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Original Paper

An Approach to the Design and Implementation of Clinical Trials of Empirical Antibiotic Therapy in Febrile and Neutropenic Cancer Patients

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The results of many clinical trials on empirical therapy in febrile, neutropenic cancer patients cannot be readily transferred to the clinical practice, because the methodology is often flawed and definitions, study endpoints and eligibility criteria differ from trial to trial. This article critically reviews some issues related to the design and implementation of randomised clinical trials of empirical antibiotic therapy in cancer patients. Within the definition of phase III clinical trials, two approaches co-exist, based on the trial's specific aims: the "explanatory" approach and the "pragmatic" approach. The usual "explicit" aim of clinical trials of empirical therapy in febrile, neutropenic patients has been that of comparing the "efficacy" of two regimens. However, this term has been more often used with reference to the antibacterial activity of the regimen under study (explanatory aim) than to indicate the practical benifits it draws to the overall patient population treated for fever and neutropenia (pragmatic aim). These two meanings are often taken as perfectly interchangeable, while, conversely, they are completely distinct (though not independent) treatment effects. Most trials conducted in this patient population in recent years are explanatory trials, though not explicitly so, but their results have been widely applied to clinical practice, as they were pragmatic trials. In an explanatory trial the appropriate endpoint is success or failure (defined by clinical and laboratory data) among those patients affected with the specific infection for which the study drug is being given, while in pragmatic trials survival is probably the more appropriate outcome variable, since they are designed to assess the practical benifits that the overall population of febrile and neutropenic patients can obtain from the new empirical treatment. Unfortunately, survival is not a practical study endpoint for the difficulty in assessing the cause of death in this patient population and, especially, for the need for very large sample sizes, which might render the implementation problematic even for large, multicentre groups. Both types of trials need an intention to treat analysis, but this is especially crucial for pragmatic trials, which should not differentiate those cases in which success was obtained through multiple treatment modifications from those who did not require any treatment change. Obviously, this implies that no conclusion should be drawn about the antibacterial activity of the study drugs and that the number of treatment modifications should be taken into account in the interpretation of the results, especially for quality of life and cost evaluations. Information related to fever and signs of infection, age, underlying disease, neutropenia and concomitant administration of other antibiotics are crucial entry criteria that need to be clearly discussed and defined. Finally, the evaluation of toxicity is problematic in this patient population, due to the existence of a number of toxigenic factors, including the underlying disease, the type of infectious complication, the administration of chemotherapy and radiotherapy and the use of parental nutrition. All these effects tend to ovelap, thus impairing the investigator's ability to detect specific drug-related side-effects.

Key words: clinical trials, infection control, anti-infective agents, neutropenia, neoplasma, immunocompromised host, fever

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INTRODUCTION

DESPITE MAJOR improvements in clinical care and supportive measures, infection still remains one of the leading causes of morbidity and mortality in cancer patients [1–7]. In addition, neutropenia and fever are probably the most important factors limiting the projected dose intensity of antineoplastic chemotherapy, sometimes compelling oncologists and haematologists to delay treatment courses or to reduce dosages, with obvious potential effects on the effectiveness of antineoplastic therapies [8]. The availability of haematopoietic growth factors has certainly disclosed new perspectives. Some clinical trials have actually shown a significant reduction in the duration of neutropenia and in the incidence of fever with these cytokines, especially in patients with solid tumours and in those undergoing autologous bone marrow transplantation, but more severely immunocompromised patients may respond less promptly in terms of granulocyte recovery, and may still experience prolonged periods of neutropenia [9–12].

Fever during neutropenia represents the commonest presentation of a potentially overwhelming infection, and it is usually considered as a medical emergency [6]. It has been shown that if an empirical treatment is not promptly undertaken, mortality can approach 40% [13]. Based on this information, the early empirical administration of broad-spectrum antibiotics has become common practice in this patient population, with substantial improvements in prognosis [13–16]. The specific composition of the empirical regimen remains controversial and subject to change, due to the changing pattern of pathogens, the rapid development of bacterial resistance, the emergence of new clinical entities and the availability of new effective drugs [17]. In addition, some investigators have recently criticised the indiscriminate use of aggressive intravenous empirical therapies in all febrile and neutropenic patients, suggesting that subgroups of patients at lower risk of unfavourable outcome do exist and might be identified and treated accordingly [18–21]. Finally, there is an increasing need to decrease costs of medical care and to improve patient's quality of life. All these considerations justify the implementation of clinical and laboratory research aimed at updating and improving management procedures in febrile and neutropenic cancer patients.

The standard method to assess the clinical effectiveness of new treatment modalities is represented by phase III, prospective, randomised clinical trials comparing the new treatment versus the standard one [22, 23]. Unfortunately, the results of many clinical trials on empirical therapy of infections in cancer patients cannot be readily transferred to the clinical practice, for several reasons. Firstly, the methodology is often flawed, undermining the statistical validity of the trial. Secondly, the generalisability of the results is impaired by many factors, including differences in study populations (e.g. underlying diseases, pattern of infecting pathogens, level of immunosuppression), participating institutions (e.g. availability of adequate microbiological facilities, level of care), and factors correlated with study design (definitions, study endpoints, eligibility criteria, etc.) Thirdly, the variability of these factors from study to study often precludes comparisons among different studies that were conducted on the same issue [24, 25].

With the aim of making methodologies and definitions as uniform as possible, the International Immunocompromised Host Society, the Infectious Disease Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Disease (ESCMID) have published Consensus Reports on the design and implementation of clinical trials of empirical therapy in febrile and neutropenic cancer patients [26–28]. Although representing a remarkable progress in this area, these publications were forced to deal with general principles, without focusing on specific methodological aspects.

In the present article, we have critically reviewed some issues related to the design and implementation of randomised clinical trials of empirical antibiotic therapy in cancer patients. The basis for this discussion stems from manuals dealing with the general principles of the design and implementation of clinical trials [22, 23], from the IHS, IDSA and ESCMID guidelines [26–28] and from other available publications on this subject [24, 25, 29–33]. In addition, we have taken advantage of our own experience as members of the International Antimicrobial Therapy Co-operative Group (IATCG) of the European Organisation for Research and Treatment of Cancer (EORTC), a group which completed several clinical trials on this subject over the last 20 years [34–41].

PLANNING AND ANALYSING A CLINICAL TRIAL OF EMPIRICAL THERAPY

Choice of the experimental and standard treatment

The antibiotic regimens most commonly used in the empirical therapy of fever and infection in neutropenic patients are summarised in Table 1. Over the last 10 years, most clinical trials have attempted to assess the efficacy of (i) monotherapy with third generation cephalosporins or carbapenems [42–44]; (ii) early anti-Gram-positive coverage with glycopeptides, either as part of a three-drug regimen [45, 46] or in combination with a beta-lactam [47]; and (iii) double beta-lactam combinations [48]. With some exceptions [42, 43], the reference regimen was represented by the classic combination of an aminoglycoside (gentamicin, amikacin or netilmicin) with an antipseudomonal beta-lactam (an acyl-ureido-penicillin, a second or third generation cephalosporin or a carbapenem). More recently, new approaches have been tried, such as single-daily therapy with ceftriaxone and amikacin [41] or monotherapy with intravenous or oral quinolones [49]. The introduction of new and more effective antimicrobial compounds, together with the general amelioration of supportive care in cancer patients, has led to a fairly good response rate to the initial antibiotic regimen and to major improvements in survival. For example, in the last

Table 1. Empirical antibiotic regimens for febrile, granulocytopenic cancer patients

Monotherapy	3rd generation cephalosporins carbapenems
Two-drug regimens	3rd generation cephalosporin + aminoglycoside Single-daily ceftriaxone + single-daily amikacin Carbapenem + aminoglysoside 3rd generation cephalosporin + ureido-penicillin 3rd generation cephalosporin + glycopeptide Ureidopenicillin + glycopeptide Ureidopenicillin + aminoglycoside
Three-drug regimens	3rd generation cephalosporin + aminoglycoside + glycopeptide Ureido-penicillin + aminoglycoside + glycopeptide

20 years, among 701 single-agent bacteraemias observed in therapeutic trials I, IV, V and VIII performed by the IATCG of the EORTC, the average global response rate to the initial antimicrobial regimen approached 60%, and the attributable infectious mortality rate decreased from 21 to 6% of febrile episodes. (EORTC–IATCG unpublished data). It appears unlikely that this response rate could be improved substantially. However, due to the emergence of new pathogens and to the development of resistance in old pathogens, a continuous surveillance should be maintained. In addition, new approaches, such as those proposed in Table 2, should be investigated and a more rational use of antibiotics should be promoted, for example by tailoring treatments according to the individual risk of unfavourable outcome or of being affected by a specific type of infection [18–20].

Table 2. Suggested hypotheses to be tested in phase III, prospective, randomised clinical trials of empirical therapy in febrile neutropenia

1. Testing new drugs in standard combination regimens.
   Is a new broad-spectrum antibiotic (a cephalosporin, a carbapenem, an ureido penicillin, with or without a beta-lactamase inhibitor or a quinolone) more effective, as effective as but less toxic or as effective but less expensive than standard beta-lactam regimens, in combination with the same aminoglycoside?
2. Testing new drugs in monotherapy.
   Is monotherapy (a cephalosporin, a carbapenem, an ureido-penicillin, with or without a beta-lactamase inhibitor, or a quinolone) in combination with placebo as effective as and less toxic and expensive than the standard beta-lactam–aminoglycoside combination?
3. Testing the role of early empirical anti-Gram-positive coverage.
   Is the early administration of a specific anti-Gram-positive antibiotic advantageous with respect to the standard two-drug combination or to monotherapy, with placebo?
4. Testing single daily doses.
   Is single-daily therapy with an aminoglycoside and a long-acting cephalosporin as effective as and more comfortable and less expensive than the standard beta-lactam–aminoglycoside combination?
   Is single-daily therapy with a single drug safe and effective?
5. Testing early antifungal coverage.
   Is the early administration of an antifungal drug at fever advantageous with respect to the standard combination or to monotherapy, with placebo?
   Is there an advantage in starting empirical antifungal therapy at the development of fever rather than in persisting fevers?
6. Testing pre-emptive therapy.
   Is there a difference in terms of efficacy, toxicity or cost between starting an empirical antibiotic regimen at neutropenia (neutropenia-oriented empirical therapy) or at fever (fever-oriented empirical therapy) in cancer patients at high risk of bacteraemia or other medical complications?
7. Testing early discharge or outpatient treatment.
   Is there a difference in terms of efficacy, toxicity or cost between outpatient or inpatient treatment of febrile neutropenia in patients at low risk of bacteraemia or other medical complications?
8. Testing clinical prediction rules.
   Is it possible to individualise empirical treatments according to patient's generic risk of severe infection or to patient's probability of a specific aetiology?
9. Testing oral treatment.
   Is there a difference in terms of efficacy, toxicity or cost between standard intravenous treatment and oral treatment?
10. Testing intravenous-oral sequential treatment.
    Is there a difference in terms of efficacy, toxicity or cost between standard intravenous treatment with a given drug and the sequential use of two dosing forms or of two routes of administration of the same drug?

Primary objectives and endpoints

Within the definition of phase III clinical trials, two approaches coexist: the "explanatory" approach and the "pragmatic" approach [50]. These can be represented by two prototypes, which show remarkable differences in several essential design features (Table 3). Whether any given trial should be designated as "explanatory" or "pragmatic" depends on its specific aims. The aim of an explanatory trial is usually to test a therapeutic hypothesis under ideal conditions, while the aim of a pragmatic trial is to assess the actual efficacy of a treatment approach in clinical practice.

The specific aims of most clinical trials of empirical antibiotic therapy in febrile, neutropenic cancer patients are not free of some degree of ambiguity. The usual "explicit" aim has been that of comparing the "efficacy" of two regimens. However, the term "efficacy" is equivocal, when used in this context. It has been more often used with reference to the antibacterial activity of the regimen under study (explanatory aim) than to indicate the practical benefits it draws to the overall patient population treated for fever and neutropenia (pragmatic aim). These two meanings are often taken as perfectly interchangeable, while, conversely, they are completely distinct (though not independent) treatment effects. The presence of the first (antibacterial activity) is a necessary but not sufficient condition for the presence of the second (beneficial effect for the patients). In fact, in several instances, a regimen may be more active against specific types of infection, and yet it may fail to bear any benefit to the patients, for example because these infections are uncommon in a specific population of patients or because of its toxicity.

This is not a trivial problem, since the difference in aims results in remarkable methodological differences, as many scientists apparently fail to recognise. As already hinted by some authors [31, 32], much of the controversy over the interpretation of the results of clinical trials just arises from a failure to appreciate the relationships between the objectives and the design of the trial, and "from disagreements (often unrecognised) or ambiguities over the questions posed by these trials" [51]. This ambiguity is not peculiar of studies in neutropenic patients, since a clear distinction between "activity" and "clinical effectiveness" is often missing in other areas of medical research. For instance, in clinical oncology, only in recent years has it been clearly recognised that tumour response to treatment is a marker of the activity of a treatment, but cannot be used as an endpoint in clinical trials aimed at assessing its clinical efficacy, that has to be evaluated in terms of survival and/or quality of life.

Study design in explanatory trials

Trials of this type are close to phase II trials, in terms of aims, endpoints and patients selection. Yet, owing to the high variability in response rates from one population to another, comparisons should be made with a randomised control group, treated with the best available treatment. The specific objective of these trials is the assessment of antibacterial activity. This should be expressed very clearly in the study protocol, because the conclusions cannot be directly transferred to the clinical practice, unless exceptionally favourable results are observed.

The appropriate endpoint in these trials is success or failure

Table 3. Explanatory trials versus pragmatic trials: main characteristics

	Type of trial	
	Explanatory	Pragmatic
Aims	Mechanisms Activity Maximal efficacy	Practical effectiveness Feasibility Cost-effectiveness
Contrast	Comparison of two detailed protocols	Comparison of two policies
Endpoint	Pathological modifications Laboratory tests Response Biological measures	Mortality Quality of life Outcome
Masking	Double-blind Single-blind	Not necessary (often undesirable)
Study population	Highly selected (good compliers, "ideal" patients, etc.)	General population of unselected patients
Compliance	Must be close to 100% and should be promoted by all possible means (run-in to exclude non compliers)	Must reflect clinical practice
Follow-up protocols	Frequent examinations Specific tests	Routine follow-up
Size	Small to moderate	Very large
Exclusions (from analyses)	Non-compliers? Ineligible patients? Early events (deaths)?	None
Emphasis	Precise estimation of the "maximum" effect	Statistical validity Generalisability

among those patients with that specific infection for which the study drug is being given. As the information on the diagnosis of the febrile episode becomes available only several hours, or days, after initiation of the empirical treatment, many patients will be randomised that are going to be excluded from the analysis of the results because they are affected by other types of infection or by unexplained fever. Consequently, in order to prevent selection bias, it is crucial that exclusion of these patients is made on objective grounds by observers that are blinded to the outcome and to the assigned treatment, and, in general, to any information collected after randomisation (beside the results of blood cultures). Similarly, it is extremely important that the classification of each patient as "responder" or "non-responder" is not influenced by the knowledge of the treatment assignment. Obviously, the best way to eliminate biases related to the existence of prejudices on the activity of the trial drugs, would be to perform double-blind studies, thus masking the allocations to both patients and physicians. Unfortunately, this approach can be precluded both by the existence of study drugs characteristics (side effects, colour, production of gas at dilution, etc.) able to unmask the allocation, and by the fact that in many hospitals (especially in Europe) drugs are not delivered by the pharmacy already diluted and ready to be injected, but are prepared at the bedside by nurses or even doctors. In addition, many investigators refuse the principle of being unaware of what their patients are receiving, especially in this clinical situation. Whenever masking is impossible, the classification of each patient as "responder" or "non-responder" should be carried out by "blinded" evaluators, and should be based on a classification protocol, using objective criteria as much as possible. An analysis of the proportion of febrile patients on each day of treatment in the two arms of the study is also helpful, with the aim of detecting differences between the two treatment arms in terms of management of the same clinical situation (e.g. persistence of fever). In addition, a statement should be included in the trial protocol, establishing the policy to use when a pathogen resistant to the allocated antibiotic(s) is isolated as cause of infection in a patient who is nevertheless responding "clinically" to the treatment (i.e. showing defervescence and clearance of signs of infection and negative blood cultures). All patients should be evaluated for response to treatment, according to the "intention to treat" principle, independently of compliance to the assigned treatment, but the analysis should focus on the subgroup(s) for which the study was designed. Treatment compliance should be an important variable in the interpretation of the results. Response rates for other types of infection may be examined as well, but only for exploratory purposes.

Some definitions of success and failure are proposed in Table 4. Of note, every modification of the initial antibacterial regimen in target patients should be considered as a failure, while, addition of antifungal or antiviral agents should not be regarded as a failure, since in this type of trial investigators are interested in the antibacterial activity of the study drug. The classification of a death as failure depends on the cause of death, that needs to be carefully ascertained, possibly by autopsy, in all patients affected by the infections under study. If death is due to a documented non-bacterial cause, the case should not be recorded as failure.

The sample size calculation for an explanatory study should be based on the observed (historical) response to treatment in the specific subset of patients under study, and on the increase that can be expected in these rates. The number of patients to

Table 4. Definitions of success and failure

Factors defining "clinical" failure	Factors defining "clinical" success
Deterioration of vital signs	Defervescence
Development of a new clinical localisation of infection with persistent fever	Clearing of symptoms and signs of infection
Instrumental evidence of progression of the initial infection	Eradication of the pathogen (if the infection was microbiologically documented)
Persistence of positive blood cultures	No relapse of the primary infection
Unexplained fever higher than 38°C for at least 5 days	No modification of the initial antibiotic regimen
Fever higher than 39°C persisting after 72 h of antibiotic therapy	
Relapsing infection	
Breakthrough bacteraemia	

Modified from refs [27] and [28].

randomise should then be increased based on the expected proportion of specific "target" patients within the overall population of febrile and neutropenic patients. Most trials of empirical antibiotic therapy in neutropenic febrile patients conducted in recent years belong to this category, although not explicitly so. However, owing to the abovementioned ambiguity, their results have been widely applied to clinical practice.

Study design in pragmatic trials

Once the activity, and the toxicity, of a new treatment have been evaluated, the scientific community (and the regulatory agencies) need to know whether it is more convenient to use this new treatment, instead of the standard one, in the "typical" febrile, neutropenic patient. By "typical", we mean any patient presenting with fever and neutropenia (regardless of his final diagnosis) in the routine clinical activity of those centres in charge of treating the patients, in the absence of any specific characteristic (e.g. age, concomitant diseases, short term prognosis, clinical presentation specific for or highly suggestive of a specific aetiology, etc.) that requires an individualised approach. For this purpose, a different type of trial is required, that is designed to assess the practical benefits that the overall population of febrile and neutropenic patients can obtain from the use of the new empirical treatment. The term "pragmatic trials" refers to trials of this type: they are meant to produce results that can be directly transferred to clinical practice. Few, if any, true pragmatic trials of empirical antibiotic therapy in cancer patients are reported in the scientific literature. Conversely, in other medical areas, this type of trial has become the gold standard for the evaluation of new (and old) treatments.

From a methodological viewpoint, pragmatic trials of empirical antibiotic therapy in febrile and neutropenic cancer patients present several peculiar problems. First of all, all randomised patients should be included in the analysis, independent of the final diagnosis and of treatment compliance. This requirement, often referred to as the "intention to treat" principle, is warranted by the need to prevent biases due to the exclusion of non-compliant patients, and of preserving the generalisability of the results. A second problem is the identification of the appropriate outcome measure (endpoint). The assessment of efficacy based on the proportion of clinical "successes" has several shortcomings, when used in pragmatic trials. In a pragmatic trial, a treatment is successful inasmuch as it positively affects quality of life and/or mortality. Whether (and how consistently) an increase in the proportion of clinical success is correlated with a decreased mortality or with an improvement in quality of life remains to be demonstrated. Moreover, it appears difficult to use this definition in episodes of fever not definitively linked to an infectious aetiology (e.g. unexplained fevers), and also because some investigators consider persistence of fever as a marker of failure, requiring treatment change, while others consider the patient as stable, although still febrile, and continue the same treatment. The latter situation was actually well documented in a recent EORTC–IATCG trial [39].

Based on these considerations, some investigators have advocated and used survival as the main endpoint in trials aimed to assess treatment efficacy [42–44, 52]. Indeed, if one considers that the very rationale for administering empirical antibiotic therapy is to decrease early mortality from bacterial infections, one should agree with these investigators and conclude that the best definition of success is patient's survival at the end of the neutropenic period. Unfortunately, the use of survival as the outcome variable also has several drawbacks. The first and most often quoted is the difficulty in assessing the cause of death in this patient population, even when autopsy is performed. This difficulty could be overcome by using mortality from all causes within a specified period of time following randomisation. This approach might even be considered as more appropriate in a pragmatic perspective. Secondly, the overall mortality rate from any cause at 30 days from the onset of fever in episodes of febrile neutropenia is now relatively low (11% in the recent EORTC–IATCG trial VIII), thus rendering any further improvement difficult to detect. Consequently, a study having mortality as the primary endpoint would require a large sample size, rendering its implementation problematic even for large, multicentre groups. For instance, a trial aimed at detecting a 3% absolute reduction in mortality (from 11% to 8%) with a power of 80%, would require more than 3000 patients. Incidentally, the trials that used survival as the main endpoint of efficacy, did not base sample size calculations on the historical and expected survival rate, but rather on the "clinical" response rate. This incredible confusion has led to studies of inadequate power and to the possibility of false negative conclusions, which was not recognised by the authors, nor by the reviewers [42, 44].

The analysis of a trial having survival as the endpoint of effectiveness should be strictly based on the intention to treat principle, without trying to differentiate those cases in which success was obtained through multiple treatment modifications from those who did not require any treatment change. Therefore,

investigators should resist the temptation of drawing conclusions concerning the antibacterial activity of the study drugs. This does not mean that the issue of treatment modification is a negligible one. The frequency of treatment modifications in either arm should actually be taken into account in the interpretation of the results, especially as far as quality of life and costs are concerned.

Despite the almost prohibitive number of patients required for trials using survival as the main endpoint, it is possible that, in the future, crucial clinical questions are identified that deserve, and need to be tested in large scale clinical trials. Alternatively, it would be desirable to identify subgroups of patients at very high risk of death, and to concentrate clinical and research efforts on these patients. For the time being, it is reasonable to expect that some "clinical" definition of success continues to be the main endpoint in the large majority of the trials in this area. Since many of these trials have pragmatic aims, great caution should be used, in the light of the above discussed limitations, both in the study design and in the interpretation of the results.

We have already discussed the procedures required to prevent a biased assessment of response in explanatory trials. In pragmatic trials, these requirements are even more stringent. Conversely, masking procedures are unlikely to be implemented in pragmatic trials, nor are they really desirable, since in these types of trial one would like to mimic as much as possible the actual clinical situation.

The evaluation of secondary fevers and infections

Episodes of fever and infection following the primary and developing during the same period of neutropenia are usually defined as secondary episodes. As first shown by Bodey and coworkers several years ago [53, 54], the more prolonged the period of granulocytopenia, the higher the risk for the patient to undergo multiple episodes of fever and infection. In addition, with new and more effective antibiotics, more patients survive the primary episode and can, therefore, undergo a secondary one. The evaluation of secondary fevers and infections as failures or successes of the initial regimen depends on the aim of the trial and on the aetiology of the episode. Based on clinical and laboratory data, secondary episodes can be either related or unrelated to the primary one and can be either documented or non-documented.

Relapse of the primary infection. A relapse of the primary infection could be defined as the reappearance of an infection, due to the same pathogen as the primary, in the same or another site, during the same episode of neutropenia. If the site of isolation is the blood and this occurs during antibiotic therapy, it is usually defined as a breakthrough bacteraemia. Such episodes are usually classified as failures of the initial empirical treatment.

Further febrile/infectious episode. A further febrile/infectious episode could be defined as a new fever (or a new infection without fever) occurring during the same episode of granulocytopenia, either not documented or caused by an organism different from the initial one (if an initial pathogen was identified), occurring or being recognised more than 72 h after inclusion in the trial and during or within the week after discontinuation of protocol therapy.

The occurrence of this type of further episode should not have any influence on the evaluation of the performance of the initial empirical regimen, provided that the primary episode was successfully treated and the patient had remained afebrile for at least 72 h. Sometimes, no interval between the two episodes (i.e. no defervescence lasting at least 72 h) could be observed. This case should be considered in the protocol for the assessment of response.

ENTRY CRITERIA

The relevance of a clinical trial and the generalisability of its results are strongly affected by the characteristics of the study population that are related to study entry criteria. Some of these issues are listed in Table 5. Among them, we will briefly discuss factors related to fever and signs of infection, age, underlying disease, granulocyte count and the administration of other antibiotics in addition to the study drugs.

Fever and signs of infection

Fever may remain the only clinical sign of infection. For example, in the fifth therapeutic trial of the IATCG of the EORTC, more than 50% of the patients presented at randomisation without any sign of infection other than fever [39]. When clinical signs and symptoms of a localised infection coexist with fever (or when they are the only sign of infection), one might wonder if the patient is still eligible for enrolment in a clinical trial of empirical therapy. The question is not trivial and the answer is probably "yes", with the possible exception of patients in whom the clinical signs are so specific as to indicate the pathogen most likely involved. It appears logical that, in this case, the patient deserves a pathogen-oriented approach, even though the pathogen has yet to be identified. According to the Consensus Report of the IHS and to the IDSA and ESCMID guidelines, fever should be defined as an oral temperature higher than 38.5°C in a single observation or higher than 38°C in two or more observations, during a 12-h period [26–28]. The same thresholds are also usually considered valid for axillary temperature. Based both on the clinical course and on microbiological data, each febrile episode is classified retrospectively in one of the following categories [15]:

(1) Microbiologically documented infection with or without bacteraemia, when there are definite signs and symptoms revealing the existence of an infection that is microbiologically proven by cultures of blood, tissue samples or material obtained from the infected site.
(2) Clinically documented infection, when there are definite

Table 5. Information potentially affecting eligibility

Age and sex
Underlying disease
Previous inclusion in other studies
Renal and hepatic function
Allergy to the study drugs
Performance status
Other causes of immunodeficiency
Pregnancy
Administration of other experimental medications
Administration of growth factors
Presence of fever and infection
Absence of signs and symptoms suggestive of a specific aetiology
Granulocytopenia
Previous antibiotic therapies
Antibiotic prophylaxis

signs and symptoms of infection with an identified site but without microbiological proof revealing the aetiologic agent.

(3) Unexplained fever (also named fever of unknown origin, fever with suspected infection or possible infection), when neither a defined site nor a microbiological proof are present. These fevers might be non-infectious in origin.

(4) Microbiologically documented viral, fungal or protozoal infection, in the presence of clinical or microbiological data documenting this aetiology.

The definition of bacteraemia is somewhat controversial (Table 6). According to the EORTC group, bacteraemias are those microbiologically documented infections in which the pathogen is recovered from blood, regardless of the presence of a microbiologically documented non-haematogenous site [15]. The IHS, IDSA and ESCMID documents [26–28] suggest that bacteraemias should be subdivided according to the presence or absence of a microbiologically documented, non-haematogenous site. Bacteraemias with an infectious site (same pathogen) are classified among localised microbiologically documented infections, while only bacteraemias without a site are included in the bacteraemia group. In our opinion, it seems a pathophysiological nonsense (and an unnecessary complication) to split a single dominant entity (bacteria in blood) into two subgroups, and priority should be given to the isolation of pathogens from blood, even when a localised infection is evident. A single positive blood culture is sufficient for classifying a febrile episode among bacteraemias, except in the case of common skin contaminants, such as coagulase-negative staphylococci or non-JK corynebacteria. For these pathogens, at least two positive blood cultures should be required, unless the same pathogen is concomitantly isolated from another infected site [38].

The distribution of febrile episodes among the aforementioned categories has remained relatively stable over time, although in recent years a decreased documentation rate has been reported [55]. Unexplained fevers usually account for approximately 40% of febrile episodes. Bacteraemia is documented in 20–30% of the episodes, other microbiologically documented infections in another 10–20% and clinically documented infections in the remaining 10–30% [13–15, 34–41]. Classification of febrile episodes is crucial in explanatory trials, but is very useful in pragmatic trials as well, since it may help providing a clear picture of the study population and interpreting the results of the study.

Age

A controversial issue in this area is whether or not it is appropriate to enrol children and adults in the same clinical trial. Indeed, although it has been suggested that once rendered granulocytopenic, children and adults share the same risk of severe infection [56], both common sense and clinical evidence suggest that the management of immunocompromised children with cancer differs from that of adults [57]. Underlying diseases and patterns of care tend to be different, and many antibiotics show age-related pharmacokinetic characteristics and tolerance. In addition, the incidence of fungal infections, as well as the infectious mortality, appears to be lower in paediatric patients (EORTC–IATCG unpublished data). These considerations should probably suggest not to include children and adults in the same clinical trial, or, at least, to stratify randomisation by age.

Underlying disease

The population of patients with cancer included in multicentre, comparative clinical trials for empirical treatment of febrile neutropenia is very heterogeneous [6, 7]. It usually includes both patients with haematological malignancies and with solid tumours, as well as patients undergoing first induction chemotherapy and those with multiple relapses. Even among leukaemic patients, remarkable differences can be found between patients with acute and chronic disease. Similarly, patients undergoing autologous bone marrow transplantation can hardly be compared with those receiving allogeneic grafts from unrelated donors. As a consequence, the underlying immunological deficiencies may vary enormously from patient to patient, thus introducing problems in the interpretation of the results. Some of these potentially confounding variables are listed in Table 7. In addition, some clinical trials have included, together with neutropenic cancer patients, patients with neutropenia due to primary bone marrow failures, such as aplastic anaemia or autoimmune granulocytopenia. As recently pointed out [58], patients with primary bone marrow failures have associated risk factors, patterns of infectious complications and outcomes that differ from those of cancer patients. Chemotherapy-induced granulocytopenia appears to be an "acute" process, with a relatively predictable duration, in which bone marrow recovery is ultimately expected, while primary granulocytopenia is a "chronic" process of unpredictable duration. Therefore, we

Table 6. Classification of febrile episodes in clinical trials of antibiotics in cancer patients (based on refs [15, 26–28])

	Immunocompromised Host Society and Infectious Disease Society of America	European Organisation for Research And Treatment of Cancer
Microbiologically documented infection	The infection is clinically detectable and microbiologically proven (includes bacteraemias with a localisation site)	The infection is clinically detectable and microbiologically proven (excludes bacteraemias, even in presence of a site)
Bacteraemia	The pathogen is isolated from blood and there is no site	The pathogen is isolated from blood, regardless of the existence of a site
Clinically documented infection	The infection is clinically detectable but no microbiological proof can be obtained	Definite signs of localised infection, in absence of microbiological proof
Unexplained fever	Fever, without any clinical or microbiological documentation	Episode compatible with infection, in absence of any clinical or microbiological proof

Table 7. Factors inducing internal variability in a population of cancer patients

Age
Type of underlying disease
Stage of the underlying disease (remission, relapse)
Antineoplastic chemotherapy regimen
Supportive care
Presence and type of intravenous devices
Allogeneic bone marrow transplantation
Different policies for prophylaxis of infection

recommend not to include patients with primary bone marrow failures and cancer patients in the same clinical trial.

Neutropenia

As already mentioned, the incidence and severity of infection in this patient population is inversely related to the absolute neutrophil count and it is highest when the granulocyte count falls below 100 cells/mm^3 [53, 54]. The Consensus Report of the IHS and the IDSA and ESCMID guidelines define the concept of neutropenia as the presence of an absolute granulocyte count lower than 500 cells/mm^3. However, since a rapid decline is more often associated with infection, patients with a granulocyte count between 500 and 1000 cells/mm^3, but expected to decrease within few hours, are also eligible for inclusion in most trials. Profound neutropenia is usually defined as fewer than 100 neutrophils/mm^3. The duration of standard and profound granulocytopenia, defined as the number of days spent with a granulocyte count below 500 and below 100 cells/mm^3, respectively, is used for classifying patients into different subgroups on which to evaluate response rates and survival for explanatory purposes [17, 31, 53].

Administration of other antimicrobials

A sensible interpretation of the results of a therapeutic clinical trial would require that prophylactic measures (especially antibiotic prophylaxis) have been as uniform as possible among patients enrolled into the trial. If a total uniformity is impossible, a limited number of options should be allowed for a patient to be eligible. For example, only patients who received a common prophylactic regimen, or no chemoprophylaxis at all, could be eligible for the trial.

In conclusion, the ideal trial should include only cancer patients in the same age group, with the same underlying disease and having received the same type of chemoprophylaxis (or no prophylaxis). Unfortunately, this approach can be rarely applied because even large cancer centres and co-operative groups may have difficulties in recruiting an adequate number of patients with the same underlying disease, in the same stage. For these reasons, the Consensus Report of the IHS agreed that patients of different ages, with different neoplastic diseases at different stages could be included in the same clinical trial. However, in the light of the high degree of internal variability (Table 7) it seems reasonable to recommend the application of some corrective measures, with the aim of ensuring that variables potentially affecting outcome are distributed as evenly as possible in all treatment groups. It is not among the purposes of the present article to review these measures in detail. We would only like to briefly discuss the most obvious corrective measure, i.e. stratification. For example, the IATCG of the EORTC in its large multicentre trials usually prepares separate randomisation lists for each participating group and, within each group, for patients with leukaemia and bone marrow transplantation, on one hand, and for patients with lymphoma and solid tumours, on the other. In addition, stratification by centre usually implies stratification by age, as well, since few centres enrol both paediatric and adult patients. It is also worth remembering that stratification for more than one or two factors is neither practical, nor effective in preventing differences in the composition of the study groups [22, 23]. Despite stratification, imbalances between study groups not evident at first glance may still affect credibility of results. For this reason, referees of scientific journals sometimes require that a multivariate analysis of factors potentially able to influence the outcome is used, in order to adjust for these imbalances between the two study groups [59].

PROBLEMS IN THE ASSESSMENT OF TOXICITY

The evaluation of toxicity is problematic in these patient populations. According to the EC Guidelines on Good Medical Practice [60], an adverse drug reaction is defined as "a reaction which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of biological functions. In the case of clinical trials, interactions with other medicinal products should be considered as adverse drug reactions". This definition is hardly suitable for cancer patients, where a number of toxigenic factors, including the underlying disease, the type of infectious complication, the administration of chemotherapy and radiotherapy and the use of parenteral nutrition, tend to overlap, thus impairing the investigator's ability to detect specific drug-related side-effects. In addition, the fact that the detection of some adverse effects usually require a prolonged follow-up, further complicates the matter, since these particular patients may have already received additional courses of chemotherapy. It seems, therefore, realistic to conclude that optimal evaluation of antibiotic-related toxicity cannot be provided by studies performed in the population of cancer patients. This does not mean that an evaluation of toxicity should not be performed, but rather that the results of this evaluation cannot be readily extrapolated to other patient populations. In addition, since some biological functions may already be altered at randomisation, as a result of previous chemotherapy or radiotherapy cycles, the evaluation of toxicity should include any modification from baseline values and not only from normal values.

CLINICAL AND LABORATORY EVALUATIONS

Multicentre trials allow a larger patients' accrual and a larger representation of disease states and patients than single-centre studies. However, they have also some shortcomings that should be recognised. Among others, the problem of the uniformity in clinical and laboratory performance (especially in the microbiological laboratory) is tremendously important, especially in explanatory studies, since it might influence the study endpoint. In order to minimise discrepancies, pretrial meetings, aimed at making methods and definitions as uniform as possible, should be organised. In addition, a microbiological reference centre should be constituted, to centralise bacterial strains (at least those isolated from blood), in order to provide uniformity in pathogen identification and sensitivity testing and to check the quality of the group's work [31]. At the time of enrolment in a clinical trial of empirical antibiotic therapy, and then at least twice a week, each febrile, neutropenic patient should undergo a comprehensive clinical and laboratory evaluation, aimed at assessing eligibility criteria and infection documentation. In

addition to history and physical examination, laboratory evaluations should include haematological studies, coagulation, blood chemistry and urinalysis. Although this approach has never been proven cost-effective, most authorities recommend that all patients, regardless of symptoms, have a chest X-ray, at randomisation. Every effort should then be made to isolate the causative pathogen from blood or from any clinically suspected site of infection. The cultures should be taken before starting intravenous antibiotics and should include two or three blood cultures taken, if possible, both from the central intravenous line and from a peripheral vein (at least one of the three), urine culture and throat and oral swabs.

CONCLUSIONS

Clinical trials of empirical therapy in neutropenic, febrile patients, represent an important area of research, with major clinical and financial implications. The overall strategy of these trials should be reconsidered, taking into account the close relationship among the aims of a study, its design and the conclusions that can be drawn from its results. A more precise definition of the study aims appears to be necessary in the future, in order to prevent unwarranted conclusions from studies designed to answer different questions. A trial that is appropriately tailored on its aims, usually costs less, and offers more in terms of validity and generalisability of results.

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