INFECTIONS IN HEMATOLOGICAL MALIGAIANCIES

Febrile neutropenia—Seven frequently asked questions and answers

VLADIMIR KRCMERY, Jr. & PAVOL BENO

St. Elisabeth University of Health and Social Sci., Bratislava, Slovakia and St. Elisabeth Cancer Institute, Bratislava, Slovakia

Introduction

Febrile neutropenia (FN) is one of the commonest complications of antineoplastic chemotherapy. New antimicrobials and new strategies created by the EORTC Antimicrobial and Invasive Fungal Infections cooperative groups, and MASCC (Multinational Association of Supportive Care in Cancer) [1–14] have been successful in decreasing the mortality from 15–20% in 1960–1980 to 2–5% in 2000–2004 [12–14]. Within last 5 years however many new strategies were introduced. Here are the most frequently asked questions/FAQs concerning FN:

1. Is there a change in etiology of infections in cancer patients?
2. Is there an increase of antimicrobial resistance among pathogen in FN?
3. Is prophylaxis with antimicrobials necessary?
4. Is combination therapy with aminoglycosides better than monotherapy?
5. Is addition of an glycopeptide in empiric therapy necessary?
6. Is oral therapy possible?
7. Do we need new antibiotics or new strategies?

Those are frequent questions asked by oncologists and hematologists to ID and microbiology staff, and always new questions will arise.

Is there a change in etiology?

In 1960–1980, first EORTC studies showed predominant gramnegative etiology [1–5]. In 1990–2000 grampositive cocci, mainly *streptococci* and *viridans streptococci* represented up to 70% of all bloodstream isolates, probably because of quinolones were introduced for prophylaxis supressing gramnegative bowel flora. Nowadays, again, gramnegative bacilli are emerging, mainly *Pseudomonas aeruginosa* and *Enterobacteriaceae*, represents about 50% of all documented infections [11–14]. Yeasts since 1980 and molds after 1990 are emerging as well, and represents more than 10% of all isolates, mainly in profoundly neutropenic patients after BMT and those with acute leukemia [15].

Is there an increase of resistance?

Is antimicrobial resistance in isolates from cancer patients a real problem or is just a propaganda of fear from the microbiologists? In 1990–2000, there was a significant increase of betalactam (methicillin, ampicillin and penicillin) resistance in *Streptococi* (MET, OXA), *viridans streptococci* (PEN) and *Enterococci* (AMP) probably due to empiric therapy with cephalosporins and penicillins (plus aminoglycosides) proven in first EORTC trials [1–10]. *E. scherichia coli* resistant to ciprofloxacin emerged after 1992 due to massive use of quinolones in prophylaxis [16]. Similarly, however in much less extend non albicans *Candida* spp. With decreased susceptibility to azoles emerged, possibly because large use of ketoconazol, fluconazol and itraconazol prophylaxis in leukemia and BMT [15]. All those resistance pathways were controlled due to increased use of glycopeptides (vancomycin, teicoplanin) and oxazolidinons (linezolid). Voriconazol decreased unacceptably high mortality in *C. glabrata*, *C. krusei* and *Aspergillus/Fusarium* spp. infections. However, because of much less innovation in new strategies (prevention other than chemoprophylaxis) and new antigramnegative compounds (meropenem was the last one, 18 years ago!). Multiresistant gramnegative bacilli such as meropenem resistant *Ps. aeruginosa* and *Acinetobacter baumanii*, quinolone resist. *E. coli* and ESBL positive (including cefepime resistant *Klebsiella/Enterobacter*,...
and voriconazol resistant \textit{Zygomycetales (Mucorales)} emerged within the last 5 years. Last year isolates resistant even to colimycin (\textit{Ps. aeruginosa}) emerged, and those organisms were resistant to all available antibiotics, so 2004/2005 are the first years of post-antibiotic era [17].

Is antibiotic prophylaxis necessary?

EORTC study (trial IX) documented borderline efficacy of quinolones plus V-Penicillin in prevention during afibrile neutropenia in 503 patients and since this time 1992 most centers uses oral quinolones in long lasting and profound neutropenia, in combination with fluconazol when Slavin et al. in 1995 reported decrease of mortality in BMT patients in ciprofloxacin plus fluconazol prophylaxis [18]. When Cruciani et al. [19] summarized in metaanalysis in 1996, 19 randomized studies with 2112 patients, and showed no benefit on mortality (despite decrease of grampositive bacteremia) a more conservative approach is advisable.

Akova et al. in 2005 from Turkey, on behalf on EORTC group [20] documented that superinfections and breakthrough bacteremias/fungaemias (occurring despite of quinolone or azole prophylaxis), are associated with higher mortality (5.5 vs. 2.6%, \(P < 0.001\)). In addition, resistance in \(E.\) \textit{coli} to ciprofloxacin in same hematologic units increased from 1 to 15–20%. Therefore growth factors, isolation/cohortation, LAF and other non-antibiotic strategies are advisable. Antifungal chemoprophylaxis in centers without emergence of azole resistant \textit{Candida} spp., \textit{Aspergillus} and \textit{Mucorales} with fluconazol or voriconazol may be still usefull in combination with other regimen-based strategies such as sterilisation, disinfection, isolation and microbiologic surveillance. However, new “anti-grampositive” quinolones may bring a new approach also into the field of “classical” chemoprophylaxis. Renter et al. after 10 years of Cruciani et al. meta-analysis showed significant benefit of levofloxacin in both prevention of infections and also reduction of mortality [21].

Is combination with aminoglycoside better than monotherapy?

Several meta-analyses published by at least 3 groups showed no benefit of adding an aminoglycoside to cephalosporin on piperacillin [22,23] within the last 3 years analysing 7807 neutropenic and 7586 other bacteremic patients showing no benefit on mortality, but higher toxicity related with combination therapy. The results of EORTC ATCG study from 1987 [5] favoring long course of amikacin in bacteremia and FN cannot be extrapolated to clinical practice anymore. However, this EORTC study [5] was done at a time with much less potents betalactams (no IV generation cephalosporins and carbapenems were available in 1987) and much less AGL resistance, than 18 years later.

In addition, another meta-analysis [23] showed no benefit on prevention or decrease of ATB resistance in those receiving combination therapy. Therefore, monotherapy with betalactam (IV gen. cephalosporins, carbapenem, piperacillin-tazobactam) is less toxic, equally effective and not related with high resistance and adding an aminoglycoside is not necessary in empiric therapy of febrile neutropenia and should be used only in cases of documented \textit{Ps. aeruginosa} or other MRGN bacteremia upon susceptibility results.

Is addition of a glycopeptide in empiric therapy necessary?

Similarly to the previous question, the answer is no. Early EORTC study from 1991 [8] did not support the initial use of glycopeptide. Vardakas et al. [24] 15 years later summarized results of 2413 patients and showed that despite initial vancomycin, added to betalactam was related to better outcome (OR 1.63) in those with bacteremia and severe leukemia. Overall treatment success was similar [24]. Last published EORTC study in 2003 [14] favored to demonstrate that, addition of vancomycin is of benefit in febrile neutropenia [14]. Therefore, use of glycopeptides or oxazolidinons should be limited only to documented grampositive bacteremia due to MRSA or Amp/Gen–resistant \textit{Enterococci}, PEN-R \textit{viridans streptococci} and other multiresistant grampositive cocci.

Is oral therapy possible?

There were several attempts to simplify initial combination intravenous therapy with a betalactam plus aminoglycoside during last 30 years. In 1991, EORTC the first study trying to demonstrate equality of ciprofloxacin monotherapy (intravenous) failed, so 2 years later the scientific community was hapy to demonstrate, that once-a-day regimen (ceftriaxon plus amikacin) is equally effective than thrice (3x) daily. Second step was monotherapy study with carbapenem [12] and piperacillin-tazobactam [14] showing that monotherapy is equal to combination therapy. During those studies, stratification studies has been conducted both in US [25] and MASCC in Europe [26] trying to identify subpopulation of patients, who may not need intravenous antibiotics. Such a group of patients was previously defined as “low risk group” (without stomatitis, catheters, hypotension, old age, etc.) and “historical” first study [13] showed the possibility to treat such low risk group of febrile neutropenia patients with oral ciprofloxacin plus amoxicillin/clavulanate. Next step was undertaken within the last 3 years by the EORTC
study with a design of “oral monotherapy” study with moxifloxacin, however, the preliminary results will be available in 2006.

Explosion of new antibiotics and antifungals: Do we need new molecules or new strategies?

Last EORTC studies showed, that trials with “new molecules” are not always the solution of particular problems with febrile neutropenia, because they being only temporary solution (until resistance emerges).

If we look to the design of EORTC ATCG or IFICG (antimicrobial and invasive fungal infections therapy cooperative groups) from 14 studies, 6 are on new strategies (e.g., monotherapy versus combination, or oral versus intravenous, etc.). After 1990 an explosion of new antibacterial agents has been noted accompanied by advent of 6 new antifungals after explosion of new antibacterial agents has been noted. Unfortunately, all antibiotics, developed after 1990 were developed only for management of grampositive multiresistant cocci – 4 new quinolones against PEN-R pneumococci, oxazolidinons against MRSE, daptomycin and tigecyclin against MRSA and VRE, quinupristin/dalfopristin against VRE and PRP. Six new antifungals (3 new azoles – Voriconazol against Aspergillus, Fusarium and Non albicans Candida, Ravuconazol and Posaconazol against Mucorales and Aspergillus, Caspofungin, Micafungin and Anidulafungin against Aspergillus) came to the drug market within the last 3 years. Both group of molecules were successful in decreasing the mortality of gramppositive bacteremia, and after 17 years from the first EORTC “fungal” study in 1989 [6] also mortality on mold infections [27–30]. New antifungals, mainly lipid formulation of Amphotericin B and new azoles, are expensive, and therefore again search for preventive strategies and/or early diagnosis and dosing optimization [28] are advisable. The problem however is that from 12 new group of “molecules”, introduced after 1990, none is against grampnegative bacteria, and therefore we have currently nothing against meropenem and colimycin resistant Pseudomonas aeruginosa and Acinetobacter baumanii.

Conclusion

We have limited our mini review to 7 most frequently asked questions, what we receive from oncologists and hematologists. We did not have space to answer problems of antiviral therapy what requires separate review and only marginally discussed fungal infections. Despite limitations, some answers are better than none, because the slogan “no news – good news et al.” used in diplomacy and politology is not valid in management of FN.

References


1499