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Editorial Open Access

Dosing of Chemotherapeutic Drugs – Time to Leave the Stone Age

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Therapeutic success of anticancer chemotherapy needs appropriate dosing. Clearly, the efficacy of chemotherapy is strictly dose dependent. Unfortunately side effects are dose dependent as well. Thereby, dosing of chemotherapeutic drugs is a delicate balancing act between killing tumor cells and severe toxicity in other tissues. Unfortunately, this delicate balancing act is done in mere blind flight.

Even though the pharmacokinetic characteristics of almost all chemotherapeutic agents are well known, common dosing schedules are most often not based on pharmacokinetic/pharmacodynamic considerations, but on rather simple empirical dose finding studies. Even more disturbing, most dosages are based on century old rough estimations of body surface [1], given as mg/m^2. In early dose finding studies, the dosage is increased, until side effects become too harsh to be tolerated. The so called "Maximum Tolerated Dosage" (MTD) is then tested on a larger collective, corrected, retested, and finally approved. In modern chemotherapy, often substances are combined, hoping that efficacy is synergistic while side effects are not. Unfortunately, this hypothesis is too good to be true. Most often, side effects are additive as well, and simply, dosing of each substance is reduced. Then again, one or the other MTD is found in empirical studies, with combinations, timing and intervals widely varied. Surprisingly, even in the more complex dosing shedules, pharmacokinetic/dynamic parameters are not considered. This way of empirical dose finding based on rough estimations of primitive body characteristics was appropriate for our ancestors in the dimly lit caves of early anticancer chemotherapy, but can not be considered appropriate today.

Dosing as empirical average based on a rather rough estimation of external body characteristics leads to incredible high individual variability in plasma concentrations and related parameters. For example, maximal plasma level (C_{max}) of doxorubicin has been shown to vary by factor >10 (!!!) in a group of 27 children [2] receiving the same dosage as 30 mg/m^2. Even with simple bolus injection, differences as high as factor 4 are not uncommon. Obviously, patients with high individual levels are at higher risk to suffer side effects, while patients with very low levels are likely below therapeutic effective dosage. As already established for other very toxic drugs like immunosuppressive drugs, Therapeutic Drug Monitoring (TDM) of common chemotherapeutics is needed urgently.

Calling for TDM of chemotherapeutics is neither innovative nor new. Why is individual TDM not already established in clinical practice?

First of all, analytical methods used so far are inappropriate for common use. Most often, plasma level measurements are based on High Performance Liquid Chromatography (HPLC), thereby elaborative, time consuming and expensive. Second, for many drugs little to nothing is known about the pharmacokinetic/dynamic parameters relevant for efficacy and toxicities (like, for example "maximum tolerated AUC" and "minimal effective C_{max}"). Third, dosage regimens have to be based on individual pharmacokinetics, observed by individual TDM. This will need a complete revision of common protocols, leading to numerous new dose finding studies.

As always in science, things are rather pretty complex than easy. Genetically based models of individual plasma levels are not very promising, as often not only high inter individual but also intra individual variabilities in plasma levels are observed. Thereby observed pharmacokinetics within a first regimen are hard to extrapolate on the next. Thus there is a need to monitor each cycle of each patient individually. In order to allow dose modifications based on existent plasma levels, fast methods have to be established. For bolus injections, these essays must be much faster than respective initial half lives. For continuous infusions, the essays may take little more time, but still HPLC processing is not feasible. On the other hand, very fast essays may not need to take drug metabolites into account and might be designed much simpler then common essays to monitor pharmacokinetics. With new methods based on immunoassays or offline mass spectrometry after minimal sample processing, time scales might be greatly reduced. Lab-on-a-chip solutions might allow for point of care online measurements.

Establishing a relationship between efficacy, side effects and relevant pharmacokinetic parameters might be elaborative, but done with already available common analytical methods. Probably old studies might be used when stored samples (and ethics) allow for measurement of drug levels. Unfortunately most regimens are based on more than one drug, thereby establishing relationships might be more difficult.

Once fast and easy methods for individual TDM are developed and the relevant pharmacokinetic parameters are identified, individual dosing based on existent plasma levels can be evaluated in clinical studies. In the age of so called evidenced based medicine, this might be a rather hard challenge. Since many common chemotherapeutics are generic, big pharmaceutical companies have little to no interest in paying lots of money for clinical studies on old drugs without patent protection. Whether diagnostic companies can cope for this is more than questionable. More likely public founding is needed to establish individual TDM of common chemotherapeutics. But public founding of large clinical studies is rather difficult and relies on highly motivated individuals. Hopefully, this editorial helps to motivate some of our readers to venture into this highly needed topic.

Relying on public founding and highly motivated physicians and scientist, open access of results in TDM of chemotherapeutic agents is a must. Fast and world wide access will speed up the process of sharing expertise and developing new chemotherapy regimens. I wish

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this journal will contribute to a topic that is of great benefit for future cancer patients.

Common dosage does not reflect individual needs in modern chemotherapy. TDM of individual plasma levels might be of great benefit for the patients subjected to chemotherapy. In the age of so called "Nanomedicine", leaving the Stone Age in daily dosing of common chemotherapeutics is overdue.

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