

Change of dosing paradigm in oncology

Research Article

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Abstract: Drug dosing based on the body surface area (BSA) has been the mainstay of oncological treatment over the last decades. Although this seems to be an adequate measure of an individual's appropriate dose for traditional chemotherapeutic drugs according to their somatometric data, it is currently being questioned due to the delivery of novel treatments such as monoclonal antibodies. Most modern regimes require either a flat (fixed)-dosing model, independent of body weight, or a weight-based administration pattern, mainly depending on specific pharmacokinetic data. However, even in this case, some controversy exists about whether this model is sufficient. Given the recent findings from pharmacokinetic studies, perhaps we should reconsider the solid hypothesis that drug efficacy correlates with dose, as many molecules seem to be efficient even in the lowest doses administered, with minimum toxicity.

Keywords: *Chemotherapy dosing • MTD • novel therapies • monoclonal antibodies • sotorasib*

1. Introduction

In daily practice of oncology, many conventions are often employed to define standards, to facilitate scientific dialog, and to enable organization of chaotic phenomena or conversion of continuous variables to binary attributes. Such assumptions represent “linear” interpretations of a chaotic reality and shape our understanding of biological phenomena. However, we should be aware that these approaches are artificial by nature and comprehend the specific needs that they intend to cover.

From the medical oncologist's perspective, it is essential to accept these reasonable assumptions and operate within their context. However, as the scientific background is a constantly evolving field, perhaps recalibrating the values is an emerging need.

2. Traditional oncology dosing

Nearly 65 years ago, when systemic chemotherapy was applied in cancer treatment, scientists thought the determination of the maximum tolerated dose (MTD) of a given drug was key. MTD relied on the sample, as it was defined as the dose of a drug or treatment that caused unacceptable side effects to more than one-third of

patients. This definition was clearly arbitrary and reflects the paucity of available drugs at that time, along with the physicians' anxiety to attain maximum clinical benefit of the agents they provided. Probably, a modern oncologist would not use such a definition of MTD, given the high toxicity rate considered acceptable.

It soon became obvious that MTD could not possibly depend on the individual's body weight solely. If the drug dosage was calculated per kilogram of body weight, it would lead to large discordance in therapeutic doses among obese and thinner individuals or even among children of different age groups. In general, thinner patients can handle a substantially higher dose of a medication per kilogram of body weight than the average person; the opposite is true for overweight patients. The answer to this problem was based on physiology studies that had already revealed linear correlation between variables, that is, the basic metabolic rate or the cardiac output, and the body surface area (BSA), instead of body weight. Donald Pinkel, in his publication in 1958^[1], demonstrated that the dosing model based on BSA adequately described MTD of methotrexate, actinomycin-D, mechlorethamine, and triethylthiophosphamide for laboratory animals, children, and adults; all the above drugs could optimally be dosed using the same formula of mg per m². Calculation of BSA was based on the DuBois equation: $BSA = 0.007184 \times$

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weight $0.425 \times \text{height } 0.725$. The same methodology was successfully applied on dosing of chemotherapeutics over the following decades and is generally used to date.

3. Challenging the Paradigm

This fundamental principle hypothesizes that there is a positive correlation between dosage and therapeutic effect and, therefore, the higher dose a patient tolerates, the better the outcome will be. This assumption seems to be true for traditional chemotherapy drugs. Megatherapy (MT) can benefit patients suffering from certain malignancies. Intensification of treatment (mainly through increased frequency of administration) has demonstrated positive results in both hematological cancers such as lymphoma and in solid tumors such as breast cancer, bladder cancer, etc. However, it is an oversimplification to suppose that the pharmacokinetics and pharmacodynamics of a drug are identical between two individuals with the same BSA index. There are several confounding factors such as age, muscle mass, percentage of body fat, nutrition factors, organ dysfunction, drug interactions, as well as individual factors, likely dependent on the genetic background. This seems to be in line with our clinical experience, showing that two patients with a given BSA demonstrate distinct patterns of toxicity. Such is the variability in pharmacokinetics and pharmacodynamics, which led certain researchers to create a grouped dosing model: 1. adult patients with $\text{BSA} < 1.77 \text{ m}^2$ received a standard dose, which was calculated based on a fixed $\text{BSA} = 1.55 \text{ m}^2$; 2. patients with $\text{BSA} > 1.9 \text{ m}^2$ received a separate standard dose based on a fixed $\text{BSA} = 2.05 \text{ m}^2$; and 3. patients with intermediate BSA received a separate standard dose based on a fixed $\text{BSA} = 1.8 \text{ m}^2$ ^[2]. This study demonstrated that deviation from the desired AUC in both models (standard vs grouped) was the same, indicating that the variability of pharmacokinetics is able to overcome the appropriateness of the typical BSA-based dosing. Such evidence underscores the insufficiency of the accepted BSA-based model to accurately predict the most suitable dose for each patient, when a certain AUC is desired.

Several observations also challenged the BSA-dosing model and highlighted the importance of the kinetics of certain enzymes related to the metabolism of the drug. As an example, studies on the pharmacokinetics of gemcitabine, a prodrug that undergoes intracellular conversion to a triphosphorylated molecule to disrupt DNA duplication, showed that conversion to the active metabolite increases with increasing dose only for doses 35–350 mg/m², reaches a maximum rate at 350 mg/

m², and does not further increase afterward. This fact exists due to saturation of the enzymatic mechanism that produces the active phosphorylated metabolite^[3]. Or the positive dose–effect correlation ceases and plateaus thereafter, when it approaches one-third of the usual dose administered in clinic. Furthermore, in breast cancer patients, it is doubtful whether an increase in anthracycline dose results in further clinical benefit, as opposed to dose-increase effect of older chemotherapy regimens^[4,5]. In fact, an increase in dose intensity not only failed to demonstrate a statistically significant improvement in DFS, but also actually caused an increase in toxicity^[5]. In addition, an increase in dose density of anthracycline has not been found to improve chemotherapy efficacy^[4]. Thus, a fit-to-all dose could be determined, lying between the dose required for the enzyme's saturation and the classical MTD, without a compromise in drug effectiveness.

However, due to lack of a more practical dosing model, clinicians continued to apply the BSA-based approach. This seems to be correct, as in many instances, the main determinant of outcome is the underlying biology of the tumor. Thus, the “undertreatment” implied by lower BSA in some patients does not seem to cause substantial difference in treatment effect, while “overdosed” patients are self-regulated by dose reductions dictated by toxicity.

4. New drugs in search of optimal dosing

The introduction of monoclonal antibodies in cancer therapeutics has added another challenge in the established dosing model; the MTD concept cannot be applied here because toxicity does not correlate with the administered dose; immunoglobulins aim at specific targets that are saturated at lower doses than those administered in the clinic. As a result, neither pharmacodynamics nor toxic effects alter with higher dose administered. The standard dosing model would result in extreme MTDs of hundreds of grams. So, how should the ideal dose of monoclonal antibodies be determined? In daily practice, administration of a higher-than-demanded dose to efficiently bind the target is often employed. The excess drug amount plateaus at the reaction curve, and this serves as a safety valve to benefit all patients.

When monoclonal antibodies were introduced, their dosing was based either on BSA or body weight. Rituximab dose, for instance, was calculated based on BSA, while other antibodies such as trastuzumab were administered per kilogram of body weight. As stated above, this approach is not solid in the case of

monoclonal antibodies, as there is no dose–response curve. For this reason, certain regimens of monoclonal antibodies were soon developed to suggest a fixed dose for all patients. This is especially the case for conversion of intravenous (IV) to subcutaneous (SC) forms, such as those of trastuzumab and rituximab, which are given at a flat SC dose. Ultimately, the idea of flat dosing of monoclonal antibodies was widely accepted.

Therefore, administration of therapeutic antibodies in doses much higher than the minimum active dose does not increase toxicity, as the latter is not affected by dosage. However, this does not apply to micromolecular enzyme inhibitors, which generally exhibit pleiotropic activity with many known or unknown targets of variable affinity. Doses higher than required for maximum therapeutic effect are usually associated with an increase in toxicity due to undesirable on-target effects. As toxicity is dose related and not negligible in this case, the MTD-method applies to these molecules as well, with the assumption that a positive correlation between concentration and therapeutic effect always exists. However, this hypothesis is often rejected because drugs also interfere with enzymatic processes. Delivering them at MTD may not be required, especially if there is high affinity for the target. In fact, clinical observations indicate that dose reduction due to side effects does not diminish efficacy. Real-world data have shown that reduced dose of afatinib might be equally beneficial in terms of treatment outcome with reduced toxicity^[6,7]. Similarly, regorafenib is usually employed in the clinic at lower-than-approved doses, as efficiency is maintained and toxicity is also reduced^[8].

Recently, the need for a paradigm shift was highlighted by the US regulatory authority, the US Food and Drug Administration (US FDA), triggered by the Phase I study of sotorasib, an agent against KRAS G12C mutation^[9]. The study included 129 patients and evaluated predetermined doses from 180 to 960 mg, all achieving drug concentrations equal to or greater than the inhibitory *in vitro*. No dose-limiting toxicity was observed at any dose level, although the highest dose caused more side effects. The latter was eventually approved for clinical use; however, the FDA has mandated that the company conduct a post-marketing study to compare the lowest to the highest dose,

challenging the dogma “more is better.” The arguments for this requirement can be summarized here: There is no correlation between dose and steady-state drug exposure, there seems to be no correlation between dose and clinical efficacy, gastrointestinal toxicity is lower at lower doses, preclinical inhibition studies correspond to doses between 30 and 240 mg and, finally, the approved dosage requires the administration of eight tablets of 120 mg, which is problematic^[10].

5. Conclusions

As stated above, the dosing model for novel drugs is in the process of undergoing radical changes. It has been understood that determining MTD of newer agents is not required (unless there is a specific need to define the therapeutic window). In the future, we will need to seek a dose that is sufficiently greater than the minimum needed to block the therapeutic target. Most probably, this dose will be flat, as it will, by definition, be active against the target for all patients regardless of the individual drug elimination and pharmacodynamic variance; it is also expected to be safer, as it is expected to be lower than the maximum tolerated dose.

Flat dosing offers a significant and rationale convenience, albeit it may give rise to certain concerns: Should we use two distinct flat dosages for thinner and heavier individuals? Is the distribution altered in SC forms if the percentage of body fat is bigger? The magnitude of resource utilization sparing has not been properly established. Last but not least, flat dosing does not seem to represent a viable solution in pediatric oncology patients, mainly due to large differences among different age groups. It seems we have a long way to go in that field. Nevertheless, it is due time to replace the established BSA-based model with a friendlier dosing paradigm that will shape cancer therapeutics in the modern era.

Conflict of interest

There is no conflict of interest.

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