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Metronomic maintenance therapy for high-risk paediatric malignancies: one size will not fit all.

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ABSTRACT

Maintenance therapy sometimes relies on the use of metronomic chemotherapy; that is the continuous administration of low dose chemotherapy. Maintenance therapy has been successfully used for decades in pediatric patients with acute lymphoblastic leukemia and recent results have demonstrated improved outcomes in patients with pediatric high-risk rhabdomyosarcoma on maintenance therapy. Here, we review the use of metronomic maintenance therapy in pediatric cancer and discuss its mechanisms of action on the tumor micro-environment and cancer cells. We also discuss its potential use as a chemotherapy alone or in combination with targeted therapies, immunotherapies, or agents for drug repurposing.



Metronomic and maintenance therapy

Although 80% of pediatric cancers can be cured, 20% of patients with pediatric malignancies still die of their disease (1). Among survivors a significant proportion display long term sequelae resulting from damage caused by the tumor and/or by the treatments used against the tumor (2). Therefore, there is a need for more active and less toxic treatment for patients with pediatric cancer.

Such a complementary approach could rely on maintenance therapy. Maintenance therapy is defined as using low doses of drug after initial induction treatment in patients in apparent remission following the first round of treatment. The aim of maintenance treatment in many advanced or high-risk cancers is to prolong survival while maintaining optimal patient quality of life. Therefore, maintenance therapy requires minimal toxicity to ensure prolonged compliance of treatment. Although not acknowledged as metronomic, maintenance therapy has been used for decades in pediatric hematology against acute lymphoblastic leukemia (ALL) (3), but the recent successful use of maintenance therapy in pediatric patients with rhabdomyosarcoma (RMS) has put it back into the spotlight (4).

In any case, this definition does not explain how this treatment might work on tumor cells that have survived and could therefore potentially develop resistance to previous lines of treatment. Looking at maintenance therapy as a metronomic chemotherapy (MC) treatment might open some interesting perspectives. Just like maintenance therapy, MC relies on the use of low dose chemotherapy that is given more frequently without long breaks (4,5), resulting in a treatment that has lower toxicity profiles and higher overall tolerance among patients. As we will discuss below, its mechanisms of action are distinct from that of

conventional, MTD chemotherapy explaining why MC can be active even in tumors that are resistant to the same anticancer agents given at or near the maximum tolerated dose (MTD) (5,6,7). Globally, MC is now regarded as a form of multi-targeted therapy (5,9, 10). The use of MC in daily oncology practice has been mostly tasked in palliative settings in relapsed/refractory disease, but nevertheless associated with good response rates and favorable toxicity profiles. Pre-clinically, MC seems to be more efficient at treating distant metastasis than primary tumors (11), consistent with its classical use as a maintenance therapy for hematological malignancies such as ALL (3), where maintenance aims at eradicating diffuse minimal residual disease. Furthermore, due to its limited toxicity, MC can be rationally combined with various targeted agents, immune therapies or agents used for drug repurposing (12) for more personalized treatments.

Although the concept of metronomic maintenance is also relevant in adults, here we evaluate the reasons behind the successful use of maintenance therapy in pediatric cancers including ALL, RMS, non-Hodgkin lymphoma, and neuroblastoma as well as reasons for failed attempts in acute myeloid leukemia (AML), osteosarcoma or Ewing sarcoma. We also discuss potential drawbacks in the use of this treatment such as compliance, uncertainty of duration of treatment, as well as discuss future developments for its use.

MC regimens in pediatric cancer: Success and Failures

The development of maintenance therapy in pediatric patients has been inspired by the successful results obtained in patients with ALL (3). Successive trials have shown that the probability of obtaining long-term remission of ALL was significantly improved, when pediatric patients received several years of post-remission maintenance therapy relying on

daily oral 6-Mercaptopurine (6MP) and weekly methotrexate (MTX) (3). Therefore, maintenance therapy became a standard in all protocols for ALL.

The successful use of metronomic maintenance therapy has also been reported in neuroblastoma although results were not as good as those observed with high-dose chemotherapy followed by hematological peripheral stem transplantation (14) (Table 1). Building on a previous report in RMS (15), a statistically significant increase in overall survival (OS) was observed for pediatric patients with localized high-risk RMS receiving a metronomic maintenance regimen consisting of weekly vinorelbine and daily oral low dose cyclophosphamide versus observation only (16). The type of relapse events was similarly distributed in both groups with a reduction of distant tumor relapses and also loco-regional relapse in the maintenance therapy group. Of note, it is impossible to discriminate the respective role of weekly vinorelbine or metronomic cyclophosphamide in the observed clinical benefit.

Unsuccessful results have also been reported (17-19). For instance, in a randomized clinical study involving 296 patients with non-metastatic osteosarcoma, the addition of metronomic chemotherapy with oral low dose methotrexate and cyclophosphamide during induction chemotherapy and as a maintenance therapy did not lead to an increase in event free survival (EFS) (17). A randomized trial in pediatric patients with anaplastic large cell lymphoma (ALCL) revealed that the addition of weekly vinblastine during induction chemotherapy for 1 year significantly delayed relapse for 1 year but did not reduce the risk of death (19). Elsewhere, a clinical trial (20) in which patients with pediatric AML were randomized into two groups: i) no maintenance therapy and ii) 18 months metronomic maintenance therapy consisting of 6MP and cytarabine revealed that the 5-year disease-free survival was not significantly different between patients who did or did not receive metronomic maintenance

therapy when in complete response after consolidation therapy. Nevertheless, the OS at 5 years was significantly better in patients who did not receive maintenance therapy due to a higher salvage rate after relapse, suggesting that previous exposure to metronomic treatment could lead to more drug resistance (19) (Table 1).

Collectively these studies suggest that metronomic maintenance therapy is beneficial in some disease settings, such as ALL (3), RMS (16, 25, 26), neuroblastoma (14) and some brain tumors (5, 24). However, it does not seem to be active in other diseases such as osteosarcoma (17) or AML (19). The reasons for failure or success is likely multi-factorial. We discuss rationales for success and failure of using MC in the treatment of pediatric cancers.

Timing

It is usually believed that maintenance therapy should be given when a disease relapses shortly after treatment completion. In RMS, median time to relapse calculated from the randomization date to the event was 7 months in the group given no further treatment and 10 months in the MC group (16). MC may also be better at controlling metastases than primary tumors (11) and does not work as efficiently on metastasis depending on their localization (*i.e.* lungs or bone). Indeed, metronomic maintenance therapy in patients with metastatic RMS led to an increase in OS in patients without bone metastasis while no benefit was reported in patients with bone metastasis (26). However, in the European pediatric Soft tissue sarcoma group (EpSSG), the type of relapse events was similarly distributed in both groups with a reduction of distant tumor relapses and also loco-regional relapse in the maintenance therapy group.

Choice of drugs

The choice of drugs to be used is critical. The maintenance phase can be an opportunity to introduce new drugs in the treatment of a disease. This may be part of the explanation of the success of the vinorelbine-cyclophosphamide maintenance in high-risk rhabdomyosarcoma (16). Indeed, vinorelbine treatment is effective in refractory/relapsed RMS (15, 27) but is not administered and has not been tested during the induction chemotherapy phase yet. In sharp contrast, in osteosarcoma, methotrexate and cyclophosphamide were used during the induction phase and used for maintenance therapy too. However, this protocol did not increase OS or EFS (17). Similarly, the addition of weekly vinblastine during induction chemotherapy and as a maintenance significantly delayed relapse for 1 year but did not reduce the risk of death in patients with pediatric ALCL (18). Anyhow, a single agent vinblastine was an efficient treatment for patients with recurrent ALCL leading to seemingly contradictory findings (28,29) : when given as a single agent at relapse (therefore both as “induction” and “maintenance”) vinblastine increased OS and EFS but when added to first line treatment did not improve OS. We could speculate that MTD chemotherapy given during induction may therefore trigger overlapping resistance mechanism(s) between anti-angiogenic and cytotoxic effects. They may in turn secondarily hamper the anti-angiogenic efficacy of MC. Although tumors that are resistant to the MTD of a given drug can still be responsive to that same agent given metronomically, partial or full cross-resistance can still occur (7). Therefore, new drugs should still be introduced during the maintenance treatment phase. Due to low toxicity, targeted drugs can be introduced and easily combined with MC during the maintenance treatment phase. Furthermore, repositioning drugs, *i.e.* drugs not already known to have a specific cytotoxic effect, could be of value during maintenance therapy. Preclinical data suggest that the β -blocker, propranolol could be used in combination with MC for neuroblastoma (30), while the antihelminth drug, mebendazole could be combined with MC for treatment for high-grade glioma (31).

Lastly, the number of agents to be added to each course of treatment is likely tumor- and drug-dependent. The use of a single agent such as vinblastine for maintenance therapy might work in patients with low-grade glioma (22), while a 2- or 4-drug maintenance therapy should be used for patients with RMS (16, 25), and a 5-drug maintenance regimen might be needed for treatment of certain types of brain tumors (24).

Dosing

Despite relying on low doses, dosing is still important for successful use of MC. Giving too high of doses can result in pro-tumoral host responses and prevent desired effects (32). For instance, capecitabine can be given metronomically to specifically target MDSCs (9), seemingly regardless of the tumor type, but if too high a dose is administered, MDSC cannot be selectively killed, resulting in lympho- and neutropenia that precludes any strengthening of the anticancer effect mediated by the immune system. Recently, a phase 1 trial confirmed the dose of capecitabine that should be used in adults with glioma to obtain a decrease in MDSCs (33). Similar issues can arise for depletion of Tregs (34) or inhibiting the maturation of dendritic cells (35). Finding the right dose can even be trickier when combinations of different chemotherapy drugs are used with crossed toxicities.

In contrast, too low of a dose will lead to a less or non-toxic but also less efficient treatment. In ALL, relapse during maintenance therapy has been associated with insufficient treatment intensity, secondary to differences in drug metabolism or adherence to treatment (3). Of note, these findings also suggest that a minimum level of exposure to anti-cancer agents is necessary to obtain a meaningful clinical effect.

Duration of treatment

Another crucial issue relies on the duration of treatment. In ALL, the duration of treatment still ranges from 2 to 3 years and the value of prolonged low dose therapy is acknowledged as crucial, even if the exact mechanism(s) of action are not known (3). By contrast, in patients with ALCL, the median duration of vinblastine treatment is 8 months of monotherapy (18). Furthermore, there was a trend toward lower percentages of relapse in patients receiving longer vinblastine maintenance therapy, although the difference did not reach statistical significance further highlighting the importance of duration. In patients with RMS, the duration of maintenance therapy for high-risk patients was 6 months (16), but in the follow-up European EpSSG protocol (FAR–RMS), a 1 year maintenance therapy regimen has already been proposed for patients with high risk RMS. A randomisation between 1 and 2 years of maintenance of this combination of therapies has also been proposed for stage IV RMS. These protocols suggest that the duration of maintenance might be tailored relative to the risk level of the disease.

Mechanisms underlying the success of MC

Despite being used for several decades, the mechanisms of MC still need to be fully determined and more specifically how it works in a given patient, at a given time and how it can kill or affect cancer cells that have survived to the previous phase of treatment such as induction chemotherapy. The main reason is that MC does not aim at directly killing cancer cells but aims at treating tumors by switching the target and modifying the tumor micro-environment. MC initially gained interest as a new anti-angiogenic strategy that could overcome conventional resistance to chemotherapy (8) but is now regarded as a multi-targeted therapy. Indeed, additional anticancer mechanisms have since been unveiled, including stimulation of an anti-tumor immune response. It can also prevent stromal cell activation (9) and negate pro-tumor host responses (32). MC can also directly target and kill cancer cells

(10) including cancer stem cells. Of note, most of these mechanistic findings have been made in a variety of adult tumor models.

Inhibition of angiogenesis

Most chemotherapeutic drugs exert potent anti-endothelial effects at low concentrations (picomolar to nanomolar) (35). By targeting rapidly dividing tumor endothelial cells, MC can both destroy existing vessels and prevent neo-angiogenesis, in turn leading to hypoxia and nutrient deprivation (5). The antiangiogenic effects of MC can also be mediated by an increase in endogenous angiogenesis inhibitor such as thrombospondin-1, a decrease in proangiogenic factors like VEGF. It can also induce apoptosis in circulating endothelial cells, impair the angiogenic potential of vascular endothelial cells and/or inhibit endothelial progenitor cell mobilization in many adult and pediatric tumors (5). Additionally, MC may act *via* its direct effect on hypoxia inducible factor- α (HIF-1 α) inhibition with anticancer agents like doxorubicin or topoisomerase I inhibitor as demonstrated in pediatric patients (36).

The anti-angiogenic effect of MC is easy to conceptualize and can be regarded as an important mechanism for bulky masses. In minimal residual disease that are avascular, its role is more difficult to conceive. Still, inhibition of angiogenesis by metronomic maintenance might perturb the tumour stem cell niche where endothelial progenitor cells play a crucial role (9).

Regulation of immune responses

Among the additional anticancer mechanisms that have been unveiled, stimulation of an anti-tumor immune response (5,9) is gaining interest from the oncology community because of the recent revolution brought by immune checkpoint inhibitors (37). MC can thus switch the

immunological balance from immunosuppression to immune-stimulation (37). MC can modulate different steps of the cancer-immunity cycle and its immune-stimulating properties are being more and more detailed (5,9,38). They mostly depend on the drug, dosing and schedule used (5,38). For instance, anti-tubulin agents such as vinblastine can induce dendritic cell maturation, promote antigen presentation and therefore recognition of tumor antigens by the immune system (39). Then, metronomic cyclophosphamide and temozolomide can deplete regulatory T cells (Treg) in various tumor types (9, 34, 38). The detailed molecular mechanism is well described: the selective depletion of Treg cells relies on their lower ATP levels as compared to regular CD4⁺ T cells, leading to a decreased glutathione synthesis and subsequent altered cyclophosphamide detoxification, and ultimately an increased sensitivity to low-dose cyclophosphamide (40). Karachi *et al.* also reported that metronomic temozolomide prevented T-cell exhaustion observed with standard dose temozolomide (41). Myeloid derived suppressor cells can be targeted by gemcitabine or 5FU/capecitabine (42). Elsewhere, metronomic paclitaxel can also induce the differentiation of immunosuppressive MDSCs into functionally active dendritic cells (43), switching their potential from immuno-suppressive to anti-tumoral.

An array of indirect evidence suggests that, in the context of maintenance, the immunostimulating impact of MC is critical to its clinical efficacy. Indeed, while the immunological effects of MC have not yet been demonstrated in the clinic during maintenance, MC can increase the activity of several immunotherapies such as vaccine, virus injection, dendritic cells (44). As a result, combinations of MC with anti-PD1, such as the association of metronomic vinblastine-capecitabine-cyclophosphamide with nivolumab (NCT03585465), are currently being investigated in children and teenagers with refractory diseases.

Regulation of the tumor microenvironment

Beyond anti-angiogenic and immuno-modulatory effects, MC can affect the entire tumour microenvironment. Indeed, MC may induce a host response that differs from MTD chemotherapy, consequently preventing or even overcoming resistance (32). Thus, Shaked *et al.* using a high-throughput cell analysis in comparison with metronomic capecitabine. The more aggressive phenotype was associated with changes in the microenvironment (32). Similarly, Chan *et al.* have shown that MC could prevent therapy-induced stromal activation and resistance through the induction of tumor-initiating cells in desmoplastic cancer (45)

Direct effects on cancer cells and Cancer Stem Cells

MC can also directly kill cancer cells including cancer stem cells (9). Interestingly, the way a given anticancer agent works can significantly differ when it is given following a MTD schedule or metronomically (4). For instance, low-dose paclitaxel decreased nuclear expression of calcium-binding protein S100A4 in a model of cholangiocarcinoma but did not change neither cell proliferation, apoptosis, or microtubule cytoskeletal integrity (46). Another direct effect of MC on tumor cells is the induction of the immunogenic cell death pathway that can activate both innate and adaptive immune responses (9, 37). Effects of MC on cancer stem cells have also been reported. Folkins *et al.* demonstrated that glioma cells isolated from tumors treated with metronomic cyclophosphamide significantly formed less primary and secondary tumor spheres (47). Elsewhere, metronomic cyclophosphamide induced a reduction in CD133+ precursor cells and CD133+/CD44+/CD24+ cancer stem cells in human pancreatic tumour xenografts (48). Direct anti-leukemic effects of maintenance therapy or targeting of ALL stem cells have also been proposed (3). Lastly, the lower selective pressure induced by MC on cancer cells allows the preservation of clonal biodiversity (4) through avoidance of selection of highly resistant clones. It is commonly accepted that the combined effects of MC on cancer cells and their microenvironment can lead to re-induction of tumor dormancy (9).

Concluding Remarks

Despite not being sophisticated, the potential of metronomic maintenance therapy to increase survival in pediatric malignancies should be further investigated in high-risk diseases. A single metronomic maintenance protocol will not work for all patients and against all diseases (see Outstanding Questions). A global strategy should be established to move toward personalized maintenance therapy (FIGURE 1). Currently metronomic maintenance therapy is tested in patients who display a high- risk of early relapse after intensive treatment, as this indicates that minimal active disease is still present and that additional therapy is needed to help control occult disease. However, more work is needed to identify which maintenance regimen could be beneficial to which tumor type. Developing adapted preclinical models is a first mandatory step. Unfortunately, most pediatric (and adult) models rely on neoadjuvant treatment and rarely on maintenance therapy in the metastatic setting after induction chemotherapy and surgery. Preclinical models could also help us to identify drugs and drug combinations for a given disease as well as how to integrate personalization by introducing targeted agents, immunotherapies or drug repurposing.

Dose optimization beyond classical parameters (*e.g.* age, obesity, sex) is also a key issue that requires further evaluation. Oral metronomic maintenance therapy may bring additional interpatient variability in PK (see glossary). Therefore, PK should be monitored more often and thoroughly (49). It well known that patients metabolize anticancer agents differently, and changes in dosing accompany this kinetics. The use of purinethol in pediatric patients with ALL is routinely adjusted based on pharmaco-genomics data (6) and similar approaches should be employed for other drugs used in cancer treatments. Such data could contribute to the generation of PK-PD models (see glossary) with clinical and biological variables and ultimately to individual dose tailoring (6). Computational modeling might also contribute to

dose optimization (50). Mathematic mechanistic modeling was used to optimize the dosage of gemcitabine and identified a low dose metronomic regimen as the best way to administer gemcitabine in neuroblastoma (51). However, more work is needed to confirm these results in patients.

Biomarkers may also guide the duration of maintenance therapy. While cellular and molecular angiogenic markers have largely failed, new biomarkers that monitor minimum residual disease such as circulating DNA (52) might help clinicians to stop treatment at the right time or to recognize patients who may relapse earlier.

Several groups have reported poor treatment adherence to maintenance therapy in a significant proportion of pediatric ALL patients (3, 54). Adapted formulations (oral suspension) could overcome pill swallowing difficulties often encountered in young children. Recently, a liquid formulation of 6MP has been marketed and can contribute to increasing compliance (54). Using e-health techniques (55) with messages sent via mobile phone and smartphone applications can also help reminding patients or their guardians to take medications. Drug dosage in the blood or urine such as routine measurements of Ery-6TGN/MeMP/MTX_{PG}, for patients with leukemia (3) or molecular tracers could also be incorporated in the anticancer formulations and then used to check for optimal compliance (55).

Lastly, for low and middle income countries, metronomic maintenance therapy can represent a unique opportunity. Indeed, local constraints such as cost of treatment, access to treatment, lack of local medical infrastructure, impossibility to install a central catheter and poor general condition, prevent the use of treatment with high intensity and high toxicity and relapsed patients can rarely be helped. Therefore, MC constitute an attractive therapeutic alternative in

resource-limited countries as a low-cost, well-tolerated, and easy to access strategy. MC and more specifically when given as maintenance treatment has recently been recognized as a promising strategy for these patients in an international survey (57,58). This strategy has the potential to fulfill unmet needs in these patients and it shall be explored with clinical trials (59, 60)

Figures and tables:

Table 1: Examples of maintenance therapy in pediatric hematology/oncology

tumor type	nb. of patients	type of study	maintenance regimen	duration of maintenance	PFS, OS	main toxicities	remarks	Author (ref number)
non metastatic OS	296 139	randomized	none mitx (1.5 mg/m ² 2x/d 2x/w) PO cyclophosphamide (25 mg/m ² /d) PO	73 weeks				Senerchia (17)
Ewing sarcoma	19	prospective series	trofosfamide (150 mg/m ² /d d1-d10/28d) PO	1 year	2 months; 61% at 2 years	renal toxicity (3 patients)	all patient not in CR at initiation of maintenance died	Rachborska (20)
DSRCT	60 5	retrospective series	none cyclophosphamide (40mg/m ² /d) PO vinblastine (6mg/m ² /w) IV or trofosfamide (2 × 75 mg/m ² /d d1-d10) PO etoposide (2 × 25 mg/m ² /d d1-d10) PO trofosfamide (2 × 75 mg/m ² /d) PO idarubicine 5 mg/m ² d1, d4, d7, and d10) IV irinotecan containing	x 1 year	3years EFS: 0% 3 years EFS: 60% 3 years EFS: 12%		maintenance correlates with prolonged time to relapse given in patients in CR	Scheer (21)
LGG	3				3 years EFS : 67%			
DIPG	4 41	series series	vinblastine (6mg/m ² /w) IV thalidomide (3 mg/kg/d) PO etoposide (50 mg/m ² /d) PO celecoxib (100-400 mg 2x/d) PO	12 months	EFS 100% at 15 months 12 months OS : 61% 24 months OS : 17%	hematological none		Heng (22) Portholm (23)
HR brain tumors	10	series	etoposide (50 mg/m ² /d) PO cyclophosphamide (2.5 mg/kg/d) PO temozolomide (90 mg/m ² /d) PO celecoxib (100 mg/d) PO	6 months	Mean PFS 10 months 2 relapses/ 10 patients	hematological		Choi (24)
HR RMS (lung metastasis)	29 8	series	isotretinoin PO (100 mg/m ² /d) PO O-TIE		5 years EFS 75% (vs 24%) p<0.01		maintenance is a favorable pronostic factor	Dantonello (25)
HR RMS	74 37	non randomized comparison	etoposide (2 × 25 mg/m ² /d D1-D10) PO trofosfamide (2 × 75 mg/m ² /d) PO idarubicine (5 mg/m ² d1, d4, d7, d10) IV trofosfamide (2 × 75 mg/m ² /d d1-d10) PO	6 months	5 years OS 52% vs 15 p<0.01		maintenance is a favorable pronostic factor no increase in OS when bone marrow involvement	Klingebiel (26)
HR-RMS	186 185	randomized	none navelbine (25mg/m ² /w 3/4 w) IV cyclophosphamide (25mg/m ² /d) PO	6 months	5 years EFS 78% vs 70% P=0.06 5 years OS 86% vs 74% P 0.0097	hematological	increase in OS but not EFS	Biogno (16)
HR neuroblastoma	146 149	randomized	cyclophosphamide (150mg/m ² /d d1-d8) PO high dose chemotherapy + PHSCT	4 months	3 years EFS 47% vs 31% p 0.02 3 years OS 62% vs 53% P0.08		increase in EFS but not in OS 5 toxic deaths in the high dose chemotherapy group	Berthold (15)
non metastatic OS	98,07239924	randomized	none	74 weeks				Senerchia (17)

Abbreviations used: OS: osteosarcoma // DSRCT : desmoplastic round cell sarcoma // LGG: low grade glioma // DIPG: Diffuse infiltrating Pontine Glioma // HR : High Risk // RMS: Rhabdomyosarcoma// CR: complete remission // PHSCT : peripheral hematological stem cells transplantation.

Figure 1: A way forward for metronomic maintenance therapy.

Building a metronomic maintenance therapy should rely on available or/and specifically generated clinical and preclinical (*in vitro* and *in vivo*) data regarding a given disease. The maintenance regimen will focus not only on the choice of anticancer agents but also on dose, schedule, sequence of administration and duration of treatment. Compliance might be improved by using adapted formulation and connected devices. During treatment pharmacokinetics, pharmaco-genomics and PD biomarkers shall be evaluated and incorporated into computational model to further personalize treatment.

8. Glossary box:

Metronomic chemotherapy: Treatment in which low doses of anticancer drugs are given on a continuous or frequent, regular schedule (such as daily or weekly), usually over a long time.

Drug repurposing: involves the investigation of existing drugs for new therapeutic purposes.

Metronomics: is the combination of metronomic chemotherapy and drug repurposing

Maintenance: type of treatment that is given to prevent progression after it has been controlled successfully with the initial therapy.”

MTD: maximum tolerated dose

PK: determine the fate of substances administered to a living organism. Pharmacokinetics is the study of how an organism affects a drug

PD: is the study of the biochemical and physiologic effects of a drug. Pharmacodynamics is the study of how the drug affects the organism.

PK-PD: relationships between the pharmacokinetics (PK) and pharmacodynamics (PD). They are usually described using mathematical models

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