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Management of infection in cancer patients: studies of the EORTC International Antimicrobial Therapy Group (IATG)

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Abstract

Infection remains an important cause of morbidity and mortality in cancer patients, especially those undergoing chemotherapy for haematological malignancies. The practice of instituting an empirical broad-spectrum antibiotic therapy as soon as possible after the onset of fever has substantially reduced the clinical impact of this complication. In the last 25 years, the International Antimicrobial Therapy Group of the European Organisation for Research and Treatment of Cancer (EORTC-IATG) have published nearly 30 articles and a number of abstracts on several facets of the epidemiology and management of infection in cancer patients. With a progressive methodological refinement, the EORTC-IATG trials have established the standard for the management of febrile neutropenia, both by setting methodologies and definitions and by testing several antibiotic regimens that are active and effective for this indication. With the aim of supporting a more rational use of antibiotics in cancer patients, the most recent trials have dealt with the management of low risk patients, showing the safety and feasibility of oral therapy.

Keywords: Cancer; Fever; Neutropenia; Infection; Clinical trial

1. Introduction

Infectious complications represent an important cause of morbidity and mortality in cancer patients, especially in those receiving chemotherapy [1]. In recent years, however, the management of these complications has improved greatly, especially in the field of bacterial infections. Among nearly 800 documented bacteraemias observed in the eight therapeutic trials (I, II, III, IV, V, VIII, IX and XI) performed by the International Antimicrobial Therapy Group of the European Organisation for Research and Treatment of Cancer (EORTC-IATG) from 1978 to 1994, the overall mortality rate decreased from 21 to 7%. In particular, the 30-day mortality rate from any cause in patients with Gram-negative and Gram-positive bacteraemia is now as low as 10 and 6%, respectively [2]. This represents a dramatic improvement compared with, for example, the findings of a classic study on Gram-negative bacteraemias performed in 1962, in which the mortality rate approached 90% [3], as well as to the first EORTC-IATG study performed in 1978, in which more than 20% of the patients with Gram-negative sepsis and about 15% of those with Gram-positive sepsis died [4]. Although the reasons for these improvements are likely multiple, the strategy calling for the rapid institution of empirical, broad-spectrum antibacterial therapy with very active antimicrobial compounds at the development of fever has no doubt played a pivotal role.

2. The EORTC-IATG

A few decades ago, a small group of investigators on both sides of the Atlantic realised that the studies performed until then on the management of fever during neutropenia, based on small numbers of patients, were absolutely inadequate for the demands of modern clinical research, and that only a large co-operative effort would afford the collection of meaningful information in the field of infections in the immunocompromised cancer patient. In 1973, within the framework of the EORTC, the IATG (formerly IATCG) was founded in order to study infections in cancer patients and to investigate which approach would best benefit the febrile

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neutropenic patient. The EORTC-IATG includes infectious disease and internal medicine specialists, oncologists, haematologists, and microbiologists from centres of several European and non-European countries. The internal organisation foresees a Management Board of elected members (Chairman, Chairman-elect, Treasurer and three at-large), appointed members (Deputy Treasurer, one financial advisor, and, if not among the above, the Data Review Committee Co-ordinator and ongoing Trial Co-ordinator) and *ex officio* members (Group Statistician and the Assistant to the Chairman). In addition, there are currently three standing sub-committees, dealing with educational/communication activities, research planning and clinical trial conduct. The Data Review Committee (DRC) is composed of the Trial Co-ordinator, the Statistician and the Data Manager, as well as a number of active Group members depending on their involvement. The DRC, which is responsible for the conduct of an ongoing trial, including quality control, meets approximately every other month at the Data Center to review all clinical reporting forms coming from the various centres participating in trials. The DRC also performs site visits, in compliance with Good Clinical Practice and EORTC Standard Operating Procedures.

3. The EORTC-IATG trials and publications

Since 1978, the EORTC-IATG has published nearly 30 articles and a number of abstracts on several facets of the epidemiology and management of infection in cancer patients. Eleven full papers reported the results of nine large therapeutic trials of empirical antibacterial therapy in febrile, neutropenic patients with cancer [4–14], two articles on the results of two trials of antibacterial prophylaxis of infection in neutropenic patients [15,16] and one article on empirical antifungal therapy [17]. In addition, exploiting the extensive database of episodes of febrile neutropenia collected over the years, the Group also published a study on factors associated with bacteraemia in febrile, granulocytopenic cancer patients [18], a study on the difference in clinical characteristics and outcome of febrile neutropenia in children and adults [19] and a study on the role of antifungal prophylaxis on the rate of bacteraemia as a cause of febrile neutropenia [20]. Finally, the Group authored a review, in which many definitions commonly used in this field were discussed and established, as well as a position paper on definitions and methodology [21,22]. Another therapeutic trial assessing the need of the empirical addition of a glycopeptide antibiotic in persistently febrile neutropenic cancer patients not responding to the initial antibiotic therapy was recently completed and published in abstract form [23]. In the following section, the results of trials V, VI, VIII, IX, XI and XII will be briefly reviewed. Trials I–IV were previously reviewed elsewhere [21]. The results of the last completed study (trial XIV) will not be reported in this article, as the manuscript is currently in preparation.

3.1. Trial V

Trial V was conceived and designed in 1986 as a response to the increasing role of Gram-positive cocci (*streptococci* and *staphylococci*) in causing infection in cancer patients and to their reduced response rate to several empirical regimens. The trial was published in early 1991 [9]. The hypothesis to test was whether the addition of vancomycin to ceftazidime and amikacin at the onset of fever would benefit the population of febrile neutropenic patients, because of an expected improved response rate of Gram-positive infections. Unfortunately, the study was not designed in a double-blind fashion. Briefly, 747 episodes of fever and neutropenia in patients with cancer were randomised to receive ceftazidime plus amikacin with or without vancomycin. Initially, a crude analysis of the results showed that the overall response rate in the group of patients receiving vancomycin was better than that seen in the control group (76% versus 63%, $P<0.001$) and that this was particularly evident in the population of patients with Gram-positive bacteraemias. However, after the reasons for establishing failure were analysed in detail in this patient population, it turned out that most of the failures were due to a lack of clinical response and persistence of fever, and that failure (i.e. treatment change) was established very early, after the onset of fever. In other words, failure was never documented by objective reasons, such as persistence of pathogen or development of septic shock, and only three infection-related deaths were reported (none in the first 3 days of empirical therapy). In addition, a comparison of the febrile days in the two treatment groups clearly showed that patients with fever of unknown origin (FUO) or with a Gram-positive infection, who were persistently febrile after 3 or 4 days of therapy, were treated differently based only on the antibiotic regimen they were receiving and irrespective of any objective clinical reasons. Thus, the better response rate in patients receiving ceftazidime/amikacin/vancomycin was only apparent and was not due to true failures, but only to attending physicians' discretion. This trial yielded important information on febrile neutropenia and how several haematologists and oncologists were used for managing these patients. It became clear that, the more prolonged neutropenia and fever were, the more likely it was that physicians added or replaced antibiotics even without objective reasons for doing so. The overall conclusion of this trial is that the data did not support the practice of including a glycopeptide antibiotic in the initial antibiotic regimen for febrile neutropenia.

3.2. Trial VI

This trial was based on the simple, but important concept that all febrile neutropenic patients are not the same; that patients at low risk of medical complications exist and might deserve a less intensive antibiotic approach. This trial, published in 1991 [10], compared monotherapy with ciprofloxacin at the low dosage (200–300 mg every 12 h) with combined therapy with piperacillin and amikacin in a selected population of febrile and neutropenic patients, such as those with lymphoma and solid tumours, normally considered to be at lower risk of severe infection in comparison to patients with acute leukaemia. The trial was prematurely discontinued because patients treated with ciprofloxacin had a statistically significantly poorer response rate than those in the control arm at an interim analysis (65% versus 95%, $P = 0.002$), with a 14.5% death rate in evaluable patients compared with 6% in the control arm. We speculated that this difference might have been due to the too low dosage of ciprofloxacin we were allowed to use by the drug company sponsoring the study [10]. The overall conclusion of this study was that low dosage of ciprofloxacin is inadequate for the management of febrile neutropenia, even in low-risk patients.

3.3. Trial VIII

Trial VIII was conceived and designed in 1989 and published in 1993 [11]. The objective was to show that febrile neutropenic patients could be treated successfully with an antibiotic regimen given once a day, with the obvious advantages of cost savings and patient convenience. A once-a-day antibiotic regimen could easily become an out-patient regimen as well. Specifically, a single, large daily dose of amikacin, in combination with a long-acting cephalosporin (ceftriaxone), also given once daily, was compared with a combination of amikacin and ceftazidime administered in three separate daily doses. The response rate among 350 episodes treated with the single-daily dose of ceftriaxone plus amikacin was 71%, compared with a 74% response in 344 patients treated with the classic amikacin-ceftazidime regimen given three times a day. Efficacy was similar in all patient subgroups, including patients with Gram-positive and Gram-negative bacteraemia. Toxicity results showed that the single, large daily dose of amikacin achieved higher peak levels (median 45.5 μg/ml), compared with the 8-h group. Nephrotoxicity was 3% in the single daily dose group versus 2% in the control group. Increase in serum creatinine was lower, occurred later and was primarily seen with other nephrotoxic agents in the 24-h group than in the 8-h group. Similarly, ototoxicity, which was measured in 144 patients (21% of the study sample), was not higher in the single daily dose group. The conclusions of this study were that amikacin, combined with a third-generation cephalosporin, could be given safely once daily, and that febrile neutropenic patients could be treated effectively with single daily antibiotic administrations.

3.4. Trial IX

Trial IX was conceived and designed in 1991 and was published in 1995 [12]. The objective of the study was to investigate whether an extended-spectrum penicillin combined with a beta-lactamase inhibitor, such as piperacillin-tazobactam, would improve the coverage of Gram-positive infections, yet retaining a good activity against Gram-negative bacteria, compared with ceftazidime plus amikacin. Briefly, piperacillin-tazobactam plus amikacin performed slightly better than ceftazidime plus amikacin (61% of 342 episodes compared with 54% of 364, $P = 0.05$). The conclusion was that piperacillin-tazobactam was a new important weapon for the management of febrile neutropenia, thus giving physicians more possible choices to tailor treatments. Beyond trial results, more important, perhaps, were the two methodological modifications we introduced for the definition of failure. Our previous studies had not established any policy regarding the isolation of a pathogen resistant to the allocated antibiotic(s) as cause of infection in a patient who nonetheless responded 'clinically' to the treatment. Some investigators were used to changing treatment regardless of any clinical consideration, while others opted for a more pragmatic approach, not changing therapy if the patient were responding clinically to treatment and the pathogen was eradicated. This discrepancy might have caused biases in the evaluation of treatment results in previous trials. For this reason, it was decided that infections caused by pathogens resistant to the allocated beta-lactam drug would be classified as failures, regardless of the patient's clinical evolution. This led to an improvement of our endpoint of failure, which became stronger, as well as to a logical reduction in response rates. The second modification entailed the patient population to analyse. In all previous EORTC-IATG trials, the analysis was not performed on all randomised episodes, but only on those considered 'evaluable' by the DRC. It became clear that this approach was no longer sound, and from trial IX onwards, results were reported both on 'evaluable' by the DRC (with the exclusion of fevers not related to infection, documented non-bacterial infections, toxicity-related discontinuations, and major protocol violations) and on all randomised and eligible patients in which response to treatment was assessable.

3.5. Trial XI

In this trial, two methodological innovations regarding randomisation procedures were introduced. Previous

trials had allowed for the randomisation of a patient more than once for different febrile episodes, provided that these did not occur during the same period of neutropenia. This approach had drawn the criticism of some peer reviewers, as it was deemed a potential bias of results. Therefore, from Trial XI onwards, only one randomisation per patient was allowed. Moreover, randomisation in previous trials had not been centralised and had been performed at every participating centre by opening consecutive envelopes, sealed and numbered by the DRC. Starting with Trial XV (1994), a central randomisation system was implemented. In this trial, patients were enrolled and randomised centrally by calling the EORTC-IATG randomisation computer at the Institut Jules Bordet in Brussels. The computerised randomisation system is accessible 24 hours a day, 7 days a week using a touch-tone phone and a vocal interface card installed in the computer.

Trial XI was performed in collaboration with the Infection Program of the *Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto* (GIMEMA) and was designed to provide a definitive answer to the question surrounding the efficacy of monotherapy versus combined therapy. Meropenem was compared with ceftazidime plus amikacin. Of 1034 randomised patients, 953 were evaluated, including patients in whom treatment was changed without adequate reason, non-bacterial infections and fevers not related to infection, but excluding 47 patients who were randomised despite being non-eligible and 29 patients in which response to treatment could not be assessed. As published in 1996 [13], treatment was successful in 270 of 483 (56%) patients receiving meropenem and in 245 of 475 (52%) patients receiving combination therapy. The success rates were similar by type of infection and by underlying disease. Mortality was very low (1.6% in the meropenem group and 2.7% in the ceftazidime/amikacin group). This study showed unequivocally that monotherapy with meropenem was effective and safe.

3.6. Trial XII

The concept that patients with cancer, granulocytopenia and fever are not all the same, and that there are patients who might deserve an individualised approach (less or more intensive) had already been addressed in Trial VI. In the following years, additional evidence was provided by several investigators showing that low-risk patients may be treated with simplified approaches. In trial XII, we wondered if oral therapy might have been a safe approach in these patients. Trial XII, published in 1999 [14], was designed as the first randomised, multicentre study aimed at determining whether oral empirical therapy with amoxicillin-clavulanate plus ciprofloxacin was comparably safe and effective in low-risk patients with febrile neutropenia as the classical intravenous ceftriaxone-amikacin combination. Only patients with solid tumours, lymphoma and chronic leukaemia, whose granulocytopenia was expected to resolve in 10 days, were included in this study. The trial was terminated at the second interim analysis with 353 patients enrolled. In the intention-to-treat analysis, success was demonstrated in 80% of patients receiving the oral regimen versus 77% of those treated with intravenous therapy. As expected, in both cases, patients receiving the oral combination had an higher incidence of gastrointestinal adverse events, while those receiving the intravenous combination more often had problems related to the central catheter. The results of this trial showed that oral antibiotics may safely substitute intravenous antibiotics in low-risk patients with fever and neutropenia. Moreover, this study—which, it is important to bear in mind, was conducted in hospitalised patients only—also provided relevant data on convenient new ways of treating fever and neutropenia in patients with cancer.

3.7. Trial XIV

The addition of a glycopeptide antibiotic has become common clinical practice in granulocytopenic patients with persistent fever, despite the absence of clinical deterioration and/or the documentation of an infection due to a micro-organism resistant to the allocated regimen. However, no study has documented that this empirical approach is of any true benefit in these patients. In addition, the indiscriminate use of glycopeptides is expensive and might result in the emergence of resistance among *staphylococci* and *enterococci*, which would have major clinical implications. Trial XIV was designed as a prospective, randomised, multicentre, double-blind trial aimed at testing the clinical impact of adding vancomycin between 48 and 60 h after the start of empiric piperacillin/tazobactam monotherapy in high-risk cancer patients with persistent fever and granulocytopenia. The results of this study have recently been presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2001) [23] and the manuscript is currently in preparation.

3.8. The next IATG trial

To improve our ability to reliably identify low-risk patients is a key priority for our Group. Recently, the issue was addressed by a study performed by the Multinational Association for Supportive Care in Cancer (MASCC), which validated a risk prediction score, able to correctly identify low-risk patients with sensitivity/specificity values of 78–74% or 92–51%, depending on the score used [24]. This score will be adopted in our next study to select low-risk patients. The next EORTC-IATG trial (whose protocol was

approved in the fall of 2001 by the EORTC Protocol Review Committee) will be a double-blind, prospective, randomised, multinational, multicentre trial assessing the efficacy of a once-daily oral therapy for low-risk febrile neutropenia. An important feature of this trial is that, for the first time, investigators will be given the possibility to discharge patients and to continue therapy at home, on an outpatient basis. Moxifloxacin, a new extended-spectrum fluoroquinolone with a half-life allowing once-daily dosing, will be used for oral monotherapy. This regimen will be compared with combination therapy with ciprofloxacin plus amoxicillin/clavulanic acid.

4. Conclusion

Since its inception, the EORTC-IATG has set an excellent track record, reflected by a remarkable series of articles published in renowned scientific journals, in the conduct of clinical research for the prevention and management of infectious complications in cancer patients. These trials have set the standards for the clinical management of febrile neutropenia in cancer patients. All definitions that are presently used worldwide in studies of febrile neutropenia are based on EORTC-IATG definitions [25]. However, several issues pertinent to the improvement of anti-infective care in cancer patients are still unsettled. Although mortality is relatively low and most likely strongly related to the degree of control of the underlying disease, morbidity is still high.

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