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Feature Articles

EORTC New Drug Development Office Coordinating and Monitoring Programme for Phase I and II Trials with New Anticancer Agents

G. Schwartsmann, J. Wanders, I.J. Koier, H. R. Franklin, O. Dalesio, H.W. Hornstra, M. van Glabbeke, J. Renard, A.T. Van Oosterom, S.B. Kaye and H.M. Pinedo

INTRODUCTION

THE NEW DRUG DEVELOPMENT OFFICE (NDDO) is part of the Research Branch of the EORTC, being the executive office of the New Drug Development Coordinating Committee (NDDCC). The NDDO is directly involved in the coordination of all preclinical and early clinical steps in the development of new anticancer agents, i.e. the acquisition of new candidate compounds, the performance of *in vitro* and *in vivo* drug screening, the preparation of a suitable drug formulation for clinical use, the production of drug in enough quantities for toxicology and early clinical studies, the generation of animal toxicology data to allow a safe starting dose in humans, and the planning, data handling and monitoring of phase I and early phase II trials (Table 1) [1, 2].

Considering the importance of study monitoring for the achievement of high-quality standards of clinical trials and for the acceptancy of the data by the scientific community and regulatory authorities, it is very important that the procedures adopted by different monitoring organisations are frequently re-evaluated and discussed on the basis of the ethical and scientific values. The current operational procedures applied by the NDDO for the monitoring of phase I and II trials strictly follow the recommendations of good clinical practice (GCP) for trials on medicinal products, as defined by the Commission of the European Communities [3]. These guidelines are summarised in this paper.

PHASE I TRIALS: STUDY END-POINTS AND METHODOLOGY

When a new compound has completed preclinical evaluation, the first methodological step towards its clinical development is the phase I trial. In this type of study, patients with progressive malignancies no longer amenable to any form of available anticancer therapy are invited to participate in an experimental trial with a new anticancer agent. In phase I trials, the main

Correspondence to G. Schwartsmann, EORTC-NDDO, Free University Hospital, De Boelelaan 1117, 1082 HV Amsterdam, The Netherlands.
G. Schwartsmann, J. Wanders, I.J. Koier, M.R. Franklin, O. Dalesio are at the EORTC New Drug Development Office (NDDO); O. Dalesio is also at the EORTC Protocol Review Committee (PRC); M. van Glabbeke and J. Renard are at the EORTC Data Centre; A. T. van Oosterom is at the EORTC Quality Control Committee (QCC); S.B. Kaye and H.M. Pinedo are at the EORTC Early Clinical Trials Group (ECTG) and New Drug Development Coordinating Committee (NDDCC).

Table 1. The main steps in anticancer drug development

Acquisition
Screening
Formulation/production
Animal toxicology
Phase I clinical trial
Phase II clinical trial
Phase III clinical trial
Phase IV clinical trial
Introduction of new agent into routine management

study end-points are the identification of the toxicity profile, dose-limiting toxicities and maximum tolerated dose (MTD) of the agent by that specific schedule of administration (Table 2) [4].

In order to avoid the occurrence of toxic deaths at the initial dose escalation steps, the starting dose in phase I trials is intentionally safe and low, being a fraction of the toxic dose in mice that is well tolerated by a larger species, such as rat or dog [5, 6]. Although this approach benefits patients in terms of the risk of unexpected toxicity at entry into the study, the low dose administered to the patient markedly reduces the chances of therapeutic effect [7, 8]. Therefore, patients considered for phase I trials should be fully aware of the characteristics of such studies and sign a written informed consent [9, 10].

Phase I trials are designed in such a way that an initial group of patients (3–5 patients) is given the new compound at the starting dose level and the toxic effects are carefully observed. If no acute toxicity is observed after a predetermined period of observation, or if toxicity is mild to moderate (WHO grades 1–2) and reversible before the start of the next treatment course, the dose is escalated in another series of patients, and toxicity is again documented [11]. The dose escalation procedure is repeated successively, using proportionally smaller dose increments as the dose is increased and toxicity is being observed, until the maximum tolerated dose (MTD) is reached. The latter is defined as the highest dose that can be safely given to patients, producing significant, but yet manageable and reversible toxicity (WHO grades III non-haematological or grade IV haematological toxicity) in at least 2 out of 5 or 6 patients. The MTD has to be defined for each specific drug regimen and according to the presence of good-risk or poor-risk subgroups of patients in relation to the predicted tolerance to chemotherapy [12, 13].

Once the MTD is determined, the dose to be utilised during phase II trials is recommended, being usually the dose escalation step immediately before the MTD, or a dose level representing a 15–20% reduction from the MTD. In any case, additional patients are entered at this dose level before the study is completed (usually a total of 5 or 6 patients) to increase the clinical experience with the dose to be recommended for further trials [2, 11, 14]. In addition to the documentation of toxic effects, preliminary antitumour activity can be evaluated in patients having measurable disease and pharmacokinetics data are usually obtained during the trial [11, 12]. Recently, the use of pharmacokinetic parameters in mice and man has been applied experimentally to guide the dose escalation procedure in phase I trials of several agents. It has been observed that by using information on the preclinical pharmacology and toxicology studies with new agents for the planning of dose escalation, less patients are needed in initial clinical trials, saving time and resources, without affecting the safety of this procedure [15, 16].

Table 2. The main study end-points in phase I trials

Spectrum of toxic effects
Dose-limiting toxicities
Maximum tolerated dose
Recommended dose for phase II trials
Clinical pharmacokinetics
Antitumour activity

Table 3. The main study end-points in phase II trials

Determination of objective antitumour activity
Spectrum and frequency of toxic effects
Drug adjustments
Additional information on the agent

PHASE II TRIALS: STUDY END-POINTS AND METHODOLOGY

In contrast to phase I trials, where the emphasis is on the determination of the qualitative and quantitative toxicity profile of the new agent in man, phase II trials are primarily aimed at the documentation of antitumour activity (Table 3). Obviously, the toxic effects of the new agent are carefully registered to give an indication of the therapeutic index of the new agent [17]. In order to determine the percentage of objective responses, series of patients with the same tumour type, having progressive disease, and measurable lesions (including a disease specific group of eligibility criteria concerning performance status, prior therapy, sites of disease involvement and other conditions) are treated at the recommended dose derived from phase I studies [17, 18].

Phase II trials can be done by entering consecutive patients with the same diagnosis into the study in a non-randomised fashion, up to a number of patients large enough to allow an estimation of the percentage of objective responses to the experimental agent based on statistical grounds. For instance, if the percentage of objective responses required for activity is 20%, compounds having lower levels of activity in early phase II trials can be rejected and priority for further development is given to other candidate compounds. Should the response rates be considered high enough to justify pursuing its development, confirmatory studies are performed including a larger number of patients [17–20].

Another strategy used during phase II evaluation is the use of a prospective randomised design between an experimental agent versus the standard agent with the best known objective response rate in that specific tumor type disease. The latter approach is specially valid to identify activity of analogues or pro-drugs of standard agents, once it has been established that the experimental agent possesses some activity [18, 19, 21].

Should a new agent prove to have significant antitumour activity during phase II trials, the next question to be addressed is whether its use could be justified as part of the anticancer therapeutic armamentarium. Therefore, the advantages of the incorporation of the new agent should be assessed in prospective randomised phase III trials, including an adequate number of

patients. These studies and the further utilisation of the new agent in a large number of patients will provide more detailed information on the spectrum of side-effects of the new agent and the risk of long-term toxic effects. On the basis of the results of such studies, a new agent may find its clinical use justified by showing a better therapeutic index than the standard agent, either by providing a superior antitumour activity and, consequently, leading to a survival benefit, or by having a better toxicity profile, resulting in a better quality of life [2].

THE PREPARATION OF THE STUDY PROTOCOL

Phase I trials

The protocols for phase I and II trials coordinated by the NDDO are prepared by the clinical monitor and referred to the study chairman and sponsor for a final construction. They are prepared according to EORTC guidelines and should include the following sections:

(a) A cover page with the specifications of the study, title, principle investigator(s), study coordinator, sponsor, clinical monitor and the status of the current version, project number, and relevant dates of review, amendments, approval by the Protocol Review Committee (PRC) and/or date of activation of the study.

(b) An introduction and the scientific background which led to the selection of that specific new agent for human trials. Details on chemistry and structure, mechanism of action, antitumour activity in animal models, preclinical pharmacokinetics, animal toxicology studies and the rationale for initiating clinical studies should all be given.

(c) The objectives of the study and the eligibility criteria for patients entering the study, as well as the reasons for exclusion from the study should then be spelt out.

(d) A description of the treatment itself, including information regarding drug formulation and supplies, scheme for drug administration, dose schedule and rules for dose escalation or dose reduction. The definition of the MTD and the method to be applied for deriving the recommended dose for phase II trials, the number of patients per dose level, the policies for retreatment of individual patients, discontinuation of treatment and the use of concomitant medications should all be clearly stated.

(e) Information regarding the study parameters, such as the required observation time after drug administration, follow-up tests or provisions for the case of post-mortem examination.

(f) A detailed description of the guidelines for the documentation of qualitative and quantitative toxic effects, as well as tumour responses according to the WHO criteria [22]. Instructions should also be given as to the type of case report form (CRF) to be utilised in the study. Presently, the NDDO provides its own CRFs, based on those utilised by the US National Cancer Institute (NCI), which are coupled with the Automated Clinical Evaluation System (ACES) for the conduct of phase I trials.

Serious, unexpected and/or life-threatening adverse events (WHO grades III or IV, including myelosuppression) should be reported within 24 hours by telephone, telefax or electronic mail to the NDDO. The investigator should also send a written report containing a description of any adverse drug effects that could potentially represent a significant hazard, contraindication, or which would urge caution regarding the administration of the experimental agent for new patients entering the trial. This should be addressed to both the study coordinator and the clinical monitor. Then, the latter should guarantee that all interested parties receive the relevant information.

In the above section, instructions regarding the termination or discontinuation of the study should be provided. The phase I study is completed when the MTD and a safe dose for phase II trials are established. In that sense, recommendations of doses should be given for both good-risk and poor-risk patients. Provisions for the handling of situations such as the unscheduled discontinuation of drug administration should also be included in the protocol. In addition, the operational procedures to be used for the coordination and monitoring of the study should be detailed.

(g) As a separate section in the study protocol, the procedures for the pharmacokinetic part of the study should be detailed, including instructions regarding blood sampling, preparation of samples for analysis and a brief description of the analytical method to be utilised for the quantification of the drug in body fluids. This section does not have to be a necessary component of the study protocol, as some agents may reach the clinic before the availability of a reliable analytical method for its detection and quantification.

(h) A final section of the protocol should include a statement on the confidentiality of the study, as well as the signature of the representative of all parties involved in the execution of the study protocol once it has been approved. If appropriate, a list of references should be added, including scientific information available in the literature, or official documents mentioned in the study protocol. Finally, tables summarising grading systems that are anticipated to be necessary for the proper data recording should be included in the appendix section.

Phase II trials

For phase II trials, Early Clinical Trials Group (ECTG) master protocols for 12 different tumour types have been prepared and approved for use by the EORTC/PRC and these are being updated regularly. When a new phase II trial is being considered, the ECTG designates a study coordinator. With the assistance of the clinical monitor and the agreement from the sponsor, the study coordinator will adapt the master protocol to the characteristics of the new compound. Although the basic structure of the phase II study protocol resembles that applied for phase I trials, the following sections need to be addressed specifically:

(a) A summary of the available phase I data on the compound should be described, giving details of the spectrum of toxicities, pattern of recovery, dose-limiting toxicities and findings at the MTD. Should antitumour activity have been observed during phase I studies, the characteristics of the patients and the responses should be clearly reported. Then, the rationale for bringing the new agent into phase II trials should be presented.

(b) The objectives of the study should be clearly stated, which include the determination of the percentage of partial or complete responses to the new agent; the assessment of the probability that the level of antitumour responses warrants further evaluation; and the characterisation of the toxic effects of the compound in that specific patient population.

(c) A description of lesions to be considered as measurable or evaluable should be given. For instance, skin nodules, superficial lymph-nodes or lung lesions surrounded by aerated lung are considered as bidimensionally measurable lesions. In contrast, previously irradiated lesions are in principle not acceptable, unless they have been documented as new lesions arising in a previously irradiated field. Computed tomography or echographically identified lesions greater than 3 cm in at least one diameter can be accepted as measurable, as long as they are

multiple. For single lesions, pathological proof of malignancy is required. Clinical hepatomegaly has been considered as measurable but errors of clinical assessment are considerable, and measurement of liver metastases by imaging techniques is clearly preferable. For this, and other reasons, the definition of measurable lesions is currently under discussion within the EORTC.

(d) Statistical considerations are very important in the design of phase II studies. ECTG trials are usually performed using a two-stage design. In the first stage, 14 consecutive evaluable patients are entered in the study. If no objective response is documented, the trial may be closed. This approach ensures that if the aim is to identify a drug which may produce at least 20% objective responses, the chance of rejecting it after the first 14 patients is 0.044. Should one or more objective responses be observed at this stage, up to 11 additional patients should be entered in order to estimate the response rate with a standard error of 10%. The calculations for numbers required will vary if the response rate of interest is less than or greater than 20% (e.g. in the use of analogues of existing compounds).

In our phase II unit, protocols are usually drafted by the clinical monitor and reviewed by the study chairman and the sponsor. CRFs are designed and printed under the responsibility of the NDDO data manager, who defines a database and is reponsible for the supervision of data entry and handling. For the latter, the Scientific Information Retrieval software is utilised. The unit reports bi-weekly on patient accrual to the ECTG chairman and the sponsor. Incoming CRFs are copied and sent to the study chairman. Data entry and verification are supervised by the clinical monitor and a system of double entry of the data is utilised. The remaining sections of the phase II protocols follow the same instructions as described for phase I trials.

ETHICAL CONSIDERATIONS IN PHASE I AND II TRIALS

In order to ensure protection of trial subjects, the declaration of Helsinki as adopted by the 18th World Medical Assembly in 1964, revised in 1975, 1983 and in 1989 in Hong Kong is accepted as the basis for the performance of clinical trials. Up to now, phase I and II trials with new anticancer agents with the coordination and monitoring by the NDDO are performed within the framework of the EORTC ECTG. Therefore, both the NDDO and the ECTG should guarantee that these recommendations are followed by all investigators involved in the clinical studies.

THE PROCESS OF APPROVAL OF THE STUDY PROTOCOL

The personal well-being of patients included in experimental trials is the final responsibility of the investigator concerned. This is further assured through the testimony of the scientific and ethical validity of the study by the EORTC PRC, the local Institutional Review Board (IRB), and by obtaining freely informed consent of the patient before entering the trials (Table 4).

The EORTC Protocol Review Committee (PRC)

The PRC reviews and approves EORTC study protocols with respect to their scientific value, feasibility and relevance. Only those protocols approved by the PRC can be coordinated and monitored by the NDDO and will subsequently carry the EORTC label in publications. Protocols for phase I and II trials are submitted by the study chairman to the PRC at least 1 month prior to its regular meetings. The study protocols can be either accepted, accepted pending modifications, revised and resubmitted or rejected by the PRC. Should any modification in the original version of a protocol be needed during the course of the study, the procedure for the approval of protocol amendments is essentially the same as for the submission of new protocols.

The Institutional Review Board (IRB)

The local IRB reviews the study protocols also with respect to the above-mentioned criteria, taking into consideration the medical, regulatory, ethical and cultural characteristics of the country and the institution where the study will be performed. As is the case for the PRC approval, a study cannot be activated before receiving the offical agreement from the local IRB. It is the duty of the investigator to report to the local IRB on all unusual, severe or unexpected adverse reactions that might occur in the trial, ensuring that all protocol amendments are approval by them before its incorporation into the study design. It is also required that the IRB gives its written approval for the continuation of studies with a prolonged duration, at least on a early basis.

The IRB should always include at least five members with different scientific backgrounds, who are highly motivated and engaged in the detailed review of research activities conducted by the institution. The IRB should be composed of a balanced group of individuals of both genders, including at least one representative of the non-scientific community (for instance, a lawyer or a priest) and one member not linked to the institution by any form of professional or family bonds.

The investigator

In the case of the ECTG, participants are accepted through a system of probationary membership applications, which are open to physicians acting in the field of clinical or experimental oncology, and who agree to comply with the statutes of the group. The approval of a new probationary membership is obtained by vote of full members during an official ECTG meeting. Should the contribution of the probationary member be considered satisfactory during the first year of activities in the group the member receives full membership and the right to vote.

The ECTG investigator is expected to be thoroughly familiar with the properties and the handling of experimental anticancer agents, specifically agents under evaluation by the group. The member has to dedicate sufficient time to the conduct of the studies, according to the guidelines laid down in the study protocol. The institution where the ECTG investigator is chiefly active should have well-trained medical and paramedical staff as well as the laboratory facilities necessary for the performance of the tests requested in the study protocols. It is also a precondition for acceptance of a new ECTG investigator, that the applicant has an organised patient registry system, as well as the assistance of a responsible pharmacist to ensure that the experimental agent on study is adequately stored, properly handled by the staff and that any unused product is returned to the sponsor.

The investigator is responsible for the data collection, recording and reporting of the data produced in the study. For that purpose, he may designate a local study associate coordinator and a responsible data manager to assist in the administrative aspects of the trial. The investigator has the duty to notify all the interested parties in the event of serious adverse events occurring with patients included in the study, as well as to

review the information registered in the case report form (CRFs) and sign them as the responsible investigator. In addition, he should sign the final report of the trial and guarantee the confidentiality of all information generated during the study.

The CRF is defined as a record of the information on each patient included in the trial as required in the study protocol. Whenever a new study is being planned, the NDDO designs a CRF specifically for it and provides this material to the investigators. It is an operational routine of the NDDO to discuss the content and layout of the CRF with the other interested parties, especially when the agent to be studied is the property of the sponsor prior to its preparation. This approach helps in fitting the operational procedures of the NDDO to those normally utilised by the sponsor.

Once a patient is entered in the study, the investigator should provide the necessary medical care not only during the period the patient participates in the study but also after the termination of the study, for as long as the patient needs it. In this sense, the supply of an experimental agent should also be guaranteed for as long as the investigator judges it to be beneficial.

The sponsor

The sponsor can be either a pharmaceutical company, a research laboratory, an academic institution, or the legal representative who holds the rights on the compound to be studied. The sponsor should agree with and sign the final protocol and any further amendments, and provide the NDDO and the investigator with all information available on the compound to be studied in phase I and II trials. This data compilation should be clearly registered in the investigator's brochure and updated whenever new relevant information is obtained. The sponsor should also assist the NDDO in the preparation and/or submission of documentation to the legal authorities as well as to the PRC and IRB.

REGULATORY ASPECTS OF CLINICAL TRIALS

The import of experimental agents for human use is not allowed without an import licence issued by the government of the country to which the agent is being exported. In the case of agents which are sponsored by pharmaceutical companies, the sponsor itself usually handles the procedures to obtain the necessary import license. For non-sponsored agents, the import license is obtained by the NDDO. In the case of an experimental agent to be distributed to other centers through the NDDO in Amsterdam, the license to import the agent in The Netherlands is also handled by the office.

Clinical trials with new anticancer agents need government approval in most countries. This approval is given on the basis of the submission of the required documentation to the authorities. In the case of phase I and early phase II trials, the investigator requests the approval by the government and submits the documentation. With special cases, the NDDO can provide the investigator with the necessary information for submission as required in each different European country.

The clinical monitor

The clinical monitor is an essential member of the team. He/she ensures that the research is properly executed, acting as the formal link between the sponsor and the investigators. To this end, the clinical monitoring mechanism for ECTG studies has been delegated to the clinical monitoring units of the NDDO, in order to ensure that the standards of medical and ethical care demanded by the recommendations of GCP, as defined by the Commission of the European Communities are maintained [3]. GCP can be defined as the standard by which human studies are designed, implemented and reported, in such a way that the data generated in the trial gain the credibility of the scientific and non-scientific community, respecting the integrity, confidentiality and rights of the subjects included in the experiment.

The clinical monitor has to follow strictly the recommendations of GCP, starting with the protection of patients who enter clinical trials in terms of the ethical requirements defined in the Helsinki Declaration, the approval of the study protocol by the PRC and IRB, and the necessity for informed consent and the adequate recording of it. He/she should check all standard operating procedures (SOP) applied to the trial. The latter is defined as a detailed code of rules and instructions made either by the NDDO or the sponsor, or both, regarding the management of clinical trials.

The SOP provides a clear-cut system for the inspection of all items of relevance for the good quality of the trial. It includes instructions regarding the visits of the clinical monitor to the institution where the investigator conducts his/her clinical practice, specially focusing on the availability of the specific conditions for the conduct of the study protocol. This includes a visit to the main sections of the hospital, including the areas where the medications are administered to the patients, the section of the pharmacy where the medications are stored and the identification of the responsible person for the storage, handling and accountability of the drug utilised in the trial.

The clinical monitor should be aware of the professional qualifications of the members of the medical and paramedical staff involved in the care of patients included in the trial. He/she has to check the quality of the system utilised by the investigator for the documentation of events observed during the study, providing him/her with all necessary information regarding the items needed for that purpose. During the initial site visit to the centre, special emphasis should be given to the inspection of the hospital charts (or its equivalent, when forbidden by the law in that specific country), the visit to the hospital central registry and to the section where the data records of patients included in the trial will be stored.

The clinical monitor must make sure that the investigator understands that data must be promptly available for site visits and/or audits on-site. The procedure for archiving the data from the trial should be such that the items required in the study protocol are promptly identified and that its accuracy and quality can be checked during site visits. He/she has to keep a record of all relevant events occurring in the trial, including comments on issues being raised during site visits, telephone calls, letters or other forms of communications between the sponsor, the investigator and the NDDO. He/she should carefully review the information registered in the CRFs and return his/her queries to the investigator, whenever any information is missing or if there is any source of doubt in the way the data are registered.

Once the study is activated, the clinical monitor should check that CRFs are sent promptly after the completion of each drug administration course, sending queries to the investigator in case of missing information, mistakes or unclear data registered in the CRFs. In our experience, the awareness of the importance of high-quality data recording in the CRFs by the investigator and/or his/her representative, and active communication between the investigator and the clinical monitor are essential for the clarification of queries on the CRFs and for meeting high standards of study coordination.

The planning of site visits

Regular site visits are planned by the clinical monitor to each investigator participating in the trials. The site visits are usually scheduled for the period immediately prior to the start of the study, while the study is ongoing and after its completion. In certain situations, additional site visits are needed to address specific items. The data reviewed during the site visits include the patient identification numbers and initials, informed consent, eligibility criteria, medical history, drug administration, toxicity and adverse events and the parameters used for the evaluation of antitumour responses in all patients entered in the trial. In general, laboratory results are checked in a sample of the total patient population and if discrepancies are found between the patient records and the CRFs, a more detailed scrutiny is performed.

As an operational procedure, the clinical monitor will notify the investigator in advance about the planned dates for site visits, the specific patient records requested for auditing, as well as the queries still lacking clarification. For each patient record, which has been requested for verification, a patient eligibility and compliance audit form will be filled in. By doing that, the entry criteria, protocol adherence, accuracy and completeness of data recording in the CRFs can be properly verified. Thereafter, a summary of all audited patient records is officially communicated to the study chairman, under the label of clinical monitor site visit report.

During the site visit, the clinical monitor should check the drug reconciliation form (DRF), which contains the balance of drug vials, as stored in the pharmacy and released for patient use. Although the local pharmacists and/or the research nurse are usually in charge of the DRF, the proper handling of these forms and the final signature is the responsibility of the investigator. With the assistance of the investigator and his/her staff, the clinical monitor should register and update the standard procedures of each specific institution, such as the requirements of the IRB, policies for informed consent, data handling, drug storage and reconciliation. The clinical monitor will also keep an updated version of the normal laboratory values according to the institution.

ACTIVATION OF THE STUDY

NDDO coordinated phase I and II trials are activated by the ECTG chairman, once the protocol has been accepted by the PRC and the other regulatory and technical issues have been checked by the clinical monitor. The investigators then receive the CRFs and the list of operational instructions regarding the mechanics of the trial.

Patient registration in the study

Patients can be registered by telephone and/or by Eurocode. The clinical monitor, data manager and/or his/her assistant verifies the entry criteria, reviewing carefully all eligibility items as well as the reasons for non-eligibility. This step should be done meticulously to avoid the later rejection of a case due to problems of study entry criteria. It is forbidden to administer an experimental agent to a patient not yet formally accepted in the study by the NDDO.

Follow-up evaluation of the CRFs

Once the study is initiated and a patient has been registered by the investigator, it is the responsibility of the NDDO to ensure that the time-frame of the submission of the CRFs is respected. The clinical monitor checks systematically the receipt of CRFs and contacts the investigator in case of delays. Once the arrival of a CRF is registered at the NDDO, the data verification process is initiated.

Preliminary reports on the study are periodically sent to the ECTG chairman and the investigators involved in the study, being officially updated and discussed during the internal ECTG scientific meetings. It is the duty of the study coordinator to review all CRFs and to take the final decision regarding patient eligibility, evaluability of patients for response and/or toxicity, and the overall evaluation of the study.

Closure of the study

It is the responsibility of the ECTG chairman and the study coordinator to decide on the closure of the trial. This decision is based on the proper achievement of the objectives stated in the study protocol. In phase I trials, the definition of the MTD and the recommended dose for phase II trials are the essential goals. In phase II trials, the establishment of the objective response rate, as well as the toxicity pattern of the new agent are the main objectives.

As a rule, the Commission of the European Communities recommends the retention of patient identification codes for at least 15 years following the completion of the study. The latter can be held on microfiche or electronic record, provided a hard copy can be obtained from it if necessary. The NDDO keeps all originals of CRFs stored on its archives for the same period of time.

CONCLUDING REMARKS

Considering the urgent need for the discovery of new active anticancer agents in the clinic, phase I and II trials of new agents must be performed according to the highest standards. The NDDO has developed an operational system which follows strictly the recommendations of GCP for early clinical trials, as determined by the Commission of the European Communities [3]. As a result, an increasing number of studies with compounds coming from academic institutions and pharmaceutical industries is being conducted under the NDDO coordination and monitoring.

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New Views on Rejection Mechanisms and Their Relevance to Interleukin-2 as a Treatment for Renal Cell Cancer

R.T.D. Oliver

IT IS now nearly a century since the first efforts to cure cancer by tumour vaccination [1]. Most of these early efforts only helped to understand the basis of allogenic transplantation rejection [2], a paradox given that today these antigens are now proving to be of prime importance to understanding tumour rejection. Once the genetic basis of major histocompatibility (MHC) systems had been worked out [3], it was possible to demonstrate that rejection of syngenic tumours was also mediated by immune response [4] and immune memory rests in T-lymphocytes [5], as does memory for graft rejection [6].

The 1970s saw many attempts to apply the findings from animal studies to the clinic [7]. Unfortunately, most of this work failed because it used treatments with unproven effect in the measurable disease setting in patients without measurable disease [though researchers in adult solid cancer realised this error when they came to study interleukin-2 (IL-2), it is unfortunate that the same mistake is being made today in the field of leukaemia: IL-2 is being used as adjuvant after marrow transplantation without any evidence from dose-response studies in patients with measurable disease]. Only at the end of the 1970s, when interest in the idea was fading because of lack of obvious clinical benefit, did the first clues as to how to induce specific anti-autologous human tumour immune response appear. These came from understanding the differences in the molecular basis of antigen presentation to helper (HLA class II-dependent) and cytotoxic (HLA class I-dependent) T-lymphocytes. Differences of both class of antigen had to be present (though not necessarily on the same cell) to induce an effective transplantation rejection response [7] while matching of target and effector cell for these same antigens proved necessary for effective antiviral [9] and antitumour immune response [10].

The first clue that these observations might be relevant to human malignancy came from the study of adults with acute myeloid leukaemia in remission [11–13]. These studies demonstrated that the pretreatment leukaemic blast cells, though expressing more serologically detectable class II antigen than remission lymphocytes, failed to provide an effective stimulus to provoke either an autologous or allogenic cytoxic T-lymphocyte response [11]. However, when the autologous blasts were presented to the remission lymphotyces in association with an allogenic class II antigen cytotoxic, T-lymphocytes with specificity restricted to the autologous leukaemic blast were produced [12, 13]. Recently studies in melanoma and colon cancer have provided even more convincing evidence that loss of functional class II antigen occurs quite frequently as a mechanism of escape from immune surveillance. In melanoma, Alexander *et al.* [14] have demonstrated that cell-lines developed from metastatic melanoma, though expressing excess serologically detectable class II antigens, failed to function in an assay of antigen presentation to helper cells. The same group was able to demonstrate that the defect could be overcome by transfecting a normal class II DR beta gene into the metastatic cell line [15].

Additional support for the importance of class II came from

Correspondence to R.T.D. Oliver, Department of Medical Oncology, London Hospital Medical College, University of London, Turner St. London E1 1BB.
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