Benefit of TDM depends on therapeutic class of anticancer drugs

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Scope of the lecture:

Relationships between plasma concentrations and either antitumoral effects or side effects will be compared for the four groups of anticancer drugs: cytotoxics, hormonal drugs, targeted therapies, and immunotherapies.

Learning objectives:

1. To understand why TDM is developed and applied for some groups of anticancer drugs, but not others.
2. To compare the different methods of individual dosing which could be applied for a same drug depending on the cancer disease and the corresponding chemotherapy protocol.

Extended abstract:

Anticancer drugs represent a heterogeneous group of drugs which are used for diseases which are very different from one another (due to unique molecular alteration versus multifactorial processes) with different objectives (curative, adjuvant, or palliative). Consequently, the benefit of dosing based on PK characteristics differs for each cell of the matrix corresponding to these multiple combinations, but the main features can be raised illustrated by examples. Also as a general comment, it should be emphasized that patients receiving the same anticancer treatment present different characteristics which amplify the interindividual PK variability compared to patients not suffering from cancer: elderly patients, metastases of solid tumors may impact hepatic or renal functions, drug-drug interaction (DDI) with an associated drug may occur to decrease the side effects of chemotherapy, heterogeneous performance status … This point together with the low therapeutic index of all anticancer drugs justifies the principle of individual dosing for these drugs. However, achievements in this field are very different dependent on the group of anticancer drugs.

Cytotoxics are drugs interfering directly or indirectly with DNA without any antitumoral selectivity, which are therefore responsible for hematopoietic and mucositis (potentially) dose-limiting toxicities (DLT). Most of the protocols are based on intermittent administrations every 21 days, a period required for recovery from neutropenia in particular. Close relationships have been shown between AUC and neutrophil counts at nadir for many if not all cytotoxics. Hence, individual dosing has been implemented for drugs with predictable PK clearances (CL) such as carboplatin which is mainly eliminated by renal glomerular filtration. However, for all other cytotoxic drugs, doses are still calculated according to the patient's body surface area (BSA) although only around 10% of the interindividual variability on CL is explained by BSA (1). TDM is not applied for cytotoxics for several reasons. Among them, the main one is their "Day 1 = Day 21" short-time intravenous infusion schedule of administration making the results of the PK evaluation available when the whole dose has been administered (2). High dose (HD) chemotherapy based on cytotoxics does not present this limit since each cycle is often composed of repeated daily administration for 3 to 5 days. An example of TDM of carboplatin developed by our group for HD treatment of testicular cancer will be shown (3). For some cytotoxics eliminated via a main catabolic pathway subject to genetic polymorphisms such as 5-fluorouracil and irinotecan, pharmacogenetic evaluation of the patient tends to be a routine practice in order to rationally decrease the dose or contraindicate the drug in case of genotype associated with a higher risk of toxicity(4).

Hormonal treatment of breast cancer is based on daily oral administration of tamoxifen or anti-aromatase compounds. Knowledge of exposure-response relationship of anti-aromatase drugs is still limited and requires further evaluation before considering TDM. However, for tamoxifen, a threshold value has been suggested for endoxifen, its main active metabolite (5).

The mechanism of action of targeted therapy is completely different to that of cytotoxics. Most of them inhibit receptors to growth factor such as EGFR, Her-2, VEGFR, c-Kit … Their antitumoral effect is due to their cytostatic effect (rather than a cytotoxic effect) requiring continuous exposure of the tumor cells. Targeted therapy is composed of two main subgroups: tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs).
The TKIs are given orally and once (or twice for those with a short half-life) daily in monotherapy. All the prerequisites for implementation of TDM are fulfilled for these compounds. The benefit of TDM between compounds is mainly dependent on the benefit of

the drug itself in the considered disease. To take opposite extremes, on the one hand, chronic myeloid leukemia (CML) is due to a unique event (Bcr-Abl, a somatic chromosome rearrangement) whereas most of the solid tumors are multifactorial processes. The efficacy of imatinib and other TKIs is undebatable for the treatment of CML, whereas the benefit of TKIs treatment for solid tumors is generally limited, and their use is reserved to advanced disease stages with only a palliative objective. The benefit of TDM is likely to differ in the same way. Advanced kidney cancer represents an intermediate situation with a real benefit of TKI treatment and a rationale to implement TDM for drugs such as pazopanib and sunitinib (6). Implementation of TDM for TKIs raises several issues (general or specific to the drug considered) such as intraindividual PK variability, plasma protein binding, metabolites, … which may also have to be taken into account.
Exposure-response with monoclonal antibodies (mAbs) represents a more conflicting topic with some uncertainty remaining with regards to the benefit of individual dosing based on TDM. The targets of mAbs are often the same as those of TKIs (e.g., Her-2 for lapatinib and trastuzumab, EGFR for erlotinib and cetuximab). However, the PK of mAbs is very different to that of TKIs with a more limited distribution and a specific pathway of drug elimination. Their schedule of administration appears similar to that of cytotoxics (1- or 3-hour iv infusion every 2 to 4 weeks depending on their half-life) but associated with a continuous exposure due to their relatively long half-life. Retrospective studies revealed a better outcome in patients with higher AUC values suggesting that an increase of mAbs dose would be recommended in patients with higher CL (7). However, it has been also shown that the CL of mAbs tends to be higher in patients with high inflammation status (7;8). These patients are those with the more severe disease and the poorer prognosis. The link (direct or indirect) between inflammatory status and mAb elimination remains poorly understood. Fast mAbs CL is typically observed with patients with large tumor burden (who could also be impacted in some cases by target-mediated drug disposition), low albumin or high C reactive protein levels (9). Now, it cannot be excluded that the relationship between exposure and response is mainly due to the impact of the disease on PK. In this case, no significant benefit would be associated with a control of the exposure.

Immunotherapy in Onco-hematology is a new area of chemotherapy for which the benefit of individual dosing is still difficult to appreciate. Indeed, the dose-response relationships themselves need to be better understood and may be different depending on the compound. During the first-in-man phase 1 trials of these mAbs, tumor responses have been observed for several levels of dose which could differ by a ratio of 20(10). Regarding the side effects, the relationships could also be tenuous. These first observations could discourage any further PK investigations. However, further studies have revealed not only correlations between dose levels and both efficacy and toxicity, but also PK/PD relationships(11).

As illustrated by the previous examples, the improvement of individual dosing of anticancer drugs is a never-ending process, and as in every therapeutic domain, further post registration PK studies are needed to achieve these improvements.

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