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The main steps in the development of anticancer agents

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Summary

The development of new anticancer agents is a long-term process, which involves the acquisition of new compounds, screening for antitumor activity, production and formulation, animal toxicology and finally, evaluation of toxicity and antitumor activity of the compound in man (Table I). In this paper, the main steps in the early development of new cytotoxic agents up to phase II clinical studies will be discussed. However, clinical phase III–IV trials, where the efficacy of the drug has been proven, should be dealt with separately.

Drug acquisition

The development of a new anticancer agent starts with the acquisition of the compound. Usually, new compounds are obtained from pharmaceutical industries and academic institutions. During the last four decades, the National Cancer Institute (NCI) in the U.S.A. has been the major institution involved in the discovery and development of new anticancer drugs. However, industries and research centers in North America, Europe, Japan and Australia have been also engaged in the search for active new anticancer agents [21]. The main sources of compounds for drug development are

natural products, new synthetic compounds and analogs of known agents.

Natural products

The evaluation of natural products such as extracts from plants and microbial fermentations resulted in the discovery of several excellent anticancer agents. The vinca alkaloids (vincristine, vinblastine and vindesine) and the podophylotoxin derivatives (etoposide and teniposide) are examples of clinically active plant products [45]. Actinomycin D, doxorubicin, mitomycin C and bleomycin are active agents derived from fermentation products [24].

The actinomycins were isolated in the early 1950's by U.S. investigators [74]. Their antitumor activity in preclinical models stimulated further

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TABLE I

Main steps in anticancer drug development.

<i>I. Preclinical</i>	
(a)	Selection and acquisition of new compounds
(b)	Screening for antitumor activity
(c)	Production and formulation
(d)	Animal toxicology. Establishment of starting dose for human trials
<i>II. Clinical</i>	
(a)	Phase I studies: determination of maximum tolerable dose (MTD), spectrum of toxicity, dose-limiting toxicities and human pharmacology. Choice of dose and schedule for Phase II trials
(b)	Phase II studies: evaluation of antitumor activity, dose corrections for special cases such as patients with impaired organ functions
(c)	Phase III studies: comparative activity of new compound versus standard therapy. Further evaluation of late toxicities
(d)	Phase IV studies: establishment of the role of new compound in overall management of cancer patients. Evaluation of long-term toxicities. Integration of new compound in the primary management of cancer
(e)	General use of the compound.

studies on fermentation products, leading to the discovery of the anthracyclines by Di Marco and co-workers in Italy [22]. They were able to isolate several antibiotics from strains of *Streptomyces*, such as daunorubicin and doxorubicin. These compounds showed marked antitumor activity in animal studies [23]. Doxorubicin was rapidly introduced into clinical trials, revealing impressive activity against several human cancers [9]. These results were confirmed in other centers and doxorubicin was approved for clinical use by the Food and Drug Administration (FDA) in 1974.

New synthetic compounds

The acquisition of new synthetic compounds shows the importance of an extensive cooperation between industry and cancer institutes. The vast majority of compounds that entered screening in the NCI or in other institutions came from companies. The oxazaphosphorines (cyclophosphamide and ifosfamide) are examples of clinically active anticancer agents that were synthesized in the industry

and entered clinical evaluation in several institutions in Europe and in the U.S.A. [14].

The discovery of the antitumor properties of platinum complexes in the mid-1960's illustrates how a chance finding may lead to the development of a clinically active agent. Based on observations of the effect of electric fields on the growth of *E. coli*, Rosenberg and co-workers discovered that an alternating current passing through platinum electrodes caused the formation of long filaments and inhibition of cell growth [60]. As a consequence, several platinum compounds were synthesized and their antitumor properties in preclinical models were recognized [44]. Cisplatin was the first to be introduced in the clinic. In spite of serious toxicity, specially to the kidney, GI tract and nervous system, cisplatin is presently one of the most active anticancer agents in clinical use [49].

Since then, many platinum compounds were studied by the NCI, the Chester Beatty Research Institute in England and other centers, in order to find a platinum compound with a better therapeutic index.

The selection of new compounds by the NCI for clinical evaluation illustrates the broad variety of sources of new leads entering the screening process. Dihydroelenperone and anthrapyrazoles are produced by pharmaceutical companies, whereas merbarone or caracemide came from agrochemical industries. A cosmetic factory provided flavone acetic acid to the NCI drug screening [55].

Analogs of active anticancer drugs

The search for analogs of active anticancer drugs with better therapeutic index or a broader spectrum of activity is another important area of new drug development. Epirubicin is a new anthracycline which seems to show comparable antitumor activity but less cardiotoxicity than doxorubicin at equimyelotoxic doses. This analog is in clinical use, having been approved for instance in Great Britain and The Netherlands [76].

Similarly, various platinum-analogs have been synthesized with the aim of finding equally effective but less nephrotoxic or emetogenic com-

pounds. Carboplatin has been extensively evaluated and it appears less nephrotoxic and neurotoxic than cisplatin. However, it causes more severe myelosuppression and it is yet to be established whether its antitumor activity is comparable to cisplatin [31, 71].

Screening

The aim of screening programs in anticancer drug development is to discover compounds active against human malignancies. For this purpose, it is essential that preclinical models are established which exhibit a good correlation with the human situation.

The screening program of the NCI

During the last 30 years, more than 600 000 compounds have entered various screening systems in order to select potential anticancer agents. The majority of these compounds have entered screening at the NCI. After a preselection based on a computer analysis of structure novelty and presumed antitumor activity, compounds were tested in "in vivo" murine models, mainly the L1210 or P388 leukemia [26,36]. For several years, compounds with confirmed activity in this primary screen were tested in a panel of murine tumors and human tumor xenografts [37]. The murine tumors included in the secondary screen were L1210 leukemia, B16 melanoma, Lewis lung carcinoma, Colon 38, CD₂F₁ mammary tumor. The human tumor xenografts were MX-1 mammary, LX-1 lung and CX-1 colon xenografts [75] (Fig. 1).

The use of this NCI screen resulted in the identification of agents with excellent activity against leukemias, lymphomas and pediatric tumors, leading to an increase in the overall survival and cure of a significant number of patients [17]. However, the discovery of compounds with antitumor activity against the models of solid tumors such as colon or lung carcinoma did not translate into clinically active drugs against solid tumors in man [32].

Fig. 1. Compound-oriented anticancer drug development.

Compounds negative in the screening were also evaluated in the clinic, specially when they presented favorable characteristics, such as antitumor activity in other screening systems or potential organ-specific biochemical properties. Deoxycoformycin is a potent inhibitor of adenosine deaminase (ADA) which was negative in the P388 leukemia model. However, the recognition of the ADA deficiency as the cause of the combined immune deficiency syndrome in children raised the possibility that this compound could present selective activity against lymphoid tumor cells [40].

Due to the lack of discovery of drugs active against solid tumors, certain changes in the screening process of the NCI were introduced recently. Based on some modifications of the classical tetrazolium assay developed by Mosmann [53], the current approach involves the "in vitro" testing of new compounds in panels composed mainly of human tumor cell lines representing the most common solid malignancies in man (Fig. 2). Compounds exhibiting general cytotoxicity are given less priority for development, as compared to those showing evidence of tumor-specificity (i.e. differential cytotoxicity for certain tumor types in the panel) [11].

Certain methodological difficulties of an "in vitro" based primary screening may be expected. Differences in pharmacodynamics and toxicology may make drug concentrations defined in vitro to be not useful in the in vivo clinical situation.

Fig. 2. Disease-oriented anticancer drug development.

Other approaches

One of the central questions in drug screening is whether the current methodology can be improved in order to achieve a better correlation between antitumor activity in preclinical models and the clinical situation. Animal tumors tend to overpredict drug activity in man. This discrepancy may be related to differences in cell growth kinetics, total tumor burden at the time of drug treatment and the criteria for the assessment of tumor response between animal models and man [3]. Tumors in animal models are usually less differentiated than human cancers and their growth rate is more rapid [65]. Animal treatment often starts at an early stage of disease, not later than 24 h after the inoculation of about 10^6 tumor cells/mouse; in contrast human tumors are treated at a late stage when total tumor burden is about 10^{10-11} cells [4]. Tumor response in animal models is often measured in terms of growth delay or increase in life span whereas in the patient only a tumor regression of more than 50% is accepted as an objective response [3,18].

The development of preclinical models exhibiting a better correlation with the clinical situation is critical to avoid false-positive compounds entering clinical trials. Among the new strategies for drug screening are the human tumor colony-form-

ing assay (HTCFA), the human tumor xenograft (HTX) model and the subrenal capsule assay (SRCA).

The human HTCFA was developed by Hamburger and Salmon [43] and consists of the "in vitro" growth of human tumor cells derived from fresh tissue samples obtained immediately after surgical resection. Cells are cultured in the presence of drug and the ratio between the number of colonies in treated versus control plates at several time-points is determined. By this technique, a patient-oriented chemosensitivity testing can be performed as it is routinely done in microbiology. Although this technique may be limited by the low cloning efficiency of some neoplasms, its value has been validated by a series of studies showing a good correlation between activity of known anticancer agents in this assay and in the clinic [64,68,69].

The HTCFA might be a valuable option in the secondary screening of new anticancer agents. It offers the possibility of an "in vitro" phase II evaluation of new compounds before human studies are initiated. Recently, two compounds have been selected for clinical evaluation based on activity in the HTCFA: chloroquinoxaline sulfonamide (NSC 339004) and dihydrolenerone (NSC 343513). The former has shown a broad spectrum of activity against several human solid tumors in the HTCFA, whereas the latter was active against several lung carcinoma cell lines, with growth-inhibitory effects at much lower concentrations than for other cell lines [47]. Dihydrolenerone illustrates the concept of disease-oriented antitumor activity, which is the basis for the current strategy of drug screening in the NCI.

The HTX is presently under extensive evaluation for the screening of new anticancer agents. In Europe, a collaborative group for preclinical phase II studies in human tumor lines was recently formed [10]. This group is studying the feasibility of the use of HTX for the selection of compounds and tumor types for phase II trials. This technique consists of the implantation of a tumor fragment obtained from the patient in the subcutaneous tissue of a nude mouse. Nude mice present a poorly developed thymus and a state of T-cell depletion [51]

which makes the acceptance of foreign tissues possible. Their B-cell function is decreased as well [63]. For the above reasons, nude mice are highly susceptible to viral, bacterial and parasitic infections and they should be kept in a pathogen-free environment to ensure their normal life span [51]. Their number of natural killer cells [63] and macrophages [66] are increased compared to normal mice.

Many tumor types grow relatively easily as subcutaneous implants in nude mice, such as melanoma, lung cancer, colon cancer or sarcomas [70]. However, other tumor types are more difficult to grow as xenografts such as head and neck cancer, breast cancer or malignant lymphomas [12].

The correlation between drug effects in the nude mouse and clinical results appears to be good, provided some differences in pharmacology between mice and man, such as for methotrexate and 5-fluorouracil are taken into account [13,79]. The main limitations for the use of the HTX in large scale screening are the high costs, the dependence on special laboratory facilities and the extensive time needed to establish and characterize human tumor lines. Moreover, the testing of anticancer drugs takes several weeks before results are produced. However, the HTX might be an adequate model to reduce the number of false-positive compounds entering clinical trials.

The SRCA consists in the implantation of a tumor fragment obtained from a human tumor growing in the nude mice or from patient material in the subrenal capsule of mice [6]. Tests in immunocompetent mice do not allow long-term experiments and drug effects are evaluated within 6–7 days of tumor implantation. By the SRCA, tumor cell membranes, cell-to-cell interactions and tumor-stroma relations are expected to be preserved, and the “net” effect of the drug in the various subpopulations of tumor cells can be estimated [7]. The correlation between response rates in the SRCA and in the clinic is satisfactory for several tumor types, such as breast, head and neck and ovarian carcinoma [7,73]. However, there are important methodological difficulties in the evaluation of tumor response, namely the evaluation of drug ef-

fects relies on two tumor measurements only. In addition, the quality of the fragment for subrenal implantation and the amount of host-immune reaction present in the tumor specimen may interfere with the adequate interpretation of tumor responses in the SRCA. Therefore, the histopathological review of the tumor specimen is mandatory. The SRCA done in immune-deprived mice may allow more regular growth, but it does not solve the problem of the quality of the tumor specimen.

Although the best application of the above models in drug screening is not yet established, they may reduce the number of false-positive compounds entering human trials. Whether they will increase the probability of discovering more effective agents for the treatment of human malignancies remains to be proven.

Production and formulation

Once the screening process has been completed, the selected compounds must be produced in enough quantity and should be properly formulated for toxicology and clinical studies. Sometimes, the production of adequate amounts of compounds in appropriate purity can be difficult, such as extracts from plants. Homoharringtonine (NSC 141633) is an alkaloid extracted from the cephalotysaxus plant, which was difficult to be obtained [25]. The production of this extract was possible after the development of a natural products plant facility at the NCI, which allowed the processing of large quantities of natural products. Other compounds have suffered from problems of synthesis and supply, leading to a delay or even cancelation of further development such as Ara-6-MP [50].

The characterization of physical properties of the new compounds, chemical incompatibilities as well as recommended storage conditions should be available before further steps are initiated. The formulation of the compound specially regarding the analytical method for the measurement of the parent drug and/or active metabolites in body fluids and a suitable composition for intravenous administration should be defined.

Toxicology

The aims of toxicology studies are to define the target-organs for toxicity, the reversibility of these effects, the presence of cumulative and dose-limiting toxicities and the safe starting dose (SD) for phase I trials. These objectives are defined according to the schedule of drug administration and the species used for toxicology [62]. Through the different species, doses are compared on an equivalent basis (mg/m^2).

In mice, the dose that is lethal to 1/10 (LD_{10}) and to 5/10 (LD_{50}) of a series of mice are determined. In dogs, the dose that is toxic but does not cause death when doubled (TDL) is determined. Experiments in mice are usually done at single dose intraperitoneal (IP), single dose intravenous (IV), multiple doses IP and, if indicated, per oral (PO). These studies aim to define the spectrum of organ toxicity of the drug. The 1/10 of the LD_{10} dose in mice is initially tested in the rat, dog or monkey, and is only given to man, if it lacks severe toxicity in the latter species. In the NCI, the 1/3 of the TDL in the dog was routinely used as the SD in several clinical trials [58,61]. More recently, the 1/10 of the LD_{10} in mice has been applied for the SD in phase I trials, provided no major toxicity is observed in dogs or monkeys at that same dose level [38].

The equivalent of the 1/10 of the LD_{10} in mice or 1/3 of the TDL in the dog as SD for phase I trials is based on the premise that the SD in human studies should be lower than the maximum tolerable dose (MTD) in man: the SD is intentionally chosen to be low and safe. For several anticancer agents about the 1/10 of the LD_{10} in mice and 1/3 of the TDL in the dog is the highest fraction of the experimental toxic dose levels that is lower than the MTD in man [34,38]. However, there are significant differences between species, when the organ toxicities of certain drugs are considered [41]. When 1/10 of the TDL in the dog or in the monkey is given in phase I trials, there is a risk of about 1% of exceeding the MTD in man. By using the 1/3 of the TDL in those animals, a risk of about 5% of exceeding the MTD in man is expected [46,62]. Therefore, the combined information from several species, using a

fraction of the toxic dose in the most sensitive animal seems to be adequate for starting human studies.

Phase I trials

Cytotoxic anticancer drugs are usually administered to patients close to the MTD. The rationale is that such drugs are more effective when given at higher doses [33]. Due to their lack of selectivity, cytotoxic drugs are characterized by a low therapeutic index, as compared to other drugs used in the clinic. Therefore, side-effects are to be expected in patients receiving such drugs at the recommended doses. For the biological response modifiers, the optimal dose to achieve the desired biological effects should be a more appropriate goal [56,59].

Aims

Phase I trials are performed to establish the MTD of the drug in man at that specific schedule, the type of toxicity per dose level, the dose-limiting toxicities and if possible the pharmacokinetics of the drug in man. A safe dose schedule for phase II trials should be recommended (usually below the MTD) [29]. Although antitumor activity can be documented in phase I trials, this is not an essential part of the study. For this reason, patients may enter the trial with no measurable or evaluable lesions. Additional recommendations for dose adjustment in patients with poor risk factors such as renal or liver impairment, prior therapy and low performance status should be given. A similar approach may be applied for the study of new combinations of known drugs to define its toxicity and suitable dose or schedule.

Study population

Phase I trials with anticancer drugs have a specific methodology as compared to the first clinical evaluation of conventional drugs. Phase I trials with anticancer drugs are done in patients, as opposed

to normal volunteers. Patients selected are those having a cancer for which no treatment is available or who failed on standard therapy. Prior to admission into the trial, the risks of the procedure and the lack of clinical data on the drug are explained to the patient. In order to obtain informed consent of the patient, general informations about the characteristics of the drug and its potential side-effects are provided. The psychological conditions of the patient and the available support from the family are assessed. In some countries, a written informed consent is signed by both the patient and the physician [5,77].

Methodology

At the start of the trial, patients receive the SD which is based on animal toxicology. Usually, three patients are treated per dose level and the dose is escalated by steps, until the MTD is reached. Toxicity is graded based on a numerical scale (0–4) [78]. If the pattern of toxicity is not consistent or dose-limiting toxicities are not yet reached, the dose is escalated further. The MTD is reached when grade 3–4 toxicity is observed in consecutive patients at a specific dose level (at least 2 of 5 patients). Then, no more patients are entered at that dose level; and an additional number of patients is treated at the highest safe dose which is in the opinion of the investigator recommended for phase II trials.

Conventional dose escalation and pharmacologically-guided dose escalation

Because the SD in phase I trials is usually very low, there is virtually no chance of therapeutic benefit at the initial dose levels. For this reason, the methodology of dose escalation is very important. If an effective and rapid form of dose escalation could be established, less patients would be needed per trial and consequently, more patients could be entered in other studies.

Dose escalation procedures have been so far essentially empirical. They are usually based on a modified Fibonacci scale, which applies fixed and

predetermined increases of 100, 67, 50, and 30–35% of the prior dose level, respectively. In some institutions, the initial 1–2 steps include increments of 100% of the SD, followed by 50% increases of the prior doses, as long as toxicity is not observed. When toxicity is documented, further dose escalations are of 25% of the prior value. At the M.D. Anderson Hospital, this methodology has been applied to 25 compounds and in order to reach the MTD a reduction of about 1–4 steps compared to a modified Fibonacci scale was reported [48].

There are also examples of phase I studies which have applied dose escalations of 100% until toxicity was observed. However, this is dependent on the amount of toxicology data available at the start of the study, the quality of supportive care of the institution and the experience of the investigators [1].

In a recent study, several forms of dose escalation in phase I trials were compared [42]. It was concluded that about 6–9 steps were necessary to reach the MTD, either by using the modified Fibonacci scale or other forms of dose escalation. The authors suggested the utilization of a dynamic geometric progression with dose increments depending on the type of toxicity at the preceding dose levels. The entry of eligible poor-risk patients at non-toxic dose levels or the evidence of cumulative toxicity after retreatment at the same dose level, may also be useful in the planning of dose escalation in phase I trials.

It has been observed that the ratio between the AUC (area under the plasma concentration versus time) at the LD₁₀ in mice and the AUC at the MTD in man is closer to unity than the ratio between the respective doses for several anticancer agents [16]. For doxorubicin, for example, the ratio between the LD₁₀ in mice and the MTD in man on an equivalent basis is about 5.0. The advantage of AUC over dose in mouse/man correlations was also observed for other drugs such as 5-azacytidine or thiotepa. Dihydroazacytidine was the only compound which gave a better result for dose over AUC [28]. For *N*-methyl compounds, such as hexamethylmelamine, *N*-methylformamide or dacarbazine, which are dependent on metabolic activation

to exert their biological effects, the ratio between AUCs of the parent compound did not give a good correlation. For trimelamol, which does not need activation a ratio between AUCs close to unity was found [28]. The latter suggests that metabolic transformation or drug interaction at the target-cell level may influence markedly these pharmacological correlations.

In general, antimetabolites are not good candidates for this approach. For PALA or dihydroazacytidine, the ratio between the LD_{10} in mice and the MTD in man is closer to unity than the ratio between the AUCs [16].

The above hypothesis implies that, by knowing the ratio between the AUC at the SD in man and at the LD_{10} in mice, the MTD in man may be predicted and used to guide dose escalation in phase I trials. In retrospective studies, the MTD of several compounds would have been reached with less dose escalation steps than would be expected had a modified Fibonacci scale been applied [16,28].

It is very important to consider that various factors may interfere with these correlations between mice and man. Several technical aspects such as the route, schedule, vehicle of drug administration, choice of the adequate time-points for the pharmacokinetic calculations and the quality of the assay for the parent drug and active metabolites are to be considered [16, 28]. Differences in plasma protein binding, metabolism, tissue drug concentration or saturable steps in drug absorption, distribution or excretion between mice and man should be taken into account. In addition, the contribution of spe-

cific activating or detoxifying enzymes that could be relevant for antitumor activity or toxicity of the drug may also vary between mice and man [16]. All these aspects should be considered before these pharmacological correlations are applied for the dose escalation procedure of phase I trials with a new drug.

Phase II trials

The central question of phase II trials is whether the drug has sufficient antitumor activity to justify further clinical development. An analysis of phase II studies for all cytotoxic agents entered into clinical trial by the NCI, between 1970 and 1985 was recently reported [50] (Fig. 3). From 83 drugs which entered clinical trials, 47 were evaluable for antitumor activity and 24 were considered active in at least one tumor type. However, the evaluability criteria was mainly based on the results of studies with a reduced number of patients and the duration of responses was not included in the analysis. Furthermore, antitumor effects were seen mainly in rapidly growing tumors such as leukemias or lymphomas, as opposed to solid tumors; and antitumor activity in a phase II trial does not mean efficacy in terms of benefit to the patients.

The preparation of a protocol for phase II study is a critical step for the achievement of the study aims. It should include all relevant aspects for the proper evaluation of the antitumor activity and adverse reactions of the new drug [54,72].

Fig. 3. Cytotoxic drugs entering NCI-sponsored clinical trials (1970–1985). Adapted from Marsoni et al. [50].

Study population

For the proper evaluation of new anticancer agents, various well known factors which may influence tumor response have to be considered [54,82]. The performance status and prior therapy are of major importance in the analysis of results [54,82]. The response rates to several anticancer agents are usually higher in non-pretreated patients than in heavily pretreated patients. Other factors, such as age, site of metastases or histological type may influence the results of chemotherapy as well [54].

Over the past years, more patients with no prior therapy have entered phase II trials, specially when current available therapy has no impact on survival or quality of life.

Trial design

There are various designs for phase II trials. In phase II disease-oriented trials, new drugs are tested in consecutive patients with specific tumor types in a non-randomized study or as part of a randomized trial comparing two drugs [54,72].

When consecutive patients are treated with a new drug, certain statistical considerations of sample size are applied. If one intends to reject a drug which gives less than 20% true objective responses, an observation of no responses among 14 consecutive patients would allow it with a probability of false-negative of about <0.05 [35,72,81]. However, larger samples are usually used to avoid the rejection of an active drug, preferably including patients of various prognostic categories.

If a drug produces low overall response rates but with some complete responses (CR), this might be a reason to proceed with the trial because CRs are usually more meaningful in terms of impact on survival [2,20].

Phase II trials may be designed in a way to include patients with more rare malignancies, because that is an opportunity to evaluate a new drug in uncommon cancers, which otherwise would be of less priority in clinical trials [15,54]. In addition, these trials may be designed to evaluate the anti-

tumor activity of known drugs given as part of a new drug regimen (for instance, high-dose therapy or continuous drug infusion).

Assessment of tumor responses

Phase II trials should include only patients with measurable disease. The methodology for the evaluation of objective responses and duration of responses, as well as disease progression in solid malignancies is well established [54]. Clear criteria for the evaluation of tumor response should be included in the treatment protocols. In certain types of cancer, such as prostatic carcinoma, it is uncommon to find suitable indicator lesions for an objective evaluation of response. In these cases, less rigid criteria are sometimes applied, such as the utilization of non-measurable but evaluable lesions, one dimension measurements, changes in biochemical markers or clinical parameters [19,80].

The distinction between CR and partial response (PR) is very important, because CR correlates better with survival benefit and gain in quality of life. This becomes evident when CR and PR are analysed separately after chemotherapy in patients with malignant lymphomas, testicular cancer or small cell lung cancer [8,30,39]. In certain cases, such as in ovarian carcinomas, the pathological confirmation of CR is added to the evaluation of results and appears to predict better for the long-term results of treatment [57].

The duration of responses should also be carefully analysed, because short responses are usually meaningless for the patients and they are more subjected to error of measurement by the investigator [52]. Responses should be counted from the moment when an objective regression is documented until disease progression. The benefit of therapy may be difficult to evaluate in diseases which have a prolonged and variable natural history such as breast cancer [67].

Toxicity

As in phase I trials, toxicity is carefully assessed by the standard grading systems [78]. Phase II trials

are very important to complement and establish the spectrum of side-effects of the drug and also to provide information on the development of cumulative toxicity. This is of great relevance in the decision of whether the drug will proceed on its clinical development or not.

Reporting results

In order to provide reliable data for the proper evaluation of antitumor efficacy and toxicity of new compounds, results of phase II trials should be reported carefully. The number of evaluable patients, drop-outs and patients lost from follow-up, as well as early deaths should be included in the report. It should include details on patient characteristics, relevant prognostic factors, as well as the methodology for the evaluation of responses. In responses, the sites of metastases should be described. An evaluation of response rates stratified according to the main prognostic factors is recommended.

Toxicity should be evaluated according to the standard recommendations [78], which include the objective description of each toxic effect as well as its intensity. Toxicity should be quantified according to well-established grading systems (such as the WHO toxicity scale). The adequate report of side-effects may allow comparison between patients in the same study as well as toxicity reports of patients included in other studies. The description of cases of severe side-effects not previously reported and drug-related deaths is also recommended.

If no antitumor activity is documented in phase II trials, the drug is usually discarded. To avoid discarding potentially active new drugs after phase II trials, it is important that several studies are done at different institutions including sufficient number of patients per specific tumor type.

Data of many phase II studies are usually generated under the responsibility of cooperative study groups which are in close contact with the research committees of the main institutions involved in the development of new anticancer drugs.

When significant antitumor activity and/or a better therapeutic index compared to standard treat-

ment is suggested, the new drug is considered for phase III evaluation.

In these trials, the efficacy of the new drug is confirmed in studies with a large number of patients and the possibility of new types of toxicities or clinical uses for the new compound not previously reported are evaluated. The central question in these trials is whether the efficacy of the new compound is superior to the existing standard therapy.

Concluding remarks

In this paper, several aspects of the development of new anticancer agents have been discussed. Regarding the synthesis of new compounds, the use of structure-activity relationships in the design of new drugs is gathering momentum and this aspect of new drug development merits considerable attention. The limitations of the current drug-development program are highlighted by the fact that of the 600 000 compounds screened less than 40 active agents are used routinely in the clinic. Because of these problems, the use of human tumor models has been the subject of intensive developments. It is however unclear at this time whether the more expensive human tumor xenograft models have superior predictive value to in vitro methods. The recently established European Collaborative Group for preclinical phase II studies in human tumor lines [10] needs urgent support to clarify the predictive value of a panel of xenografts for each human tumor type.

In order to insure a speedy but safe transfer of new compounds from the laboratory to clinical phase I trials, uniform toxicology is essential. Recently, the EORTC have established the minimum requirements for toxicology of potential phase I drugs [27]. Emphasis is also being placed on the use of comparative pharmacokinetics between mice and men in order to allow more rapid, but yet safe dose escalation in phase I studies.

The above mentioned procedures should be evaluated adequately during the next years in order to prove their value in the development of new anticancer drugs.

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