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Review

Prediction of normal tissue damage induced by cancer chemotherapy

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Summary. Cancer chemotherapeutic agents have a low therapeutic index and require a precise and safe prescription. Hematological toxicity is the most common dose limiting side effect of cancer drugs. Therefore, Hemopoietic Stem Cells (HSC) are the most relevant targets for dose determination. Studies of total body irradiation with or without autologous bone marrow transplantation showed that HSC concentrations differ between mouse, rat, rhesus monkey, dog and man. A highly significant correlation was found between bone marrow rescue dose and kg body weight and not between bone marrow rescue dose and BSA. Kg body weight appears to offer a better prescription unit for cancer chemotherapy than BSA, because it correlates better with dose limiting, normal tissue, target cells. This prediction is borne out by the results of chemotherapy in neonates. BSA has also been used as dose unit for drugs with non hematological side effects (e.g., cardiotoxicity of anthracyclines or neurotoxicity of methotrexate). The target for such drug side effects need to be determined before the proper dose unit can be selected. A review of available data shows that for at least some non hematological side effects BSA does not offer the proper prescription unit.

The historical justifications for BSA as dose unit are re-examined (simplicity, correlation with blood volume, correlation with area under the curve) and considered invalid. The ultimate long term improvements from better prescription methods for cancer chemotherapeutic agents are less normal tissue side effects and better tumor control. The indiscriminate use of BSA as a universal dose unit for cancer chemotherapy would prevent such improvements and is discouraged. Instead, drug doses are to be expressed in units that correlate with dose limiting normal tissue cells.

Staging of the cancer patient

Prior to the initiation of treatment, cancer patients will undergo staging procedures to classify their tumor [2]. The treatment objective is to eradicate all clonogenic tumor cells in the patient. Tumor stage correlates with the number and anatomical distribution of clonogenic tumor cells in the patient and will be of help in selecting the most appropriate treatment modality and in estimating the chances for cure. When high-dose cancer chemotherapy is required for cure, it is frequently accompanied by life-threatening side effects in *normal* tissues. This suggests the need for a second type of staging in cancer patients, i.e., a prospective quantitative evaluation for the dose-limiting normal tissues. The most common dose-limiting normal tissues are the hematopoietic system and, less frequently, the oral and gastrointestinal mucosa [9, 13]. All are self-renewal systems. Infrequently damage to organ systems that are considered non-self-renewal systems, such as the central nervous system and heart, is dose-limiting to cancer treatment. The acute life-threatening complications of radiation are caused by damage done at the level of the clonogenic stem cells in self-renewal systems [7]. Chemotherapy complications are probably caused by the same mechanism. The hematopoietic stem cell (HSC) is the only cell with self-replication capacity in the hematopoietic system and thus the only cell type that can provide lasting hematologic recovery from injury [1, 17]. Therefore, the 'target surface' for the great majority of chemotherapeutic cancer drugs are the HSCs. The dose-limiting effects of the hematopoietic system have been illustrated clearly in cancer patients receiving a bone marrow transplant after high-dose drug or radiation treatment. Approximately three times higher drug doses can be given if a bone marrow transplant is used [10]. The dose escalation that can be achieved varies per drug.

Theoretically, both staging systems need to be applied to select the optimal chemotherapeutic drug dose for a given patient. The staging of the cancer will reflect the amount of treatment the patient should receive to inactivate all tumor clonogenic cells; the staging of the normal tissues indicates the maximum amount of treatment the normal stem cells (in the hematopoietic system or gastrointestinal tract) can receive.

Toxicology of cancer chemotherapy

Currently the normal tissues of the cancer patient are not staged. Instead a preset drug dose is used, which is based on prior toxicological studies in experimental animals and human patients. In the past toxicology data were considered to permit the simplifying generalization that animals and patients of all age groups could tolerate the same drug dose when expressed per square meter of body surface area (BSA) [12, 18]. The exceptions found to this generalization have precluded a rigorous application of this 'rule'.

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Instead, after completion of toxicological studies in animals, cautious dose-escalating studies (so-called phase I studies) are done in human patients, starting at a safe dose derived from the most sensitive animal model and increasing the dose until the maximum tolerated dose is found [9, 13]. However, on the basis of the 'simplicity' rule already mentioned, the dose *is* expressed in terms of BSA. The correlation between normal tissue damage and BSA as a drug unit is not self-evident. Freireich and coworkers identified this problem in their 1966 publication: "it is unlikely that the skin is the target area of action of any particular [cancer] drug." They hypothesized "more likely the skin surface is more or less proportional to the true target surface." This hypothesis requires that BSA predicts for the number of HSCs and can be used as an indirect way of 'staging' the patient for normal tissues. Recent studies and calculations have shown that HSC and BSA are *not* correlated [26–28]. Results are summarized in Table 1. A comparison of columns 2 and 3 in Table 1 shows the HSC concentration per BSA does not predict for toxicity. The HSC concentration per kilogram of body weight *does* predict for toxicity (columns 3 and 4 in Table 1). The uniform toxic dose found in all species when dose is expressed per BSA is an artifact due to the higher BSA-to-kilogram ratios in smaller species.

Small mammalian species appear to possess more HSC per kilogram of body weight than large mammalian species. This makes smaller species more resistant to systemic cancer chemotherapy as well as to total-body irradiation [28]. In addition, smaller species require fewer bone marrow cells per kilogram of body weight for hematologic reconstitution after a lethal dose of total-body irradiation [26]. The difference between the HSC concentration in the bone marrow per kilogram of man and mouse is approximately ten. However, cell concentrations in the peripheral blood are similar in these and other mammalian species. This discrepancy can be explained by the observed differences in the 'economy' of the hematopoietic system in mammalian species. Smaller animals have shorter marrow-transit times and therefore less magnification in their hematopoietic systems. In addition, end-cells (red cells, platelets) survive longer in larger species, which decreases the need for renewal [11]. In addition, or alternatively, the smaller species might have a higher proportion of their HSC in a resting stage than do larger species. At present this latter possibility defies experimental verification through lack of appropriate methodology.

The observations summarized in Table 1 indicate that the prescription of cancer chemotherapy per kilogram body weight has a better scientific base than prescription per square meter of BSA for drugs with hematologic side effects. However, the kilogram of body weight is not the definitive drug dose unit, as it is an indirect estimate of HSC concentration that will be applicable to normal physiological conditions only. It will not be reliable if normal conditions have been disturbed, such as after prior cancer treatment or with infiltration of the normal bone marrow with cancer cells. In addition, increases or decreases in body weight through changes in calorie intake are not expected to induce similar changes in HSC, and prescription should be based on idealized body weight. A direct prospective HSC determination for each patient would be the ideal drug dose unit. The technology required for such determinations is being developed.

Clinical hazards of current BSA prescription

The maximum tolerated dose of new chemotherapeutic agent is determined in a phase 1 study in adult cancer patients [9, 13]. After definition of this dose it is insignificant whether the drug dose in a new adult patient is expressed per unit of BSA or per kilogram of body weight (Table 2). The difference in total dose for adults between 100 and 50 kg will be within 15% in either direction of the dose of the alternative prescription method. Children have a larger BSA per kilogram and will receive a higher total dose if adult doses are extrapolated per BSA and not per kilogram of body weight. If children have a higher concentration of hematopoietic stem cells than adults they might be able to tolerate more (±50%) drug per kilogram of body weight than adults [28]. This appears to confirm current clinical experience [5]. However, in neonates (<8 kg body weight) the BSA prescription will lead to an

Table 1. Toxicity of cancer chemotherapy and hematopoietic stem cell concentration

Species (BSA, kg; BSA/kg)	Body surface area		Body weight	
	Equal toxicity dose[a] of cancer drugs (mg/m² BSA)	Relative HSC[b] concentration per m² BSA	Equal toxicity dose[a] of cancer drugs (mg/kg body weight)	Relative HSC[b] concentration per kg body weight
Mouse (0.007, 0.025; 0.28)	1x	125	12y	10
Rat (0.03, 0.2; 0.15)	1x	44	7y	6.7
Rhesus monkey (0.23, 2.6; 0.09)	1x	9.5	3y	2.7
Dog (0.55, 0.12; 0.05)	1x	2.3	2y	1.1
Man (1.85, 70.0; 0.03)	1x	1	1y	1

Drug dose in man standardized as x/m² BSA or y/kg body weight to bring out relative drug doses in all species

[a] [12]

[b] [27]

Table 2. Differences in total dose of chemotherapeutic agents between prescription per kilogram of body weight and prescription per BSA for human patients[a]

Body weight (kg)		BSA (m^2)	Total dose per m^2, BSA prescription	Total dose per kg, body weight prescription
100	Adults	2.35	2.35	2.64
(Reference→ 70)	Adults	1.85	1.85	1.85
50	Adults	1.50	1.50	1.30
20	Children	0.80	0.80	0.53
8	Neonates	0.40	0.40	0.21
3	Neonates	0.20	0.20	0.08

[a] Hypothetical drug example, dosed at 1 mg per m^2 BSA, which is equal to 1.85/70 = 0.026 mg per kg in the reference adult. Total doses for other patients are computed using the doses in the reference adult of 1.85 m^2 BSA and 70 kg body weight. Total body weight and BSA are correlated by Meek's formula (m^2 BSA = 0.11 kg body weight$^{0.67}$) or by the duBois formula [20]

approximately 250% higher total dose than per kilogram prescription. The National Wilms' Study Group recommended cutting chemotherapy doses by a factor of 2 in neonates, because of the high hematological toxicity experienced after 'regular' chemotherapy doses, mainly prescribed per square meter of BSA [14, 22]. This experience is entirely compatible with the calculations in Table 2. Presumably prescription in terms of body weight is safer in neonates because it correlates better than BSA with the amount of HSC present.

The application of BSA for dosing cancer chemotherapeutic agents has been followed religiously, even for agents with nonhematological dose-limiting toxicity. Bleyer and coworkers have shown that this practice is unwarranted for intrathecal methotrexate [4, 6]. BSA is not correlated with central nervous system volume or intrathecal drug distribution and concentration. A more effective and less toxic MTX regimen was designed, with MTX prescribed per volume unit of the central nervous system [6].

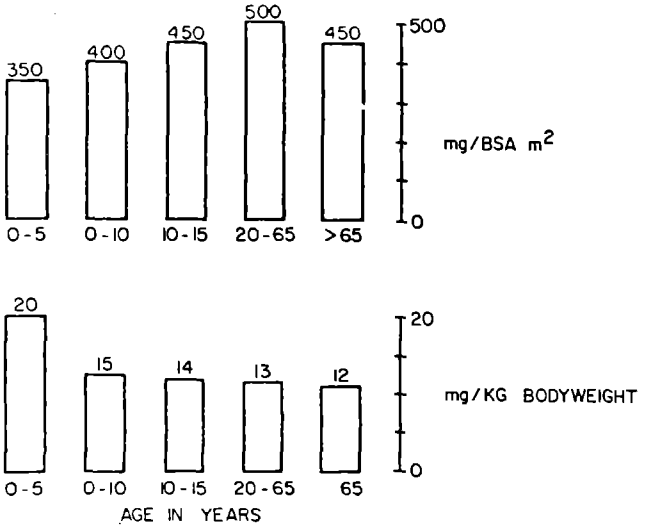

Fig. 1. Average accumulated cardiotoxic dose of adriamycin [19, 25]

Anthracyclines have been shown to cause cardiotoxicity in children at lower accumulated doses than in adults [19, 25]. In Fig. 1 the cardiotoxic doses of these studies are shown per age group and for each of two different prescription methods (per BSA or per kilogram of body weight). For the same total drug dose, different conclusions are reached for the susceptibility to cardiotoxicity. For the BSA prescription children are more sensitive than adults; for the body weight prescription the reverse is found. The BSA prescription unit might not provide the correct answer, as in children prescription per kilogram of body weight was safer than the prescription per square meter of BSA for cyclophosphamide-induced cardiotoxicity [23]. The correct prescription is the one that correlates with the target of anthracycline-induced cardiotoxicity. As long as this target is not identified, it remains unclear whether children are more or less susceptible than adults. Similar unresolved problems exist for cancer drugs with lung, skin, kidney, liver, gastrointestinal or peripheral nerve toxicity [26].

Fallacious pharmacokinetic arguments of BSA prescription

The original suggestion of prescribing cancer chemotherapy in terms of BSA was an extension of the experience published with sulfadizine, salicylate, morphine, digitoxin, and thyroid in children [8, 18]. For these drugs approximately the same effect was found in different age groups for the same drug dose, if drug dose was expressed in terms of BSA. For some drugs the concentration in the blood could only be predicted when a BSA prescription was used. Obvious differences between these drugs and cancer chemotherapeutic agents are endpoints (hematopoietic system only of importance for the cancer drugs), the reversibility of the effects of noncancer drugs, and dose scheduling. The cell killing induced by cancer drugs is irreversible and might not show a simple correlation with the concentration of the drug in the blood. Steady state drug plasma levels can be reached with multiple drug administrations, but are never reached after a single intravenous bolus injection of a cancer drug. This makes it nearly impossible to select an appropriate time or drug level as predictive for toxicity. Initial experience with actinomycin D, 6-mercaptopurine and methotrexate in children has not shown an advantage for BSA over kilogram prescription in children, in contrast to Pinkel's claim [18, 26].

Mellett has been an advocate of the area under the curve (AUC; drug levels in plasma over time) as indicative for cancer drug effects on normal tissue [16, 17]. Only a BSA prescription would give the same AUC and same toxicity in different species. Again, this simple correlation is not caused by a significant biological role of BSA, but by the high relative BSAs of small species. A review of the experience with continuous infusion chemotherapy in human cancer patients indicates that in comparison to bolus injections a larger AUC is obtained, but that bone marrow toxicity is frequently decreased [24]. Obviously the AUC concept remains unproven for normal tissue damage for most cancer drugs and cannot be used as an argument in favor of a BSA prescription for cancer chemotherapy. Occasionally blood volume has been quoted as being better correlated with BSA than with body weight [8]. In the model concerned a BSA prescription would predict better

for drug plasma levels. However, the significance of plasma levels for cancer drugs remains unclear and, more importantly, in allometric studies blood volume appears not to be correlated with BSA, being rather a fixed percentage of body weight [21].

Recommendations

The information summarized appears to indicate that BSA is not a useful drug dose unit for every cancer chemotherapy agent. We recommend that chemotherapeutic cancer agents be prescribed in units that correlate with dose limiting normal tissue. Unfortunately, accurate prospective quantification of dose-limiting normal tissues is not available yet, through lack of appropriate methodology. As an interim solution 'indirect' parameters can be utilized for drug dose units, if they show a good correlation with dose-limiting normal cells. Body weight, in contrast to BSA, is such an indirect parameter for hematological toxicity. For nonhematological toxicity of cancer chemotherapy, other direct or indirect parameters that are different from kilogram of body weight might be most useful.

The ultimate purpose of improving the prescription method of cancer chemotherapy is to increase the therapeutic ratio and curative potential of this group of very toxic pharmacological agents. We hope to have shown that the indiscriminate continuation of BSA as a drug dose unit is not supported by the available scientific evidence and will not allow for such developments. Further efforts should be directed at the quantification and reliable prediction of normal tissue damage. A candidate hematopoietic stem cell has been proposed morphologically in animals and man [3]. A routine, quick, determination of the total number of effective hematopoietic stem cells in a given patient is not available yet and will require more than morphological identification alone. If such an assay were developed, it would immediately become invaluable in predicting for hematopoetic reserve and optimal chemotherapy doses in cancer patients.

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