

Practical approach by main clinical syndromes

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Top-ten infections in onco-hematological patients (2015-2017)

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ABSTRACT

To choose the most relevant ten papers constitutes a challenge in several ways. We have elaborated this selection based on the papers we find to be most useful and ground-breaking for the clinician faced daily by the infectious problems in onco-hematological patients. The selection has been structured in four parts: bacterial infections, viral infections, fungal infections and infections related with new drugs in onco-hematological patients.

Key Words: bacterial infections, letermovir, aspergillosis.

Los mejores artículos de infecciones en el paciente oncohematológico

RESUMEN

Establecer que artículos son los "los top-ten" es difícil en varios aspectos. Hemos establecido esta selección basándonos en lo que hemos considerado más útil y novedoso en el conocimiento de la patología infecciosa en el paciente oncohematológico. Hemos estructurado la selección de los mismos en cuatro apartados: infección bacteriana, infección vírica, infección fúngica e infecciones relacionadas con los nuevos tratamientos en pacientes oncohematológicos.

Palabras Clave: infecciones bacterianas, letermovir, aspergilosis

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INTRODUCTION

During the last two years, a significative number of papers have been published on the field of infection in onco-hematological patients. To choose the most relevant ten papers constitutes a challenge in several ways. On one hand, the subjectivity of the author is unavoidable; an apparently less relevant article may, to the eyes the author, contribute with more fresh and useful ideas than one published in one of the top journals. Furthermore, on the other hand, there may be a relevant article that we forget to highlight.

Therefore, we have elaborated this selection based on the papers we find to be most useful and ground-breaking for the clinician faced daily by the infectious problems in onco-hematological patients. I apologize in advance if you do not find a paper you considered to be better or more relevant than the mentioned in the following selection.

This selection has been structured in four parts. First, we will comment the most innovative papers on bacterial infection and especially on the crucial topic of the development of antibiotic resistance in the onco-hematological patients and how to face this challenge. In a second part we will review an article on viral infection. In the third part we will review what is new in fungal infection, mainly on new risk populations and the raise in *Pneumocystis jirovecii* infections in onco-hematological patients. Finally, we will comment papers referring to new drugs for the management of onco-hematological diseases and how may they relate to the risk of infection. After each of the four sections, we will sum up the most relevant messages.

BACTERIAL INFECTIONS

The increasing number of infections caused by multi-drug resistant bacteria (MDRB) constitutes a major problem. This fact is of especial relevance in onco-hematological patients.

Given their disease and the treatments received, these patients often present significant immunosuppression. This leads to numerous infections, thus requiring frequent and prolonged antibiotic exposure. A better knowledge on epidemiology of these infections and the development and implementation of measures to reduce antibiotic resistance are crucial.

In the first study, signed by Averbuch et al [1] all Gram-negative rod resistant (GNR) bacteremias occurring during 6 months post-HSCT (2/14-5/15) were prospectively collected and analyzed for rates and risk factors for resistance to fluoroquinolones, noncarbapenem anti-*Pseudomonas* β -lactams (noncarbapenems), carbapenems, and multidrug resistance. Sixty-five centres from 25 countries (mostly from Europe) participated in the study, reporting data on 655 GNR episodes and 704 pathogens in 591 patients (Enterobacteriaceae, 73%; nonfermentative rods, 24%; and 3% others). Half of GNRs were fluoroquinolone and noncarbapenem resistant; 18.5% carbapenem resistant; 35.2% multidrug resistant. The total resistance rates were higher in allo- geneic HSCT (allo-HSCT) vs. autologous HSCT (auto-HSCT) patients ($P < .001$) but similar in community-acquired infections. Noncarbapenem resistance and multidrug resistance were higher in auto-HSCT patients in centers providing vs. not providing fluoroquinolone prophylaxis ($P < 0.01$). Resistance rates were higher in southeast vs. northwest Europe and similar in children and adults. Non-*Klebsiella* Enterobacteriaceae were rarely carbapenem resistant. Multivariable analysis revealed resistance risk factors in allo-HSCT patients: fluoroquinolone resistance: adult, prolonged neutropenia, breakthrough on fluoroquinolones; noncarbapenem resistance: hospital-acquired infection, breakthrough on noncarbapenems or other antibiotics (excluding fluoroquinolones, noncarbapenems, carbapenems), donor type; carbapenem resistance: breakthrough on carbapenem, longer hospitalization, intensive care unit, previous other antibiotic therapy; multidrug resistance: longer hospitalization, breakthrough on β -lactam/ β -lactamase inhibitors, and carbapenems. Inappropriate empiric therapy and mortality were significantly more common in infections caused by resistant bacteria. In summary, the study questions the recommendation of fluoroquinolone prophylaxis and emphasizes the necessity of empiric antibiotic protocols based on the knowledge of resistances of each centre.

Gudiol et al [2], signed the second study where β -lactam/ β -lactamase inhibitors (BLBLIs) were compared to carbapenems in two cohorts of hematological neutropenic patients with extended-spectrum- β -lactamase (ESBL) bloodstream infection (BSI): the empirical therapy cohort (174 patients) and the definitive therapy cohort (251 patients). The 30-day case fatality rates and other secondary outcomes were similar in the two therapy groups of the two cohorts and also in the propensity-matched cohorts. BLBLIs, if active *in vitro*, might be carbapenem- sparing alternatives for the treatment of BSI due to ESBLs in high-risk hematological patients. This strategy may prove useful in limiting the spread of carbapenem resistance in this high-risk population.

The last study lead by Aguilar-Guisado et al [3], also from

Spain, proposes a useful approach to reduce unnecessary exposure to antimicrobials and demonstrates that in high-risk patients with haematological malignancies and febrile neutropenia, empirical antibiotic therapy (EAT) can be discontinued after 72 h of apyrexia and clinical recovery irrespective of their neutrophil count. In four years, 157 episodes among 709 patients assessed for eligibility were randomized (78 to stop EAT after 72 h or more of apyrexia plus clinical recovery and 79 to the control group- when neutropenia was recovered). The mean number of EAT-free days was significantly higher in the experimental group than in the control group. One patient died in the experimental group (from hepatic veno-occlusive disease after an allogeneic haemopoietic stem-cell transplantation) and three died in the control group (one from multorgan failure, one from invasive pulmonary aspergillosis, and one from a post-chemotherapy intestinal perforation).

VIRAL INFECTIONS

Cytomegalovirus (CMV) infection is a leading cause of illness and death in patients who have undergone allogeneic hematopoietic-cell transplantation. Over the past 20 years, clinicians have adopted a preemptive strategy. Thus, the development of safe and effective antiviral agents for CMV prophylaxis remains a major goal in transplantation.

Letemovir is an antiviral agent that inhibits CMV replication by binding to components of the terminase complex (UL51, UL56, or both), at a dose of 240 mg per day was highly effective in preventing CMV viremia after engraftment in a study published in 2014 [4]. Three years later, a phase 3, randomized, double-blind, placebo-controlled, superiority trial [5], resulted in a significantly lower risk of clinically significant CMV infection than placebo (122 of 325 patients [37.5%] vs. 103 of 170 [60.6%], $P < 0.001$). The frequency and severity of adverse events were similar in the two groups. All-cause mortality at week 48 after transplantation was 20.9% among letermovir recipients and 25.5% among placebo recipients.

So, letermovir is a safe and effective drug for preventing CMV infection when used through day 100 after transplantation.

FUNGAL INFECTIONS

With the use of prophylaxis in high-risk hematological patients, the incidence of invasive aspergillosis (IA) has reduced in this group to below 3% [6]. On the other hand, with the use of new targeted or immunomodulatory drugs in the management of hematological malignancies an increase of IA is observed in patients considered of medium-low risk for fungal infection. We chose two articles, both of them from Livio Pagano's group focusing on the epidemiological changes based on the host.

In the first of them [7] is a unicentric, retrospective study that demonstrates that the new treatment strategies in lymphoproliferative disorders, including immunomodulating and

immunosuppressive agents, in addition to cytotoxic treatments and a more frequent application of autologous HSCT have caused an increased risk of IFIs among these patients. In this study, it seems particularly evident in MM and aggressive NHL patients, particularly when after HSCT. These changes in the epidemiology induced to modify the diagnostic workup for IFIs, now more frequent than in the past, in these patients. Although the incidence of IFI is below 5%, it is quite higher than the observed in these same patients 10 years before. Prospective studies are required to evaluate the potential usefulness of prophylaxis in these patient groups.

In the second study [8], the same group analyzed the current data regarding the epidemiology of and risk factors for IFIs in patients with HMs. The concept "non-static level of risk" for IFI is an interesting contribution. For instance, the risk of IFI could be low in patients at the time of diagnosis of the underlying hematological malignancy, while in the following months, the same patient could be considered at high risk in the case of non-responsiveness to the anti-neoplastic treatment. This review might offer a useful tool for designing future studies with the aim of optimizing the diagnostic procedures and therapeutic strategies for preventing and treating IFIs in patients with hematological malignancies.

Pneumocystis jirovecii (PJ) pneumonia is often diagnosed in onco-hematological patients undergoing chemotherapy or targeted therapies, frequently in combination with systemic steroids, that even in doses as low as the equivalent of 20 mg of prednisone a day for four weeks constitute an important risk factor [9]. In addition, PJ pneumonia in these patients presents distinctive features including higher mortality that may be aggravated by a later diagnosis and delayed treatment. On the other hand, indications for prophylaxis in oncological patients are not well established. ECIL guidelines have published three papers regarding epidemiology [10], treatment [11] and prophylaxis [12] of PJ pneumonia in hematological patients.

The following publications have provided more new data on this condition:

Takemoto et al [13], knowing that PJ can colonize in the lower airway and the air vesicles of some healthy individuals, analyzed the presence of PJ DNA with a nested PCR technique in bronchoalveolar lavage samples among outpatients during cancer chemotherapies and compared it with healthy controls. PJ DNA was detectable in 46% of specimens from cancer patients undergoing chemotherapy, and it was not significantly different among types of cancer and chemotherapy regimens. Detection of PJ DNA was lower among healthy non-smokers (20%) and high among healthy smokers (47%). They conclude that quit smoking and antibiotic prophylaxis may be necessary for cancer patients during chemotherapy.

In another study [14], as much as 27% of HIV-negative patients with PJ pneumonia presented with more than 200 / μ L CD4+ lymphocytes, thus questioning this threshold for prophylaxis frequently used in HIV-positive patients.

As a personal opinion, due to the lack of solid clinical data, prophylaxis should be considered in patients receiving immu-

nosuppressive treatment or chemotherapy, prolonged treatment of steroid and/or present persistent lymphopenia.

NEW TREATMENTS FOR THE MANAGEMENT OF ONCO-HEMATOLOGICAL DISEASES AND ITS IMPACT IN INFECTION

It is difficult to establish the risk of infection associated with a specific directed therapy due to the high number of confounders. In the first place, the onco-hematological condition itself is often associated with a higher number of infections, sometimes caused by opportunist pathogens. In the second place, treatments previously received by the patient may have a persistent effect on the immunitary system, even long after its interruption. Additionally, treatments administered for counteracting the adverse effects of these drugs, such as steroids, may further influence the risk of infection. Finally, a high number of patients receiving the treatment for a long time would be necessary, in conjunction with a significant number of infectious events, to establish an exact quantification of the risk.

An excellent review about risk of infectious complications in hemato-oncological patients treated with kinase inhibitors has been published by Reinwald et al [15] and is summarized in table 1. Recent publications have also focused its attention on ibrutinib and the increase in the incidence of fungal infections. Chamilos et al [16] presented opportunistic infections caused by *P. jirovecii* and *Cryptococcus neoformans*, ubiquitous airborne fungi in patients undergoing ibrutinib, with hematological cancers historically considered at low risk for IFI. The spectrum and severity of IFI observed in these patients implies the presence of a complex immunodeficiency that may not be solely attributed to mere inhibition of Bruton tyrosine kinase. When aspergillosis occurred, it was more frequently observed within the first 4 months of treatment and affected more frequently in patients with central nervous system disease (primary central nervous system lymphoma), also receiving steroids (71%) and with refractory or relapsed malignancies (100% of cases).

The risk of infection among patients receiving immune checkpoint blockade is unknown. After reviewing medical records of 740 patients with melanoma who received immune checkpoint blockers, del Castillo et al [17] concluded that serious infection occurred in 54 patients (7.3%). The main risk factors were treatment with corticosteroids and/or infliximab to handle complications associated with immune related adverse events. Future studies will need to address the best approach to prevent infectious complications in these patients; cotrimoxazole prophylaxis is recommended when steroids are initiated. Aspergillosis and CMV enterocolitis need also to be in consideration when adverse events are treated with immunosuppressors.

A French group [18] reviewed 2 cases of tuberculosis reported to French data-base of adverse events related with biological drugs in onco-hematological patients and 3 more pub-

Table 1 TK inhibitors, related infections and recommended prophylaxis. Modified from Reinwald M, et al [15].

Pathway target inhibitor	Drugs	Indicative infections related to drug	Possible prophylaxis recommended
BCR-ABL	Imatinib, Dasatinib, Nilotinib, ponatinib, Bosutinib	HSV, CMV and Hepatitis reactivation, Neutropenic fever Upper Respiratory tract Infections	May be considered
BCR-Pathway-inhibitory	Ibrutinib, Idelalisib	Pneumonia Upper Respiratory tract Infections	May be considered
mTOR	Temsirolimus, Everolimus	VZV and HSV reactivation Invasive Aspergilosis <i>Pneumocystis jiroveci</i> Pneumonia	Aciclovir and Cotrimoxazole must be considered
JAK	Ruxolitinib, Tofactinib	None specific	Aciclovir and Cotrimoxazole must be considered
EGFR-ALK	Erlotinib, Gefitinib, Afatinib, Crizotinib, Ceritinib	Upper Respiratory tract Infections	None
Multikinase (esp VEGF)	Sorafenib, Sunitinib, Regorafenib, Axitinib, Pazopanib	VZV and HSV reactivation Invasive Aspergilosis <i>Pneumocystis jiroveci</i> Pneumonia	None
BRAF/MEK	Vemurafenib, Dabrafenib, Trametinib	None specific	None

lished. Although tuberculosis seems to be rare (1/1000 patients in France), its reactivation may be favored by the specific action of anti PD-1 agents. All patients should probably be tested with an IGRA before the initiation of anti PD-1 treatment, and closer collaboration between infectious disease specialists and oncologists is advisable.

We are at the beginning of a new period in medical history. New drugs are being added to the onco-hematological armamentarium every day, and most of them have an immunomodulatory effect. We must learn its negative effects on the defense against infections and how to manage them, we have to think about the infections in new populations of risk, and most important of all, we have to keep working in multidisciplinary teams for the benefit of our patients.

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