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Factors causing dose variability in drug administration

Romano Demicheli[1], Antonio Jirillo[1], Giorgio Bonciarelli[1], Federico Lonardi[1], Marco Pradella[2], and Mario Balli[1]

[1] Division of Radiotherapy and Oncology, [2] Clinical Analysis Service, ULSS 28, I-37045 Legnago (VR), Italy

Summary. The variability of the drug dose actually given to cancer patients was analyzed. Three variability factors were quantitatively examined (body surface calculation, personalized dose calculation, and drug residuum in commercially available vials) and their variability was experimentally measured. A systematic reduction (mean, 7%; range, 2%–15%) and a random variability (4%–5%) of the dose given were demonstrated. These results draw attention to the role of some of the procedures of routine clinical activity in determining the amount of drug actually delivered. The analysis suggests that personalization of doses must be very accurate in both measurement and calculation and that the staff giving the drug needs to be carefully informed about the importance of drug residuum. The variability of the delivered dose can lead to the misclassification of patients in investigations on the dose-response relationship. This factor may be added to pitfalls previously reported to affect this type of retrospective analysis.

Introduction

The regression rates of drug-sensitive, transplantable solid tumors in animal systems have proven that for most drugs there is a steep in vivo dose-response curve [13], further supporting previous observations [14]. Moreover, reducing the drug doses by about 15%–30% has sharply lowered the complete and partial remission (CR and PR) rates of single-drug therapy and caused curative combination chemotherapy to become non-curative [13].

In most animal studies using these experimental solid tumors, a remarkable heterogeneity of responses has been shown, particularly when the tumor burden is quite large and when the drug activity is evaluated in terms of partial (PRs) or complete remissions (CRs) [13]. Such a heterogeneity was noted despite careful attention to the biological similarity of tumors and hosts as well as identical drug dosing. In human cancer chemotherapy, both of these findings should be considered to be potentially relevant. Furthermore, these data suggest that variations in the amount of drug that is given to individual patients could change clinical outcomes and cause an overspreading of the therapeutic results. This report attempts to quantify the variability of the drug dose actually delivered and to estimate its importance in modifying the dose level received by an individual patient.

Offprint requests to: R. Demicheli

Materials and methods

Factors causing variability. The amount of drug actually delivered to an individual patient is usually influenced by the following factors: (a) body weight and height measurements; (b) body-surface calculation; (c) personalized dose prescription, i.e. the dose actually prescribed for injection; (d) drug dilution and the drawing of drug into the syringe; and (e) i.v. injection.

Each step acts as a source of random and systematic variability. Body weight and height measurements, when carefully done with a balance calibrated in hectograms and a height-meter calibrated in centimeters, are affected by experimental errors of $< 1\%$, and such a variability is mainly random. Its influence on body-surface calculation is minimal (e.g. a variation in body weight from 70 to 71 or 69 kg and, concomitantly, a variation in height from 170 to 171 or 169 cm will change the body surface by $< 0.5\%$). Body-surface calculation is generally carried out with scales and rulers and usually produces random variability.

Personalized dose prescription, drug dilution and the drawing of drug into the syringe are sources of both random and systematic variability. In the former operation, the figures that are obtained from dose/square meter × body-surface product are rounded off, mostly without a specific rule. The round-off is quite often made downwards due to the psychological reactions to antitumor drug toxicity. The latter operations may systematically reduce the delivered dose as well, because of the drug residuum left in vials after drawing the drug into the syringe.

An exception may occur when the commercially available vial contains an extra quantity added by the manufacturer (overage) to ensure fully extractable quantities, which produces a compensating, positive systematic effect. Another exception occurs when the vial is not completely emptied. For example, there are times when 40 mg methotrexate (MTX) is drawn from a 50-mg vial, and too much or too little might be drawn. The residuum of powdered drugs is also affected by the drug's solubility and the dilution technique (e.g. to inject fresh solvent into each vial or to pass the same solvent through many vials successively). Syringe residuum after i.v. injection is generally minimal

because of the practice of washing syringes by repeated blood suctions and reinjections.

Experimental data. In the present retrospective investigation, dose variability due to factors (a) and (e) (above) was disregarded. The former has an order of magnitude of about 0.1%–0.3% and is significantly lower than the variability caused by the other factors; the latter is virtually absent. Variability caused by factors (b), (c) and (d) was experimentally measured as described below.

(b) Body surfaces of 80 patients with breast cancer who had received CMF chemotherapy [cyclophosphamide (CTX) (Endoxan-Asta), 500 mg/m^2; methotrexate (Methotrexate-Lederle), 40 mg/m^2; fluorouracil (FU) (Fluoro-Uracile-Roche), 600 mg/m^2; given i.v. on days 1 and 8 in a 4-week cycle] were recalculated from body weight and height by two investigators. Each result was compared with the recorded value, which had been calculated by one of five different physicians during several years of routine clinical activity.

(c) The differences between calculated and actually prescribed doses were examined in the same 80 patients and in an additional 50 patients given doxorubicin (DX) (Adriblastina-Farmitalia) for the treatment of various malignancies. These data were randomly selected from subjects treated in our oncology unit over a 5-year period.

(d) Residua of CTX (200 mg/vial), MTX (50 and 5 mg/vial) and DX (10 mg/vial) were measured in a sample of 120, 15, 15 and 100 vials each. The vials were taken at random from those used during a 3-month period by five well-trained cancer nurses. Each vial was drawn at the end of the morning after chemotherapy administration to both outpatients and inpatients and appropriately stored. CTX was measured by high-performance liquid chromatography (HPLC) according to the technique proposed by Kensler et al. [7] (sensitivity, 10 μg/vial). MTX was measured by a commercially available immunoenzymatic assay (SYVA Emit assay) and DX, by a fluorimetric assay (Perkin Elmer 203 spectrofluorimeter) [12] (sensitivity of both assays, 1 μg/ml). These techniques proved to be fully adequate for the purposes of the investigation. A 2% overage in DX vials but none in CTX and MTX vials were claimed by the manufacturing laboratories.

Calculations. Each variability factor was expressed in dimensionless units as the ratio between actual and planned value, and the following quantities were defined: body-surface correction factor (b.s.) = calculated surface/recalculated surface; personalized-dose correction factor (p.d.) = rounded-off dose/calculated dose; and drug-residuum correction factor (d.r.) = 1 − (residuum − overage)/nominal vial content.

Therefore, the dose of a particular drug actually delivered (AD) to an individual patient will be

$$AD = PD \times b.s. \times p.d. \times d.r., \quad (1)$$

where PD is the planned dose. The propagation of errors and the statistical analysis were carried out according to classic methods [1].

Results

The comparison between calculated and recalculated body-surface values were exact in 29 cases (36%), whereas 12 were adjusted upwards (15%) and 39, downwards (49%). The frequency of round-offs of the calculated dose in the prescription of individual drugs is summarized in Table 1. The personalized-dose correction factors for the four drugs studied are reported in Table 2, and if the whole data set (290 round-off oprations) is pooled, we obtain the overall value p.d. = 0.987 ± 0.036.

Mean residua of CTX and DX were 9.80 ± 8.41 mg and 0.46 ± 0.35 mg, respectively. In 5- and 50-mg MTX vials, 0.66 ± 0.18 and 1.78 ± 1.45 mg, respectively, were left on average. Table 2 displays the drug-residuum correction factors, which were calculated from these experimental data. The evaluation of the cumulative effect of all sources of variability on a single drug administration was carried out according to Eq. 1 and is summarized in Table 3.

When, as with MTX in the 80 CMF cases examined, vials that contain different amounts of drug are used in an individual administration, the AD/PD fraction must be

Table 1. Frequency of round-offs of calculated doses in the prescription of CMF and DX

Drug	Patients (*n*)	Upwards round-off	Exact dose	Downwards round-off
CTX	80	21	41	18
MTX	80	11	14	55
FU	80	21	3	56
DX	50	16	3	31

CTX, cyclophosphamide; MTX, methotrexate; FU, fluorouracil; DX, doxorubicin

Table 2. Mean ratio between actual and planned value of factors affecting the amount of drug delivered to an individual patient

Factor	Experimental value × 100 ± SD
Body surface	99.6 ± 1.2
Personalized dose	
CTX	99.8 ± 2.0
MTX	97.5 ± 4.1
FU	98.4 ± 4.4
DX	99.4 ± 3.8
Drug residuum	
CTX	95.4 ± 4.2
MTX (5-mg vials)	86.8 ± 3.6
MTX (50-mg vials)	96.4 ± 2.9
DX	97.4 ± 1.2

Table 3. Evaluation of the cumulative effect of all examined sources of variability, with the dose actually given (AD) expressed as a percentage of the planned dose (PD)

Drug	Vial content (mg)	AD/PD × 100 ± SD
CTX	200	94.8 ± 4.8
MTX	5	84.3 ± 5.3
MTX	50	93.6 ± 4.9
FU[a]	250	98.0 ± 4.5
DX	10	96.4 ± 4.0

[a] Vial residuum not available

calculated by weighing the data. For instance, in the above-mentioned patients, the weighed AD/PD × 100 value for MTX was 94.1 ± 2.4, since one 50- and three 5-mg vials of this drug were used on average per administration.

Discussion

The experimental data mainly prove that (a) the drug dose actually delivered to patients is systematically lower than the planned dose, and (b) the random variability of the delivered dose is approximately 5% of the planned dose for all drugs considered.

In systematic reduction, the drug residuum is the major source of error (5%–15% of the nominal dose), whereas the round-off of doses is less important and the body-surface calculation is almost negligible. It should also be pointed out that the unique overage examined in this study did not entirely compensate for the effect of the residuum after drug had been drawn into the syringe. The residuum was measured only in powdered drugs and no drug in solution was studied. Non-viscous drug solutions often contain an overage of about 15%, up to 5 ml/vial, and 10% for volumes > 5 ml. Therefore present estimates of residua could not adequately fit drugs in solution. However, since most of the commonly used anticancer drugs are supplied as dry substances, the results should be considered relevant for current chemotherapy. The question as to whether the systematic bias in drug administration remains unchanged in all phases of pharmacological studies and in all oncological institutions has never been investigated. This observation should be added to the other reasons for caution in comparing results of different clinical reports.

The dose round-off is the main source of random variability, whereas the drug residuum is a little less important and the body-surface calculation is relatively insignificant. However, the variability due to drug residua was underestimated by overlooking both the variability of the drug content of vials before the solution was removed (very often ±5% is allowed for by the manufacturer) and the variability due to vials that were not completely emptied. Furthermore, the importance of drug residuum is also related to the number of doses. As the number of cycles rises, the importance of this factor decreases, since the uncertainty of the mean value (σ_μ) is smaller than the uncertainty of the individual values (σ) of a series of n data ($\sigma_\mu = \sigma/\sqrt{n}$).

This study draws attention to a few procedures of routine clinical activity, the inaccuracy of which could negatively influence patient treatment. The analysis suggests that personalization of doses should be very accurate in both measurement and calculation and that the staff giving the drug should be carefully informed about the importance of drug residuum, which should be minimized by the adoption of a suitable technique.

Dose variability may also have some consequence in investigations of the dose-response relationship. In these studies patients are characterized by individual values of drug dose, which are used to allocate them to different subsets, separated by arbitrarily chosen cut-off levels. In the arrangement of such data, the random variability of the drug dose actually delivered may cause the misclassification of patients, i.e. the allocation to a particular group of patients who actually received a drug dose pertinent to another group. However, if the comparison between groups is expected to be reliable, the misclassification should not significantly affect the statistical results. This concept implies that any risk of misclassification higher than a given value should not be accepted and that the corresponding patients should not be considered in the statistical analysis. These patients are grouped around the cut-off levels, and their number strictly relates to the value of the maximally acceptable risk of misclassification: the higher the risk, the lower the number.

To evaluate the actual significance of these observations, we examined some published investigations. An estimate of the number of patients having a risk of misclassification of > 5% was carried out. This figure was chosen because of the critical role that may be played in human cancer chemotherapy by dose-response relationships. Calculations were accomplished with the proviso that the variability of drugs other than CTX, MTX , FU, and DX was equivalent to the mean value of the figures pertinent to these drugs. For treatments involving multiple agents, individual values were averaged and the variability of the means was calculated using standard methods [1].

We report only the analysis of data from papers examined, which enabled an adequate appraisal. None of the prospective studies that were analyzed [5, 6, 9] involved patients with a risk of misclassification of > 5%, because of the adequate interval between the dose levels that were compared. However, a quite different result was obtained in a few retrospective investigations, which attained conflicting results on the role of the dose level [2–4, 8, 10]. In each of these reports, about 25%–30% of patients allocated to a critical dose level showed a risk of misclassification that was > 5% (see *Appendix* for details on calculations). Therefore, although the misclassification of patients is unlikely to be the major cause of the differences seen, it should not be overlooked as another possible reason for the conflicting results. It may be added to pitfalls previously reported [11] to affect the retrospective analyses of data on dose levels.

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Appendix

Let us consider an individual patient receiving a drug dose $d_i \pm \sigma_i$, where σ_i is the uncertainty due to the dose variability. Using the standardized variable

$$z = \frac{|\varsigma - d_i|}{\sigma_i}$$

where ς is the cut-off level, the risk of misclassification of the patient considered may be achieved from the Gaussian distribution. Indeed, the risk of misclassification is the probability that the true d_i value is farther from the calculated d_i value than the cut-off. Moreover, since σ_i close to the cut-off level is roughly the same as σ_ς, a reliable estimate of the interval, where the risk of misclassification is greater than a chosen value, can be obtained from

$$\frac{|\varsigma - d|}{\sigma_\varsigma} \leqslant z, \qquad (1)$$

where z is the appropriate critical value of the Gaussian distribution.

For a risk of misclassification of $>5\%$, using Eq. 1 we obtain

$$|\varsigma - d| \leqslant 1.645\, \sigma_{\varsigma} \quad (2)$$

The number of patients falling into this interval can be derived from the total patient distribution (provided that mean and variance are known) using the integral of the Gaussian distribution, with the proviso that the examined population is normally distributed.

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