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In oncology, biotherapies now play a major role, offering a real hope of improving patient management and prognosis. Increasing numbers of these new molecules have been released in recent years, alongside the historical monoclonal antibodies, ADC (antibody drug conjugates) and checkpoint inhibitors.

These are highly technical therapeutic innovations which improve response and survival, although for immunotherapies, survival at 3 years is at most 20 to 40% *(1)*. Thus, with inhibitors of immune checkpoints, of 10 patients treated, only 3 to 4 will survive in the long-term, mainly those with metastatic melanoma, cancers in the ENT region, of the kidneys and metastatic lung cancer; other patients will only have a weak therapeutic response. In addition, the use of a "flat-dose" tends to lead to over-treatment of patients. As biotherapies are very expensive, they weigh heavily on public health budgets. By monitoring these molecules, their use could be rationalized for the patient, which would reduce the financial burden on institutions.

Has the mystery of ineffective biomarkers been resolved?

With the enthusiasm for biotherapies, and in an attempt to improve therapeutic responses, biological markers of response and non-response have been sought to predict the outcome for patients and their disease. Although a small number, such as HER2, KRas or NRas status, have proven their predictivity with some biotherapies, others lack robustness and there remain too many instances of unpredictable therapeutic failures *(1)*. The data are very contradictory, and we still lack robust validated markers, in particular for immunotherapeutic products.

Prof. Joseph Ciccolini explains that "unlike other molecules in oncology (chemotherapy or targeted oral therapies), the pharmacokinetics of biotherapies is highly atypical and does not depend on hepatic or renal function like other treatments. Consequently, the sources of variability and the risks of atypical exposure – very high or very low – completely escape analysis and are thus unpredictable. In chemotherapy, genetic polymorphisms, drug interactions, comorbidities affecting the kidneys or hepato-biliary systems are all warning signs that doctors consider before initiating a treatment. With biotherapies, we know nothing, we still have difficulty understanding the mechanisms behind success or failure, and we lack a method to predict exposure for a given patient". In response to this need, the idea of measuring circulating amounts of biotherapeutic molecules – neglected up to now – has emerged *(2)*.

The need to maintain a target residual concentration

Currently, when using biotherapies, the dosing regimens and frequency of administration are not really personalized. Patients who could benefit from these innovations are all treated in the same way, assuming that the molecules administered will display the same pharmacokinetic pattern and have the same pharmacodynamic effects for everyone. This is an error. Indeed, we often encounter patients who do not respond to a therapy, whereas from a pharmacological and pharmacogenomic point of view everything should function normally: the target is expressed and not mutated.

Monitoring and assay of biotherapy levels has allowed us to understand that in some patients, insufficient therapeutic agent is present at the site of action to engage the target and trigger a pharmacodynamic effect *(3-5)*. The fact that we have a bioguided molecule is therefore not enough to ensure therapeutic efficacy for some patients: it is also essential that the amount at the site of action is adequate.

The intravenous administration of biotherapies, in line with the MA recommendations, is not a guarantee of efficacy. Data show that some biotherapies are less effective below a threshold residual target concentration, set at 34 µg/mL for cetuximab, for example *(3)*. If an adequate level of circulating antibody is not reached, its concentration at the target site will never be sufficient to trigger a pharmacodynamic effect. The source of this problem is unknown, but is probably linked to genetic polymorphisms, comorbidities such as cachexia, or other specificities intrinsic to the patient's physiology.

This notion is very important as these patients are underexposed, and due to treatment failure, lose precious time, raising the risk of metastatic progression. "Monitoring of residual concentration thresholds from the initial cycles with in silico estimation at 3 months would alert the physician early on to a low probability of treatment efficacy" estimates Prof. Ciccolini. Patient management could be rapidly altered, either by adjusting the dose of the biotherapy, or by immediately switching treatment-line without waiting for imaging results. In the future, prescription aids could be developed to help select and refine the appropriate dose of biotherapies to prescribe to be prescribed to individual patients.

Limiting over-dosing and toxicity

The flipside of this conundrum is the other problem with biotherapies, specifically immunotherapies: over-treatment of patients. This has become a particular problem since "flat dosing" was introduced. Therapeutic monitoring of biotherapies associated with modelling of their pharmacokinetics would allow us to adjust, not the doses themselves, but the frequency of administration, by reducing it. Mark Ratain

and his Chicago-based team have worked extensively on this idea of over-treatment of patients. By modelling both the pharmacometrics and the residual levels of biotherapies *(7)*, they have shown that adequate levels to engage the target can be maintained despite a two-fold or even two-thirds reduction in the frequency of administration *(8)* with anti-PD1, for example. Reducing the frequency of therapeutic administrations would have an immediate corollary advantage of diminishing the "drug" cost for these treatments for public institutions, without, however, reducing the level of response and efficacy of the treatment.

Currently, even with technologies derived from artificial intelligence, we lack predictive markers that would provide a prognostic signature of drug toxicity. However, a small number of patients experience strong toxicity with biotherapies, mainly with immunotherapies. The first cases examined with anti-PD1 molecules, with the help of pharmacometric models, suggest that these patients experienced massive over-exposure linked to a pharmacokinetic anomaly of as yet unknown origin. Therapeutic monitoring of biotherapies, thanks to long-term extrapolations, would allow early detection of patients presenting a risk of severe, potentially lethal, toxicity, without confirmed toxicity factors *(9)*.

In parallel, if massive exposure of a patient could be objectively measured during monitoring, it would be possible to undertake blood filtration to eliminate the antibodies and stabilize the patient's condition.

The anti-tumoral action of biotherapies explained by pharmacometrics

In practice, pharmacometrics *(10)* involves biological sampling, with results used as input for pharmacokinetic mathematical models. With the help of simulations, exposure levels and changes to the residual levels of biotherapies over time in a patient can be retraced in silico. A patient falling outside the therapeutic window can thus be readily identified. The reason that the threshold residual levels are so important resides in the mechanism of action of biotherapies. Indeed, in pharmacokinetic and pharmacodynamic terms, biotherapies work a bit like certain anti-infectious agents. Very high Cmax values are not absolutely required to induce effective anti-cancer effects, and may even trigger toxicity. The crucial element is to maintain continuous exposure of the patient above a minimal effective threshold. Thus, the tumor must be exposed to an adequate concentration of antibodies to engage the target 24/7. This is explained by the pharmacokinetics of biotherapies. These large molecules only come into contact with cells at the surface of tumors, and have difficulty gaining access to the inner cells. Schematically, after antigen recognition, biotherapies induce apoptosis, successively removing layers of cancerous cells from the outside of the tumor, and progressing to the inside. The amount of antibody at the surface must therefore be sufficient to attack the next layer. Biotherapies have been shown to distribute weakly in solid tumors (5 to 20% of the dose), and to have difficulty penetrating into the tumor micro-environment *(11)*. An excessive concentration will not improve the anti-cancer efficacy as the excess biotherapy still cannot penetrate at depth into the tumor tissue, and will end up being eliminated.

Conclusion

Verification of the expression of the target of biotherapies or the use of a tumor marker no longer appear to be the only parameters to be taken into account for the therapeutic management of patients in oncology. The residual circulating antibody concentration could be a new biomarker, representing a promising new parameter for use in daily practice with our patients to guarantee optimal efficacy of the biotherapies administered. Unlike a genomic or molecular biomarker, the pharmacokinetics of biotherapies can be linked to specific corrective actions such as adjusting the dose or the frequency of administration. Monitoring of biotherapies would thus allow early prediction of a patient's response or non-response to a treatment while limiting toxicity, thanks to information on under-dosing and over-exposure. For this purpose, monitoring data could be an aid for decision-making by the doctor. In these economically unstable times in public institutions, it is thus possible to act for the economic well-being of the public health system while also improving management of oncology patients treated with biotherapies.

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J. Ciccolini declares having links of interest with Promise Proteomics, Pfizer, Pierre Fabre, Samsung Bioepis, Daïchi Sankyo et Esai (speaker contracts). F. Broué declares having no links of interest.

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