestimation of treatment effectiveness based on currently used methods. The model also facilitates the integration of data from tumour volume changes, with data from functional imaging.

CONCLUSION: Tumour response to therapy can be assessed with a continuous dimensionless quantity for both cytotoxic and cytostatic treatments.

Keywords: tumour; response; therapy; growth kinetics; cytotoxic; cytostatic
end point for quantification of TR, denoted as LR (log ratio) (Karrison et al., 2007).

(4) Many studies have shown that the effect of treatment on tumours can be assessed by means of changes in tumour characteristics other than size, for example, estimated by positron emission tomography (PET) or magnetic resonance imaging or spectroscopy (MRI/MRS) (Padhani and Miles, 2010). Available standards do not accommodate mathematical integration of physiological or functional imaging modalities into anatomical changes in tumour and new methods must evolve (Jaffé, 2008).

The aim of this study was to develop a mathematically accurate and biologically relevant method for assessment of TR to any type of treatment.

MATERIALS AND METHODS

Kinetics of tumour growth

Volumetric growth rate of tumours can be quantified with specific growth rate (SGR), described as relative volume change per unit time. Quantification of growth rate with SGR is mathematically more accurate and biologically more relevant than the widely used parameter tumour volume doubling time (DT) (Mehrara et al., 2007, 2009). The SGR of a tumour during time period from \( t_0 \) to \( t \) can be calculated from tumour volumes at the start and at the end of this period, \( V_0 \) and \( V \), respectively:

\[
SGR = \frac{\ln(V/V_0)}{(t - t_0)} \tag{1}
\]

More rapidly growing tumours have higher SGR values, SGR = 0 represents non-growing tumours, and negative SGR values can be assigned to tumour regression. Specific growth rate is constant for exponentially growing tumours; however, if SGR is time-dependent, as for non-exponentially growing tumours, the above equation can be rewritten as follows:

\[
\ln\left(\frac{V}{V_0}\right) = \int_{t_0}^{t} SGR(t) \, dt \tag{2}
\]

where SGR\((t)\) is the SGR at time \( t \). The value of SGR\((t)\) depends on the level of cell proliferation rate, CPR\((t)\), and cell loss rate, CLR\((t)\), at time \( t \):

\[
SGR(t) = CPR(t) - CLR(t) \tag{3}
\]

TR to therapy

If the natural growth of tumour is interrupted by therapy, an effective therapeutic agent may increase the CLR (cytotoxic effect) and/or decrease the CPR (cytostatic effect) of tumour. Specific growth rate will then decrease to SGR\(^t\) regardless of the mechanism of the therapeutic effect:

\[
SGR^t(t) = SGR(t) - ASGR(t) \tag{4}
\]

where ASGR\((t)\) is the effect of treatment at time \( t \). Temporal variation of SGR\(^t\) depends on all factors that naturally affect tumour growth as well as the effect of therapy. Readjustment and integration of the above equation over time gives:

\[
\int_{t_1}^{t} SGR(t) \, dt = \int_{t_1}^{t} SGR(t) \, dt - \int_{t_1}^{t} SGR^t(t) \, dt
\]

where \( t_1 \) and \( t \) are the time of therapy initiation and efficacy assessment, respectively. The right side of the above equation can be replaced using Equation (2), which gives:

\[
\int_{t_1}^{t} \Delta SGR(t) \, dt = \ln\left(\frac{V_n}{V_i}\right) - \ln\left(\frac{V_i}{V_i}\right)
\]

where \( V_i \) is tumour volume at the time of therapy initiation, and \( V_n \) and \( V_a \) are the volume of treated and corresponding (hypothetical) non-treated tumour at the time of efficacy assessment, respectively. The left side of the above equation is the overall effect of treatment during time from treatment initiation to time of efficacy assessment, and can be denoted as TR. Since \( \ln(V_n/V_i) - \ln(V_i/V_i) = -\ln(V_i/V_n) \):

\[
TR = \ln\left(\frac{V_n}{V_n}\right) \tag{5}
\]

TR is a general continuous dimensionless quantity for tumour response to both cytotoxic and cytostatic therapeutic effects. TR can thus be calculated by the logarithm of the ratio between the post-treatment volume of tumour and the volume that the tumour would have had (at the time of efficacy assessment) if the growth was not influenced by therapy. The value of \( V_n \) cannot be defined, but only estimated based on the natural growth model of tumour.

To estimate \( V_n \) the following assumptions were used (cf. Figure 1):

1. tumour volume at first diagnostic investigation is \( V_0 \)
2. therapy is initiated at a time point \( \Delta t_{pre} \) after measurement of \( V_0 \)
3. tumour grows exponentially with a constant SGR\((t)\) = SGR\(^0\) during the studied time period and tumour volume at the time of therapy initiation is \( V_i \)
4. tumour response is assessed at a time point \( \Delta t_{post} \) after therapy initiation and tumour volume at the time of efficacy assessment is \( V_n \)
5. tumour would continue to grow with SGR\(^0\) if the growth was not interrupted and its volume would be \( V_n \) at the time of efficacy assessment.

Application to patient data

Tumour response values were calculated for treatment of non-Hodgkin’s lymphoma patients with \(^{131}I\)-labelled anti-B1 antibody,
where data were retrieved from a previously published article (Sgouros et al, 2003). The study was selected based on the availability of tumour volumes and the time of pretreatment and post-treatment volume estimations in each patient, information necessary for TR calculation. Total tumour burden was assessed by drawing contours around all lymphoma lesions identified on whole-body CT or MRI. Two more patients are included in the original article, where tumours disappeared after treatment. Those data were excluded in this study. Average post-treatment re-growth of tumour volumes used as an estimation of the natural growth rate of non-Hodgkin's lymphomas in this study.

Another set of data were retrieved from the literature, where prostate-specific antigen (PSA) increase rates before and after treatment with a nutritional supplement were available in 12 prostate cancer patients (Guess et al, 2003). Tumour response values were calculated using PSA levels before and after treatment for assessment of treatment efficacy.

Tumour response values were calculated for non-Hodgkin's lymphoma patients using total tumour burden as reference and for prostate cancer patients using PSA level as reference, respectively. On the basis of the calculated mean and standard deviation of TR and LR in each group of patients, frequency distribution of TR and LR were approximated with corresponding normal distribution with the same mean and standard deviation values in each group, respectively.

RESULTS

When the tumour response model developed in this study (Equation 5) is applied to an exponentially growing tumour, TR is related to tumour volume and growth rate as follows (Figure 1):

\[
TR = -\ln \left( \frac{V_t}{V_0} \right) + \frac{SGR_0 \cdot \Delta t_{pre}}{e_1} + \frac{SGR_0 \cdot \Delta t_{post}}{e_2} \quad (6)
\]

The first term on the right-hand side of the above equation, LR, is the treatment effectiveness where the natural growth of tumour is neglected and is equivalent to the LR measure suggested by Karrison et al (2007). LR values less than −0.5, between −0.5 and +1, and larger than +1 correspond to progressive disease, stable disease, and partial response according to RECIST, respectively. The second term, e1, and the third term, e2, represent tumour growth before and after treatment initiation, respectively. The overall effect of tumour growth from the time of diagnosis to the time of efficacy assessment, Δt, sums up as follows:

\[
TR = -\ln \left( \frac{V_t}{V_0} \right) + SGR_0 \cdot \Delta t = LR + Err \quad (7)
\]

The above equation indicates that evaluation of treatment effectiveness by comparing the volume of treated tumour with pretreatment tumour volume underestimates the effect of therapy by Err.

If a therapeutic drug has pure cytostatic effect, that is, the drug inhibits tumour growth, but does not destroy existing tumour cells, and if the drug can completely block tumour growth, the tumour volume at the time of efficacy assessment will be the same as the tumour volume at the time of treatment initiation, V0. The cytostatic efficacy of treatment is then e2 = ln(Vf/V0) (Figure 1). If the drug can partially control tumour growth, the tumour volume at the time of efficacy assessment will be larger than V0 (closer to Vf) and the treatment efficacy will be less than e2 in Figure 1. Note that tumour volume at the time of efficacy assessment is, however, larger than tumour volume at the time of diagnosis, Vd. According to RECIST, a Vt of more than 1.73Vd (20% increase in diameter) will be considered as progressive disease. For a tumour with DT shorter than 27 days (SGR > 2.6% per day) and a treatment that completely blocks tumour growth, the drug will be considered without any effect and be categorised as progressive disease according to RECIST.

The frequency distributions of TR and LR are shown in Figures 2A and B for non-Hodgkin’s lymphoma and prostate cancer patients, respectively. The results show that LR largely underestimates tumour response compared to TR.

DISCUSSION

Traditional quantification methods used in oncology can give contradictory results to mathematically accurate and biologically relevant methods (Mehrara et al, 2007, 2009). In this article, we present a dimensionless continuous quantity for objective assessment of TR, regardless of tumour type, clinical measures other than tumour response, and the mechanism of the effect of therapy.
on tumour: cytotoxic and/or cytostatic. Studies have shown that tumour growth rate is a valuable parameter for, for example, prediction of recurrence after surgery (Cucchetti et al, 2005) and survival of patients (Blankenberg et al, 1995), and the change in tumour growth rate can serve as a surrogate end point for determination of therapy response (Haney et al, 2001). In this study, a simplified formula was derived based on the effect of therapy on kinetics of tumour growth. Tumour response was measured by the logarithm of the ratio of post-treatment tumour volume to the volume of tumour at the time of efficacy assessment if therapy was not initiated. \( TR = 0 \) indicates no effect, and the larger \( TR \) value the more effective therapy. A negative \( TR \) value indicates post-treatment tumour swelling or growth.

\( TR \) values are larger than corresponding \( LR \) values, which were used by Karrison et al (2007). The value of \( LR \) is calculated as the logarithm of the ratio of post-treatment tumour volume to the pretreatment tumour volume. The natural growth of tumour during diagnosis and therapy initiation as well as after therapy is neglected in the \( LR \) value. There might be a few weeks or longer delay between tumour diagnosis and initiation of therapy due to practical limitations or necessity of further evaluations. Tumours continue to grow during this period. As an example, the volume of a tumour with DT of 70 days will increase 23\% during 3 weeks. Repopulation of tumour cells during therapy, for example, between cycles of chemotherapy, is also an important factor that should not be neglected (Davis and Tannock, 2000; Kim and Tannock, 2005). The overall underestimation of treatment effectiveness by \( LR \) (Err) is larger when tumour is rapidly growing or the time between pretreatment and post-treatment volume assessments is long. The relative importance of Err also depends on dose–response relation, that is, for a more effective drug \( LR \) is less affected by this error.

The generally used methods when comparing the post-treatment volume of tumour with the pretreatment volume will thus result in underestimation of treatment effectiveness. It has already been shown that RECIST underestimates the effect of imatinib on metastatic gastrointestinal stromal tumour (Choi et al, 2007). The fact that treatment effectiveness is underestimated by \( LR \) or RECIST has important implications on assessing the efficacy of new anticancer drugs or combinations of therapies.

It has been demonstrated that clinical trial designs based on \( LR \) are feasible (Karrison et al, 2007), which suggests that \( TR \) can also be used for such studies. The main difference between \( TR \) and \( LR \) is the reference volume of tumour for efficacy assessment, which is the volume of corresponding untreated tumour or pretreatment volume of tumour for \( TR \) and \( LR \), respectively. The statistical aspects of using such continuous variables in clinical trials, for example, handling extreme cases as complete disappearance of lesions in two patients in this study, are discussed elsewhere (Karrison et al, 2007). Here we discuss the advantages and limitations of using \( TR \) as a quantity for tumour response.

The main limitation with using \( TR \), compared to \( LR \), is the estimation of the volume of an untreated tumour at the time of \( TR \) evaluation, which needs the natural growth tumour volume. In this study, we assumed an exponential model for natural growth of tumours. However, the presented formula for calculation of \( TR \) (Equation (5)) can be used for any growth model, provided that the non-exponential growth characteristics of tumour and \( V_0 \) can be estimated.

The natural growth rate of tumours can be estimated by appropriate techniques according to the available data in each study. Owing to lack of information, we estimated the growth rate of untreated non-Hodgkin’s lymphoma tumours from the average re-growth rate of tumours after therapy, which might be different from the true growth rate of tumours before treatment. However, these data were used only for demonstration, and no clinical interpretation of the results should be made. If tumour volumes at two occasions before start of therapy are available, for example, having two CT scans at diagnostic investigation and an investigation just before therapy initiation, natural SGR of tumour and consecutively \( V_n \) can be calculated using Equation (1). Taking both inter- and intra-operator as well as inter-scan variability into account, an increase of the measured volume by more than 25\% is needed for a 95\% likelihood of being a true growth, rather than measurement inaccuracy. For an exponentially growing tumour, increase of the measured volume will be more than 25\% if the measurement time interval between two investigations is longer than 0.32 DT.

If tumour volume before treatment is only available at one occasion, for example, the first diagnostic imaging, tumour volume at the time of therapy can be estimated by extrapolation of volume regression curve during therapy, which might be described by exponential model (Stein et al, 2008). That measure together with the first tumour volume available can be used for estimation of the natural \( SGR \) of tumour.

However, we used PSA level as reference, instead of tumour volume, for calculation of \( TR \) and \( LR \) in prostate cancer patients and the results were similar to when tumour volume was used for calculations in non-Hodgkin’s lymphoma patients. This indicates that \( TR \) values calculated based on tumour marker level can be used for quantification of treatment efficacy in some types of tumours. Measurement of tumour marker level before the initiation of treatment is usually more practical in clinical research and practice. However, other factors that may affect tumour marker level, for example, PSA decline due to debulking of the tumour as it becomes anaplastic, must be considered, when post-treatment changes of tumour marker level is studied.

Tumour structure can be rather non-homogeneous, consisting of, for example, different clones of cancer cells (with different sensitivities to an anticancer agent), stroma and necrotic areas. The value of \( SGR \) of the tumour may then be obtained from the spatial distribution of \( SGR \) within tumour, \( sgr(x, y, z) \):

\[
sGR = \frac{1}{V} \int_v sgr(x, y, z) \cdot dx \cdot dy \cdot dz.
\]

An effective treatment can reduce \( sgr(x, y, z) \) differently in different parts of the tumour depending on, for example, pharmacokinetics and dose–response of a systemically used agent. This will accordingly cause a reduction in \( SGR \) of tumour as was used in the presented model (Equation (4)). Studies have shown that functional imaging variables might be correlated with tumour growth rate, for example, using PET (Duhaaylongsd et al, 1995; Tannock et al, 2008). Further developments in this field can facilitate tumour SGR estimation by functional imaging before treatment as well as integration of \( TR \) data based on anatomical changes in tumour with other means of tumour response assessment by functional imaging with MRI (Chenevert et al, 1997) or PET (Stroobants et al, 2003; Boss et al, 2008).

In this study, we assumed that \( TR \) is evaluated at a specific occasion after treatment, as it is usually done in clinical studies. However, temporal changes of tumour \( SGR \) after treatment can also give valuable information such as progression due to the resistant clones of tumour, which can be identified with the point that \( SGR \) starts rising. However, this remains to be studied.

Time to event, for example, time to progression (TTP) or progression-free survival (PFS), is an end point that is also recommended for assessment of therapeutic efficacy (Scher et al, 2008; Eisenhauer et al, 2009). An interesting aspect of the presented method in this study is that Equations (1) and (5) imply that TTP is linearly related to \( TR \). It should be noted that in this context, the TTP refers to the progression of the tumour(s) under study, whereas from a clinical perspective, appearance of new metastatic lesions may be considered as disease progression. However, the metastases might have been settled before the start of...
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