Evaluation of Fixed Dosing of New Anticancer Agents in Phase I Studies

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Abstract. *Aim: To assess the basis of dosage of investigational anticancer agents in adult phase I trials. Materials and Methods: All nonpediatric phase I trials presented at the meetings of the American Society of Clinical Oncology and of the American Society of Hematology in 2005 were reviewed. Data regarding the type of investigational agent, the route of administration and the basis of dosing (fixed, body surface area, body weight) were collected. Results: In all, 225 phase I studies were analyzed concerning 148 new anticancer agents. Among 225 studies, 91 (40.4%) used a fixed dose. Dosages were adjusted to body surface area and body weight in 44% (99/225) and 13.8% (31/225) of all trials, respectively. Regarding drugs given orally (n=40), the majority of the trials (62/77; 80%) used a fixed dose. By contrast, only 7.5% (9/120) of studies involving intravenous agents (n=82) were conducted with a fixed dose. Most of these trials (71.6%) used a dose adjusted to body surface area. Of the 73 trials involving conventional cytotoxics, 70 (96%) used body surface area dosing. On the other hand, 78.5% (62/79) of studies investigating targeted agents used a fixed dose. Monoclonal antibodies and antisense agents were mainly administered on a body weight basis (13/25 and 4/7 trials, respectively). Conclusion: A fixed dose was used in a minority of the adult phase I trials presented at the ASCO and ASH meetings in 2005.*

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Dosing of anticancer agents in adult patients is traditionally adjusted according to estimated body surface area or body weight. For example, in France, 80% of approved anticancer drugs are administered according to body surface area and 10% to body weight. This is based on the intuitive belief that the capacities of elimination of a drug are related to body size in adults. It is assumed that this approach decreases the pharmacokinetic and pharmacodynamic interindividual variability of agents known to have a narrow therapeutic index. This practice is relatively specific to oncology and besides anticancer agents, also concerns supportive care products such as some hematopoietic growth factors, folinic acid, rasburicase, palifermin, voriconazole and glucarpidase. Curiously, this approach may be heterogeneous within a class of drugs (fixed dose, dose based on body weight or body surface area for monoclonal antibodies), or even for a single drug such as dacarbazine for which dosing is based on body weight as monotherapy or body surface area as combination and rituximab for which dosing is adjusted to body surface area in the treatment of lymphomas (375 mg/m^2) and is fixed in rhumatoid arthritis (1 g).

Practically, and when compared with the fixed dose, body size-based dosing is a complication necessitating calculations that can generate prescription and preparation errors. Scientifically, this practice is mostly either unjustified or unvalidated. In fact, body surface area or body weight should only be used if it has been demonstrated that they constitute a significant factor affecting pharmacokinetic and clinical variability. When compared to fixed dosing, administration of anticancer drugs adjusted to body weight or body surface area should lead to improvement of therapeutic outcomes. Nevertheless, in the last 18 years, numerous reports have indicated that several anticancer agents could be administered at a fixed dose in adult patients (1-10). In other words, estimated body surface area or body weight was not shown to significantly correlate with pharmacokinetic or pharmacodynamic variability. In addition, in 2002, the abandonment of the use of body surface area in dosing of new agents in phase I studies was recommended (11). To see if these recommendations were effectively implemented, we assessed the basis of dosage of investigational anticancer agents in adult phase I trials.

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Table I. *Basis of dosing of investigational anticancer agents in adult phase I trials (n=225).*

Type of drug (n)	Basis of dosing (number of trials)				Total
	Fixed dose	Body surface area-based	Body weight-based	Not reported	
Intravenous (82)	9	86	23	2	120
Oral (40)	62	13	2		77
Subcutaneous/intradermally (16)	10		3	3	16
Conventional (45)	1	70	2		73
Targeted (42)	62	13	2	2	79
Monoclonal antibody (19)	8	4	13		25
Immunomodulator (11)	6	2	4		12
Antisense agent (6)	1	2	4		7
Vaccine (15)	13			2	15

Materials and Methods

The nonpediatric phase I trials presented at the meetings of the American Society of Clinical Oncology (ASCO) and of the American Society of Hematology (ASH) in 2005 were reviewed. Abstracts including the terms 'phase I or phase I/II' in the title were identified by browsing the 20 categories of the 2005 ASCO meeting (ASCO.org) and the abstract book of the 2005 ASH meeting. Investigational anticancer agents or nononcological licensed drugs for which antitumoral activity was tested (*e.g.* everolimus) were included. Anticancer agents that were approved in the European Union at the date of the meeting were excluded.

Data regarding the type of agent (conventional, targeted or interfering with transduction pathways, monoclonal antibody, vaccine, antisense agent, immunomodulator), the route of administration and the basis of dosing (fixed, body surface area, body weight) were collected from the abstract body. Additional information concerning the type of agent was sought using PubMed. The objective of the study was to assess the rate of fixed dosing of new anticancer agents.

Results

In all, 225 adult phase I studies were analyzed concerning a total of 148 new anticancer agents. Most of the phase I (88%) studies were presented at the ASCO meeting. Of 225 trials, 143 (63.6%) were conducted for single-agent therapies and 82 (36.4%) for associations, mostly with marketed agents. Investigational agents were mainly administered intravenously (120 trials; 53.3%), orally (77 trials; 34.2%), subcutaneously or intradermally (16 trials; 7.1%).

A total of 91 studies (40.4%) used a fixed dose. Dosages were adjusted to body surface area and body weight in 44% (99/225) and 13.8% (31/225) of all trials, respectively. The basis of dosing was not mentioned in 5 (2.2%) abstracts.

Regarding drugs given orally (n=40), the majority of the trials (62/77; 80%) used a fixed dose. By contrast, only 7.5% (9/120) of studies involving intravenous agents (n=82) were conducted with a fixed dose. Most of these trials (86/120; 71.6%) used a dose adjusted to body surface area (Table I).

Among the 148 investigational compounds, there were 45 conventional drugs, 42 targeted agents (drugs interfering with signal transduction pathways such as enzyme inhibitors and antiangiogenic agents), 19 monoclonal antibodies, 15 vaccines, 6 antisense agents and 11 immunomodulators (Table I). Of the 73 trials involving conventional cytotoxics, 70 (96%) used body surface area dosing. On the other hand, 78.5% (62/79) of studies investigating targeted agents used a fixed dose. Vaccines were injected at a fixed dose (13/15). Monoclonal antibodies and antisense agents were mainly administered on a body weight basis (13/25 and 4/7 trials, respectively).

Discussion

Expression of dosing of investigational anticancer agents was heterogeneous. With regard to recommendations published in 2002 (11), the fixed dose was used in a minority of the adult phase I trials (40%) presented at the ASCO and ASH meetings in 2005. Body surface area and body weight to a lesser extent were still used in the expression of dosing but with disparities, depending on the route of administration and the type of agent.

Not surprisingly, trials of agents given orally were mainly conducted with a fixed dose. Oral fixed dosing is far more convenient than that adjusted to body size. In fact, unless a liquid oral formulation is available, accurate adjustment to body size is not possible with solid forms. Generally, the package insert mentions the number of tablets to be taken daily for a body surface area range, leading to complex dosing regimens such as those of capecitabine or oral vinorelbine. It should be mentioned that fixed dosing of a drug does not necessarily lead to a reduction of dosage presentations. Various dosages are sometimes needed to adjust the regimen based on tolerance. For example, sunitinib and dasatinib (fixed dose) are available in 3 dosage presentations (one more when compared with oral vinorelbine or capecitabine presentations). On the other

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hand, the majority (93%) of trials involving intravenous agents being conducted with a dose based on body surface area and body weight may be due to the fact that adjustment is relatively easy with a liquid formulation.

Regarding the type of anticancer drug, virtually all trials (97%) involving conventional agents used body surface area-based dosing. This probably reflects the habit that clinicians have with the dosing of cytotoxics. In addition, 78% (35/45) of conventional agents were in an intravenous formulation, which may strengthen the lack of willingness of investigators to change the basis of dosing. By contrast, the majority of studies (79%) of targeted anticancer agents used a fixed dose, perhaps in relation with their low toxicity (when compared with cytotoxics) and to the fact that they were primarily oral drugs (30/42). Currently, all approved targeted therapies in the European Union (imatinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, lapatinib, temsirolimus) are administered at a fixed dose in adult patients. Dosing of investigational monoclonal antibodies was heteregeneous. The three modalities of dosing were encountered as for marketed antibodies. Body surface area-or body weight-based dosing of monoclonal antibodies is rather an oddity since these drugs are relatively nontoxic. In addition, they display a very low volume of distribution (around 5 l) and their route of elimination is unknown (12). They are probably cleared like endogenous immunoglobulins *via* the FcRn receptor whose expression (in particular on endothelial cells) is unlikely to be related to body weight or body surface area. Rituximab or trastuzumab clearances are not related to body surface area and body weight, respectively (13, 14). However, bevacizumab clearance showed a relationship with body weight but it has not been demonstrated that the kinetic variability has any clinical impact (15). In all, this practice is traditional with monoclonal antibodies even beyond oncology (infliximab in rhumatoid arthritis or daclizumab in graft recipients for example).

Overall, it has never been proven that dosing of anticancer drugs according to body surface area or body weight leads to improvement of therapeutic outcomes in adult patients when compared to fixed dosing. Numerous marketed anticancer agents could be administered at a fixed dose but unfortunately it is improbable that their official labellings will change. Regarding investigational agents, fixed dosing could be used until it is demonstrated that body size or another variable (genotypic, phenotypic) is a significant factor of clinical variability. Fixed dosing has at least the potential to reduce medication errors (16). It was recently stated that novel agents were developed with a fixed dose (10). Based on our survey, this holds true for targeted agents in relation to their toxicity spectrum and their oral formulation. By contrast, dosing based on body surface area remains the rule for conventional agents as underscored by the dosing basis of the recently approved ixabepilone.

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