Management of infectious complications in multiple myeloma patients: Expert panel consensus-based recommendations

Corrado Girmenia, Michele Cavo, Massimo Offidani, Francesco Scaglione, Alessandro Corso, Francesco Di Raimondo, Pellegrino Musto, Maria Teresa Petrucci, Giovanni Barosi

PII: S0268-960X(18)30073-0
DOI: https://doi.org/10.1016/j.blre.2019.01.001
Reference: YBLRE 561
To appear in: *Blood Reviews*

Please cite this article as: Corrado Girmenia, Michele Cavo, Massimo Offidani, Francesco Scaglione, Alessandro Corso, Francesco Di Raimondo, Pellegrino Musto, Maria Teresa Petrucci, Giovanni Barosi , Management of infectious complications in multiple myeloma patients: Expert panel consensus-based recommendations. Yblre (2019), https://doi.org/10.1016/j.blre.2019.01.001

Management of infectious complications in multiple myeloma patients: expert panel consensus-based recommendations

Corrado Girmenia[1], Michele Cavo[2], Massimo Offidani[3], Francesco Scaglione[4], Alessandro Corso[5], Francesco Di Raimondo[6], Pellegrino Musto[7], Maria Teresa Petrucci[1], Giovanni Barosi[8]

[1.] Dipartimento di Ematologia, Oncologia, e Dermatologia, Azienda Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

[2.] 'Seràgnoli' Institute of Hematology, Bologna University School of Medicine, Bologna, Italy.

[3.] Clinica di Ematologia , Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona, Ancona , Italy

[4.] Department of Oncology and Hemato-oncology, Università degli Studi di Milano, Milan, Italy

[5.] Division of Hematology, Fondazione IRCCS - Policlinico San Matteo, Pavia, Italy

[6.] Division of Hematology, Azienda Policlinico-Vittorio Emanuele-Catania, and Department of Biomedicine and Molecular Medicine, University of Catania, Catania, Italy

[7.] Scientific Direction, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (Pz), Italy

[8.] Center for the Study of Myelofibrosis. IRCCS Policlinico S. Matteo Foundation. Pavia, Italy

Key words: multiple myeloma, infections, prophylaxis, vaccination

Corresponding author:
Corrado Girmenia
Dipartimento di Ematologia, Oncologia e Dermatologia, Azienda Policlinico Umberto I, Sapienza University of Rome
Via Benevento 6, 00161 Rome, Italy
Phone: +39-06857951
E-mail: girmenia@bce.uniroma1.it

Abstract

The introduction of new therapeutic agents in multiple myeloma (MM), including proteasome inhibitors, immunoregulatory drugs and monoclonal antibodies, has improved the outcomes of patients, but in parallel has changed the frequency and epidemiology of infections. Hence, the great strides in the indications and use of new active treatments for MM need parallel progresses on the best approach to prophylaxis and supportive therapy for infections. Moving from the recognition that the above issue represents an unmet clinical need in MM, an expert panel assessed the scientific literature and composed a framework of recommendations for optimal infection control in patients candidate to active treatment for MM. The present publication represents a consensus document from questionnaires and consensus meetings held during 2017. The issues tackled in the project dealt with: infectious risk assessment, risk management and prophylaxis, intravenous immunoglobulin replacement therapy, antiviral and antibacterial vaccination. Considering the lack of conclusive and/or enough large studies for certain topics several recommendations derived from the personal experience of the experts.

1. Introduction

In the last decades, the advent of new therapeutic agents including proteasome-inhibitors (PI), immunoregulatory drugs (IMiD) and monoclonal antibodies has improved the outcomes of patients with multiple myeloma (MM) [1,2]. These drugs are characterized by effects on the immune system different from those of conventional anti-MM agents. In addition, these drugs are usually combined with intermediate- or high-dose dexamethasone, resulting in impairment of cell-mediated immunity [2]. With this shift of treatment paradigm, patients with MM are at risk of infection, and infections continue to be a major cause of morbidity and mortality in MM. [3] Hence, the great strides in the indications and use of new treatments need parallel progress in the best approach to prophylaxis and supportive treatment for infections.

In view of these considerations, a panel of experts was convened to exploit a project aimed to provide useful guidelines for the management of the infectious complications of MM. The present publication represents a consensus document from a series of meetings held during 2017 and email correspondence. A challenging problem in the interpretation of the literature data on the infectious complications in MM is the not homogeneous definition of the infections and of the infectious risks, furthermore the lack of conclusive and/or enough large studies for certain topics made it difficult to make evidence based recommendations. Consequently most of recommendations on the management of infectious complications in MM are based on the personal experience of the experts.

We hope these recommendations will help to minimize adverse events, and we believe that an optimal management of them will be rewarded by better outcomes, and better quality of life.

2. Design and methods

Two chairmen (CG and GB) appointed an Expert Panel of 7 members, selected for who had previously published and/or expressed an interest in infection complications in MM. During an initial meeting, the EP agreed on the areas of major concern in the risk of infections in MM by generating and rank-ordering clinical key-questions using the criterion of clinical relevance, through a Delphi process [4]. The following four candidate key-questions formed the set of questions of the present document: “infectious risk assessment”, “risk management and prophylaxis”, “intravenous immunoglobulin replacement therapy” and “vaccinations”. During a second meeting, the EP examined the current state of knowledge regarding infections and MM. Then, each panelist drafted statements that addressed one or more of the preliminarily identified key questions. Subsequently,

each panelist scored his agreement with the statements made by other panelists and provided suggestions for rephrasing. The overall goals of the meetings were to reach a definite consensus over question-specific statement for which there was disagreement. According to the nominal group technique, participants first commented in round-robin fashion their preliminary votes and then a new vote was proposed [5]. At least 80% consensus on the statement should have been obtained, otherwise the choices were discussed again and a second vote taken. If an 80% consensus was still not attained, no further attempt was made declaring the issue undecidable. Recommendations were specifically given considering the time and type of MM therapy according to the current MM treatment guidelines [6,7].

3. Epidemiology of infections in patients receiving an active treatment for MM

To estimate the risk of bacterial and viral infections in MM patients, a total of 9253 MM patients, diagnosed between 1988 and 2004 and identified from the Swedish Cancer registry, were compared to 34,931 population-based controls [8]. Overall, a 7-fold increased risk of developing any infection compared to matched controls was observed in MM patients. MM population had an overall 7-fold increased risk of developing a bacterial infection compared to controls (the risk was 11-fold higher during the first year following diagnosis). The overall risk for viral infections was 10-fold higher (18-fold higher during the first year) compared to controls. The elevated risk of infections in MM patients compared to controls increased significantly with calendar period up to 9-fold higher in 2000-2004.

The incidence of infections in patients receiving IMiD or PI based treatment regimens for MM was analyzed by a systematic review and meta-analysis evaluating phase II-III randomized controlled trials of single or multi agent combination published until 2015 [9]. An overall rate of 13.4% and 9.7% of severe infection occurred in patients with a new diagnosis of MM and not eligible to ASCT who received IMiD-based and PI-based induction therapy, respectively. IMiD-based therapy for newly diagnosed patients demonstrated a relative risk (RR) of 1.74 for severe infections with respect to conventional chemotherapy/corticosteroids; however, the risk of death from infection was not significantly higher in IMiD-based therapy compared to conventional therapy. The rate of deaths from infection was 4.4%.

In ASCT-eligible patients who received induction therapy with IMiDs and PI, the rate of severe infection was 22.4% and 19.7%, respectively. IMiD-based studies demonstrated a significant RR of 0.76 for severe infection against both vincristine-adriamycin-dexamethasone

(VAD) regimen and dexamethasone alone. The RR of severe infection was comparable in patients who received bortezomib induction therapy and conventional chemotherapy (RR, 1.12).

In patients who received maintenance therapy with IMiDs after prior ASCT(s) there was a 10.5% rate of severe infection episodes. The infectious risk of IMiD-based maintenance therapy was not increased compared to placebo or prednisolone treatment, however, patients who received lenalidomide as maintenance therapy suffered of a doubling risk of severe infection compared to those treated with thalidomide (RR, 1.95).

In patients with relapsed or refractory MM the rates of severe infection were 16.6% after IMiD treatment and 23.3% after bortezomib treatment. Although the increased risk of infection in relapsed or refractory patients was probably related to the underlying disease status and the overall salvage treatment, the risk of infection with the association of an IMiD, such as lenalidomide, with corticosteroids was double than that of steroids alone.

Epidemiological data on grade > 3 infections from large phase 3 clinical trials in MM patients treated according to the current strategies are detailed in Table 1 [10-31].

4. Infectious risk assessment

4.1 Preliminary considerations

The incidence of different types of infection after active treatment of MM patients with IMiDs, PI and ASCT was evaluated during the period 2008-2012 at the Peter McCallum Cancer Centre (PMCC), an Australian tertiary referral centre for MM [32,33]. Overall, 771 episodes of infection occurred in 189 of 199 (95%) MM patients. Overall, infectious complications accounted for 1.33 per patient-year. The respiratory tract (42.4%), blood (13.0%) and skin, soft tissue (12.2%) were the most frequent sites of infection. Of 281 microbiologically defined infections, 54.1%, 5.7% and 40.2% were bacterial, fungal and viral infections, respectively. There was a bimodal peak in incidence of bacterial infections (4–6 and 70–72 months) following disease diagnosis.

Out of 152 bacterial infections, 47.4% were caused by gram-negative bacteria, 38.8% by gram-positive bacteria and 13.8% by multiple organisms. *Escherichia coli* (23.7%) and *Clostridium difficile* (11.8%) were the most frequently isolated organisms. Again, 5.3% of all episodes of bacterial infection was caused by vaccine-preventable encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*) [33]. Of 98

bloodstream infections, 40.8% were due to gram-negative organisms, 33.7% were due to gram-positive organisms, and 25.5% were polymicrobial infections.

The factors associated to an increased risk of severe bacterial infection in MM patients treated with bortezomib was analyzed in a Korean cohort study [34]. A total of 98 patients with MM were evaluated during 427 treatment courses. In the multivariate analysis, poor performance status (Eastern Cooperative Oncology Group ≥ 2), early phase of therapy (≤ 2 courses), and lymphopenia preceding treatment (absolute lymphocyte count < 1.0 × 10(9)/L) were independent risk factors in each treatment course. In courses with 0, 1, 2, and 3 of the above risk factors the probability of developing severe bacterial infections were 5.1%, 14.9%, 23.9% and 59.5%, respectively.

In a study that included 139 patients treated with bortezomib, 30 out of the 74 patients (40.5%) with lymphopenia (lymphocytes < 0.8 × 10^9/L) at diagnosis developed a severe bacterial infection [35].

High cumulative doses (over 1600 mg o) or prolonged treatment (25 mg per day for 60 day) of prednisolone-equivalents were independently associated to a six times increased risk of bacterial infection whilst a cumulative dose over 3200 mg was associated with nine times the risk of developing viral infection [32].

In patients with severe neutropenia following salvage intensive chemotherapy and ASCT the risk of colonization and infections by multidrug resistant (MDR) bacteria may depend on the hospital prevalence of such pathogens. Indeed knowledge of colonization pattern may be required in order to define infection control measures and tailored antibiotic therapy [36-40]. On the other hand, in a recent prospective Italian epidemiological study on bacterial infections in ASCT recipients, 61 of 837 (7.3%) MM patients developed a gram-negative bacteremia during the neutropenia engraftment period with only one case of carbapenem-resistant isolate [41].

Ahn et al. [42] reported 7% of pulmonary tuberculosis cases in 117 Korean patients who received bortezomib therapy and demonstrated that the infection impacted survival. In another experience from the same country in 285 patients with MM who received 349 courses of bortezomib-containing regimens no case of tuberculosis was encountered during the course of treatment, but 3 patients (1.1%) developed tuberculosis 3, 12 and 21 months after bortezomib discontinuation [43]. In the first experience, bortezomib was generally associated to thalidomide and cyclophosphamide while in the second study most of patients received bortezomid alone or with only dexamethasone: therefore it may be hypothesized that the increase in the susceptibility to tuberculosis by bortezomib-containing regimens might be also dependent on the other combination drugs.

In the PMCC study [32], out of 113 viral infections, 47% and 53% were respiratory and herpes infections, respectively. Viral infections showed a bimodal peak in incidence of (7-9 and 52-54 months) following diagnosis. Most of viral respiratory tract infections were caused by picornavirus (34·0%), parainfluenza (18·9%), respiratory syncytial virus (18·9%) and influenza (11·3%). In a further study by the same Australian group, risk factors for viral respiratory infections were progressive disease, and receipt of more than three lines of MM therapy [44].

Herpes infections consisted of reactivation of varicella-zoster virus (VZV) (68.3%), herpes simplex (23.3%) and cytomegalovirus (CMV) (8.3%). The majority (76.7%) of these episodes occurred while the patients were not receiving antiviral prophylaxis [45]. Among the current drug therapies used for MM, bortezomib was associated with a high rate of VZV reactivation (13%-36%9 [46-49]. Treatment with novel anti CD38 monoclonal antibodies deserves attention in view of the high rate of pulmonary and herpesviruses infections [25, 31, 50, 51]. In a recent retrospective study, 170 patients with relapsed or refractory MM who had receive daratumumab as single agent or in various combinations suffered of a high rate of infections (36.5%), most often viral. Infections were significantly associated with neutropenia and lymphopenia and represented a major cause of death in patients who survived less than three months [51].

A number of studies have examined the risk of CMV reactivation during the induction therapy and after ASCT. In a retrospective study from Japan, in 120 newly diagnosed patients with MM, the rate of CMV reactivation was 20% (24 of 120) and proven/suspected CMV disease was documented in 11% (13 of 120) of patients[52]. A higher risk of CMV reactivation was observed in patients with extramedullary disease and in those with a low absolute lymphocyte count [52]. CMV retinitis in the setting of heavily treated progressive disease has been reported [53,54]. To address the issue of risk of CMV infection after ASCT, the cases of 78 consecutive MM patients who underwent a tandem ASCT after induction treatment with either conventional chemotherapy (n = 42) or with novel agents (n = 36), were reviewed [55]. Considering the outcome of both the first and the second transplantations, 12 subjects (12/78, 15%) developed a total of 13 episodes of symptomatic CMV reactivation. At univariate analysis, a treatment with novel agents before transplant was the only factor significantly associated with the occurrence of CMV reactivation after the first transplant, but not after the second one.

As for other malignancies, serology for hepatitis virus infection discriminates subjects at risk or not of viral reactivation and saves unnecessary treatment in seronegative patients [56-58]. Most of available data for hepatitis virus infections in MM patients treated with new agents, derive from studies from Asian HBV endemic areas [57,58]. In a retrospective study from Japan [59] out of 5078 patients with MM treated using novel

agents and/or ASCT, 52 (1.0%) were HBV carriers (HBsAg-positive or HBV DNA positive), and 760 (15.0%) exhibited resolved HBV infection (HBsAg-negative/anti-HBc-positive). Overall, 46 of the 52 HBV carriers received prophylactic antiviral agents to prevent hepatitis; of the remaining 6 patients who did not receive prophylaxis one developed hepatitis. Out of 758 patients with resolved HBV infection followed for a median period of 101 weeks (range: 1–541 weeks), HBV reactivation (HBVr) occurred in 58 (7.7%) cases, with a cumulative incidence rates of HBVr at 2 and 5 years of 7.9% and 14.1%, respectively. Ten of 58 (17.2%) patients with HBVr did not receive prophylactic or pre-emptive antiviral therapy and developed hepatitis (one of them died of fulminant hepatitis despite the administration of antiviral therapy). The other patients who received prophylaxis and/or had regular monitoring of HBV-DNA with pre-emptive antiviral therapy did not develop hepatitis. HBVr risk was particularly high after ASCT (adjusted odds ratio, 11.56) and the cumulative incidence of HBVr in patients submitted to ASCT was significantly higher (16% at 2 years and 30.6% at 5 years) than those not treated with ASCT (4.4% at 2 years and 4.8% at 5 years) ($p < 0.0001$). In a retrospective study from Texas (USA), 107 MM patients with HBV resolved infection undergoing ASCT and 125 patients with negative HBV serology (control subjects) were compared for HBVr, hepatotoxicity and outcome [61]. Only one of these patients received lamivudine prophylaxis. HBVr occurred in 7 of 107 patients (6.5%) in the HBV resolved group a median of 16 months after ASCT but there was no difference in hepatotoxicity and non-relapse mortality in the two groups.

Risk factors for invasive fungal disease (IFD) in MM were analyzed by two observational studies [62,63]. A proven, probable or possible IFD was documented in 9 of 372 (2.4%) MM patients managed at two Australian centers from January 2009 to December 2011 [62]. Rate of invasive aspergillosis was 0.3%. The rate of IFD was 2.2% (3 of 135) and 2.5% (6 of 237) in patients who had received and had not received an ASCT, respectively. Most of the IFD episodes (85.7%) occurred after a median of 35 months between initial MM diagnosis, during the period of disease progression. The rate of IFD in patients who received 3 lines or more of therapy was 15.0%. In the second prospective, multicenter study from China, the incidence of IFD (in most of cases a possible IFD) per chemotherapy courses was 3.8 % [63]. Prior history of IFD was the only independent risk factor of IFD after chemotherapy courses.

In a recent prospective Italian epidemiological study on infections in ASCT recipients, only 2 cases of candidemia were observed in 837 (0.2%) MM patients during the neutropenia engraftment period [41].

There are no specific epidemiological data on the risk of *Pneumocystis jirovecii* pneumonia (PJP) in MM populations, however, some cases of PJP have been reported during bortezomib treatment [64-65]. Patients receiving PIs should be considered at increased risk of PJP particularly in association with high dose and prolonged steroid treatment.

4.2 Recommendations

- *In MM patients candidate to active treatment, careful evaluation of performance status and past medical history, especially for infection that can reactivate such as varicella zoster virus (VZV), hepatitis and tuberculosis, is recommended before starting first-line therapy.*
- *Controlled HIV, HBV and HCV infections, diabetes, chronic obstructive pulmonary disease, severe hypogammaglobulinemia, renal insufficiency and other recognized risk factors for infections should be seriously considered case by case in order to adopt appropriate prophylactic measures and, if necessary, to modulate MM treatment.*
- *Severe active infections (i.e. pneumonia, herpes zoster, HBV or HCV-related hepatitis, CMV disease, tuberculosis) or uncontrolled HIV-disease contraindicate, at least until their complete resolution or control, active therapies in MM.*
- *The quantitative evaluation of serum polyclonal immunoglobulins, the absolute lymphocytes count, and the absolute neutrophil count are recommended since they could be of help in defining the individual risk of infections.*
- *Information on recent vaccination history (in particular anti-pneumococcal vaccination) should be collected in order to define the pre-treatment vaccination schedule.*
- *All patients needing active treatment should undergo HBV and HCV screening with the following exams: HBsAg, anti-HBc and anti-HBs (HBV DNA if HBsAg or anti-HBc positive); anti-HCV (HCV RNA if anti-HCV positive).*
- *All patients needing active treatment should undergo HSV and VZV antibody test screening in order to identify seronegative patients in whom antiviral chemoprophylaxis is useless. However, the EP agreed that, considering the advanced age of most MM patients with a very low rate of seronegative patients for both HSV and VZV, serological screening of the entire population with the aim to save few unnecessary treatments is questionable.*
- *In high TB prevalence regions [66], all patients with a new diagnosis of MM needing active treatment should undergo screening with IFN-γ-release assays (IGRAs) or tuberculin skin testing (TST) or a combined TST-IGRA testing to detect latent TBI. In low TB prevalence regions*

[66], screening is recommended in persons with a suspected history of TB infection, in those who come from high TB prevalence regions and in those who have clinical conditions that are associated with an increased risk for TB infection.

- *In hospitalized patients candidate to ASCT and in those undergoing intensive salvage therapy, colonization screening with rectal swab culture is recommended to detect colonization by MDR Gram negative bacteria in hospitals with known diffusion of MDR pathogens. Rectal swab should be performed at hospital admission and subsequently every week.*
- *Surveillance screening of fungal antigens (galactomannan, beta-D-glucan,) or fungal cultures in patients without suspicion of IFD is not recommended.*

5. Risk management and prophylaxis

5.1 Preliminary considerations

While the epidemiological studies could define the infectious risk in the different types and phases of MM treatment, the indication of anti-infectious prophylaxis in patients receiving active MM therapy is controversial. In particular the use of antibacterial prophylaxis both in neutropenic and non-neutropenic patients is a debated issue [67,68].

The efficacy of prophylactic antibiotics on the prevention of serious bacterial infections during the first 2 months of treatment in patients with newly diagnosed MM has been evaluated in a prospective phase III study [69]. In this experience (carried out over a 10 years period) three small groups of patients (ciprofloxacin or ofloxacin, 69 cases, trimethoprim-suphamethoxazole 76 cases, and no prophylaxis 67 cases) were compared and no significant difference in the incidence of serious bacterial infections was observed. In a retrospective historically controlled study in MM patients treated with regimens including bortezomib, 80 patients who received levofloxacin prophylaxis showed significantly decreased rate of severe bacterial infections compared to 139 patients who did not (12.5 vs. 30.9 %) [70]. Prophylaxis with levofloxacin was compared to placebo in newly diagnosed MM patients in a large, randomised, double-blind, placebo-controlled multi-centre phase III clinical trial [71]. Overall, 500 mg levofloxacin or placebo tablets once daily for 12 weeks were randomly administered to 977 patients. The number of febrile episodes and or death by any cause suffered in the first 12 weeks were the primary endpoint. The use of levofloxacin was associated to a significant advantage (27% and 19% of events in patients receiving placebo and levofloxacin, respectively; Hazard ratio, 1.52, p=0.002). Levofloxacin not only impacted on febrile episodes and

survival but also significantly reduced the number of invasive gram-negative infections. In a recent prospective Italian epidemiological study on bacterial infections in ASCT recipients, antibacterial prophylaxis during the neutropenia period after ASCT was significantly associated with a reduced risk of gram negative bacteremia (hazard ratio, 0.50; p <0.001, in multivariate analysis) [41]. Considering the phenomenon of increasing antibiotic resistance among Gram-negative bacteria worldwide, important concerns were raised about the efficacy of fluoroquinolones prophylaxis and the negative impact of a widespread use of these antibiotics on resistance rates. However, a recent meta-analysis of controlled and observational studies showed that there was no significant effect of the background rate of fluoroquinolone resistance on the efficacy of fluoroquinolone prophylaxis in reducing the rates of the overall mortality, bloodstream infections and fever both in community and hospital settings [72]. However, the possible benefits of fluoroquinolone prophylaxis on infection rate should be weighed against its impact in terms of toxicity and changes in local ecology in single centres.

Targeted screening and treatment of latent tuberculosis infection (LTBI) is an important strategy for cancer patients at high risk of developing active TB [73,74]. However, with the exception of the above mentioned reports from Asian endemic areas, [42,43] there is no specific information on the risk of tuberculosis reactivation in MM populations.

The low rate of active HBV infection, particularly in Western countries, makes it difficult to carry out prospective trials, testing the effectiveness of antiviral prophylaxis in MM patients. Furthermore the significant variability in the geographic diffusion of this viral disease makes the formulation of recommendations valid for all countries complex. Routine prophylaxis of patients who are HBsAg positive load has been shown to significantly reduce the risk of HBVr [56-58,75-77]. The choice of antiviral agent and the duration of prophylaxis are critical in mitigating the risks of HBVr. There are several oral agents approved for the treatment of chronic hepatitis B (lamivudine, adefovir, entecavir, tenofovir, telbivudine), however, experience in prevention and treatment of HBVr following chemotherapy is almost entirely limited to lamivudine (100 mg daily). The possibility of viral breakthrough following the emergence of resistance mutations is a major concern with prolonged use of lamivudine. Indeed, in HBsAg-positive patients with MM administered lamivudine prophylaxis, reactivation rates of 5-9% have been reported [75-78]. In alternative to lamivudine, entecavir and tenofovir are attractive candidates given their high potency and extremely low resistance rates [56,58]. Antiviral therapy

should start before chemotherapy or transplant and should continue for 6-12 months after stopping chemotherapy or later in situations in prolonged immune suppression is required [56,58].

An important issue to be considered in the choice of antimicrobial prophylaxis in cancer patients receiving chemotherapy, immunomodulatory or other immunosuppressive treatments is represented by the interaction of concomitantly used drugs. Information on drug-drug interactions are often theoretical or deriving from in vitro or animal studies and whether or not a particular drug-drug interaction is clinically relevant may vary depending on a number of individual patient characteristics such as age, organ function, genetic pattern, comorbidity as well as concurrent medication. Clinically relevant drug-drug interactions between certain anti-MM drugs and antimicrobials may occur (Table 2).

5.2 Recommendations

5.2.1 Antibacterial prophylaxis

- *Antibacterial prophylaxis (ciprofloxacin 500 mg bid; levofloxacina 500 mg od) is recommended during the first few months of treatment both in transplant-eligible and non-transplant eligible MM patients, particularly in patients receiving IMIDs and in those at high risk of infections such as patients with a history of frequent infections or patients with co-morbidities or those with high tumor burden (International Staging System –ISS- stage group 3).*
- *Fluoroquinolone prophylaxis from day 5 until stable neutrophil engraftment is recommended after ASCT.*
- *In patients who develop neutropenia while receiving lenalidomide-based maintenance therapy the use of fluroquinolone prophylaxis may be considered but a specific recommendation is not possible in absence of reliable efficacy data. Furthermore, the prolonged maintenance period does not fit to an antibacterial prophylactic strategy.*
- *Fluoroquinolone prophylaxis is recommended in patients with relapsed/refractory disease developing treatment-related prolonged neutropenia.*
- *Due to the inhibitory effect of CYP1A2, ciprofloxacin may increase the blood levels and effects of pomalidomide. If concomitant administration with fluoroquinolones is required, levofloxacin should be preferred.*

5.2.2 Antifungal prophylaxis

- *Prophylaxis against Candida and molds is not recommended during any nontransplant treatment phase, while anti Candida prophylaxis (fluconazole 400 mg od or micafungin 50 mg od) may be considered after ASCT in patients with oral mucositis at risk of superficial fungal infections.*
- *Prophylaxis against PJP is recommended in patients receiving PIs and prolonged steroid treatment and in those with relapsed refractory disease. In ASCT it should be administered after engraftment. The drug of first choice is trimethoprim-sulphamethoxazole (160/800 mg bid for 2 or 3 days/week), alternative agents include aerosolized pentamidine (300 mg once/month), dapsone (50 mg×2/day) and atovaquone (1500 mg/day).*

5.2.3 Antiviral prophylaxis

- *Prophylaxis of HZ infection, but also of HSV infection, [Intravenous (5 mg/kg q12h) or oral acyclovir (from 3x200 mg/d to 2x800mg/d), or oral valaciclovir (from 500 to 3x500 mg/d)], is recommended during PIs therapy and following ASCT. Also for patients receiving daratumumab (and probably other anti CD38 monoclonal antibodies) HZ prophylaxis is recommended and should be initiated within 1 week of starting daratumumab, and continued for 3 months following treatment. Antiviral prophylaxis is recommended in all patients with a recent history of HZ or HSV infection regardless of the type of MM therapy.*
- *Patients with chronic HBV infection should be treated with tenofovir or entecavir under the supervision of an infectious disease or hepatology expert. Patients with resolved HBV infection should be treated with lamivudine. Close monitoring of sero-reversion and/or viremic rebound (defined as determination of HBV DNA, serum HBsAg levels and ALT every 1-3 months), and the subsequent introduction of pre-emptive therapy can be considered an alternative to universal lamivudine prophylaxis. Antiviral prophylaxis should be initiated prior (at least 1 week) or in concomitance with starting immunosuppressive treatment, it should be continued for the duration of treatment and until 1 year after withdrawal of immunosuppressive treatment. HBV DNA and ALT should be monitored every 3 months during the antiviral prophylaxis and monthly after the withdrawal of antiviral treatment*

- *In HCV-infected patients receiving chemotherapy close monitoring of liver function tests and HCV RNA is recommended. In HCV RNA positive patients with hepatic disease, antiviral treatment according to the specific indication should be considered, as soon as possible under the supervision of an infectious disease or hepatology expert.*

6. Intravenous immunoglobulin replacement therapy

6.1 Preliminary considerations

Discordant results are reported in literature concerning the use of prophylactic intravenous immunoglobulin (IVIG) replacement. In 1967 Salmon et al. [79] reported that the use of prophylactic IVIG replacement was not associated to a reduced infection rates in newly diagnosed MM patients. In 1995, Musto et al. [80] suggested that IVIG could be useful for long-term prevention of serious infections in MM. Later, in 2009, Raanani et al published a meta-analysis of randomized-controlled trials comparing prophylaxis with IVIG versus control [81]. The main limitation of this review is that the reviewed studies were old and nowadays the treatment for MM completely changed. However, the conclusion of this study was that the use of IVIG cannot be recommended. Same conclusion was reported by Blombery et al. in 2011 [82] and Park et al. in 2015 [83]: in these studies the use of peri-transplant IVIG did not result in a reduction of infections in a large cohort of patients with MM undergoing ASCT.

6.2 Recommendations

- *IVIG is not recommended routinely for patients with MM. The use of IVIG may be reserved to patients with very low IgG levels (< 400 mg/dl) and recurrent life-threatening infections.*

7. Vaccinations

7.1 Preliminary considerations

While guidelines on various vaccinations after ASCT have been published [84], few data are available specifically in MM patients out of transplant.

Patients with MM have a higher incidence of invasive pneumococcal disease and influenza infections compared to other hematological diseases and controls [6,85], and we will focus our recommendations on vaccinations against these vaccine-preventable pathogens.

A retrospective study with MM patients showed that, after a single dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) prior to ASCT, only 33% of the patients achieved a significant antibody response [86]. In a further experience in 6 MM patients who received two doses of pneumococcal 13-valent conjugate (PCV-13) vaccine both pre G-CSF mobilized hematopoietic cell collection and day +21 post-ASCT, significant immune responses was demonstrated in all patients [87]. In 91 MM patients who received PCV-13 revaccination during lenalidomide maintenance after ASCT response was observed in 58% of patients [88].

During the influenza season 1995-1996, 50 MM patients receiving conventional chemotherapy were randomly allocated to receive or not influenza vaccine [89]. During the period of study at least one upper respiratory illness occurred in 32% vaccine recipients and 72% controls ($p<0.001$). In 2000 Robertson et al. [90] evaluated the antibody titres against influenza using a conventional single-shot influenza vaccine, comparing the results with reference values of a healthy UK population: response to vaccinations was very poor. More recently intensified influenza vaccination schedules in MM patients were evaluated. A retrospective, single-center study, evaluated the immune response of MM patients to one and two doses of a trivalent influenza [91]. Patients with an insufficient response to the first vaccine dose and without any serious side effects were offered a second dose of vaccine. This pilot study suggested that a second vaccine dose may boost the immune response against influenza in MM patients. A novel influenza vaccine strategy (2-dose series of high-dose inactivated trivalent influenza vaccine) was evaluated in 51 patients with plasma cell dyscrasia during the 2014-2015 influenza season [92]. Only 3 patients (6%) experienced laboratory confirmed influenza. The rates of hemagglutination antibody inhibition (HAI) seroprotection against all 3 vaccine strains increased from 4% at baseline to 49% after the first dose and 65% after the second dose. A condition of partial response to therapy and active conventional chemotherapy were found to be associated with a lower likelihood of HAI serologic response. Alternatively, a greater likelihood of an HAI serologic response was associated to a therapy with an immunomodulatory drug alone or with a PI. The same authors compared two doses of Fluzone® High-Dose influenza vaccination (separated by 30 days) to standard of care influenza vaccination with a single age-based vaccination (standard dose <65 years and high-dose ≥ 65 years) in a double-blind, randomized clinical trial over the 2015-2016 flu season, [93]. Sero-protection against all 3 influenza vaccine strains was reached following the second vaccine/placebo in 86.3% of patients who received two high dose vaccines and in 63.9% of those who received standard vaccination. At the

end of the flu season, sero-protection was persistent in 58.5% of patients who received two high dose vaccines and in 33.3% of those who received standard vaccination.

An important issue is to understand when is useful to vaccinate (before, during, or after therapy). According to a review performed by Alemu et al. in 2016, [94] vaccines need to be administered before initiating chemotherapy or other immune modulators or waiting for at least 3 to 6 months after such therapies.

7.2 Recommendations

- *Vaccination against influenza is recommended annually. Double vaccination (30 days apart) to enhance protection against influenza in MM patients might be considered.*
- *Vaccination against S.pneumoniae with PCV-13, followed by PPSV-23 after 2 months, is recommended at the diagnosis of MM regardless of the decision to start early treatment and possibly before initiating any active therapy. A further PCV-13 booster should be administered after ASCT.*
- *While considering the variable effectiveness and risk of vaccination every center or country should give clear and well documented recommendations. Despite Guidelines recommendations, vaccination is often poorly carried out in cancer patients. The Panel points out that any effort should be made to improve the culture of the vaccination practice not only in patients but especially in their physicians.*

8. **Conclusions**

European Myeloma Network Guidelines for the Management of MM related Complications published in 2015 underlined the importance of infection monitoring and appropriate use of antimicrobial prophylaxis in MM patients [95]. The use of antibiotic prophylaxis during the first 3 months of therapy with IMiDs, HZ prophylaxis for patients receiving PI-based therapies or during ASCT and vaccination against influenza virus and *S.pneumoniae* were recommended. However, in view of the lack of randomized clinical trials testing screening problems and infection prophylaxis, the grade of evidence of most of the recommendations was uncertain and some issue of relevance in the clinical practice could not be explored. In this article, in which very recent literature on current MM therapeutic strategies and their complications was analyzed, experts in MM judged

whether the body of evidence was sufficient to provide updated and more detailed recommendations regarding the infection control in the disease. The questions raised by and the conclusions drawn from this consensus conference project may form the basis for improving efforts in the prevention of infectious complications in MM populations. A continuous epidemiological update is needed to implement the guidelines to be applied in the clinical practice.

9. Future considerations

Thanks to the availability of new treatments, the management and the outcome of patients affected by MM have changed considerably in the last years. An important effect of these therapeutic progresses was the prolongation of patients survival, however, with the inevitable appearance of new types of infectious complications. Other new therapeutic agents are under investigation, including novel PIs (oprozomib and marizomib), histone deacetylase inhibitors (romidepsin, vorinostat, ricolinostat), monoclonal antibodies (SAR650984, MOR202, isatuximab, ipilimumab), and small-molecule inhibitors (vemurafenib, venetoclax, CPI-0610, LGH447, dinaciclib, selinexor, ibrutinib, and filanesib) [96-98]. Again, the development of chimeric antigen receptor (CAR) T cell therapy for MM is a promising technological advancement in the future treatment of several malignancies including MM [99]. It is expected that all these innovative therapies will be associated to peculiar complications requiring specific approaches. With the increasing use of new therapeutic options of MM it will probably be necessary to redefine the prevention and treatment strategies of the infectious complications during the different phases of the disease. The adaptation of the infection-control measures cannot be done without the knowledge of the new epidemiological patterns. It is therefore necessary to carry out a continuous surveillance of the complications in order to detect in real time any change in the epidemiology of infections in MM patients and to establish appropriate and tailored preventive approaches.

Practice points

- New treatment strategies for MM need a parallel progress in the best approach to prophylaxis and supportive therapy for infections.

- Infectious risk assessment should be defined before and during active treatment of MM. In particular, careful evaluation of performance status and past medical history, clinical risk factors and microbiological screening for infections in order to adopt appropriate prophylactic measures and information on recent vaccination history should be seriously considered case by case.
- Primary antibacterial, antifungal and antiviral prophylaxis is recommended according to disease phase and type of treatment. Possible drug-drug interactions between certain antimicrobial and anti-myeloma drugs should be considered.
- Vaccination against *S.pneumoniae* should be administered, possibly at the diagnosis of MM regardless of the decision to start early treatment and before initiating any active therapy, and vaccination against influenza should be performed annually to the patients but also to the household members.

Research agenda

- Continuous investigation on epidemiology and risk assessment of infections is required to detect change in the risk profile of infections in MM
- Implementation of such information in registries and clinical trials are highly recommended to better define guidelines on the assessment and treatment of infections in MM patients.

Contribution of the authors

CG and GB were the chairmen of the project and wrote the manuscript; all authors contributed to the literature review, the writing and to the revision of the manuscript.

Potential conflicts of interest

C.Girmenia. has received honoraria from Gilead Sciences, Astellas Pharma, Basilea, MSD, Pfizer Pharmaceuticals, and Celgene.

M.Cavo has received honoraria from Janssen, Celgene, Takeda, Amgen, BMS.

M.Offidani: has received honoraria from Amgen, BMS, Celgene, Janssen, Takeda.

F.Scaglione: has received honoraria from Astellas, Bayer, GSK, Pfizer, MSD, Sanofi, Teva.

A.Corso has received honoraria from Celgene, BMS, Janssen, Amgen.

F.Di Raimondo has received honoraria from Amgen, BMS, Celgene, Janssen, Takeda.

P.Musto: has received honoraria from Celgene, Janssen, Takeda, BMS, Amgen.

MT Petrucci has received honoraria from Celgene, Janssen, Takeda, Amgen, BMS.

G.Barosi has received honoraria from Celgene.

We state that some authors received honoraria from companies that produce drugs used to treat multiple myeloma; including Celgene (thalidomide, lenalidomide, pomalidomide), Janssen (Bortezomib, Daratumumab), Amgen (krlfizomib) and BMS (elotuzumab).

Funding

Funding of the project was provided by an unrestricted contribution of Celgene. The funding sources had no role in identifying statements, abstracting data, synthesizing results, grading evidence, or preparing the manuscript or in the decision to submit the manuscript for publication.

References

1. Mateos MV, San Miguel JF. Management of multiple myeloma in the newly diagnosed patient. Hematology Am Soc Hematol Educ Program. 2017;2017(1):498-507.
2. Larocca A, Mina R, Gay F, Bringhen S, Boccadoro M. Emerging drugs and combinations to treat multiple myeloma. Oncotarget. 2017;8(36):60656-60672.
3. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. J Clin Oncol. 2005 ;23(36):9219-26.
4. Williams PL, Webb C (1994) The Delphi technique: a methodological discussion. J Adv Nurs 19(1):180–186
5. McMillan, SS, Kelly, F, Sav, A. Using the nominal group technique: how to analyse across multiple groups. Health Serv Outcomes Res Methodol. 2014;14(3):92–108.
6. Gay F, Engelhardt M, Terpos E, Wäsch R, Giaccone L, Auner HW, et al. From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. Haematologica. 2018 ;103(2):197-211.
7. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Castillo J, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018. J Natl Compr Canc Netw. 2018 ;16(1):11-20.
8. Blimark C, Holmberg E, Mellqvist UH, Landgren O, Björkholm M, Hultcrantz M, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica. 2015 ;100(1):107-13.
9. Teh BW, Harrison SJ, Worth LJ, Thursky KA, Slavin MA. Infection risk with immunomodulatory and proteasome inhibitor-based therapies across treatment phases for multiple myeloma: A systematic review and meta-analysis. Eur J Cancer. 2016; 67:21-37.
10. Rosiñol L, Oriol A, Teruel AI, Hernández D, López-Jiménez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012 ;120(8):1589-96.

11. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376(9758):2075-85..
12. Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011 ;118(22):5752-8;.
13. Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014 ;371(10):895-905.
14. Mai EK, Bertsch U, Dürig J, Kunz C, Haenel M, Blau IW, et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015;29(8):1721-9.
15. Moreau P, Hulin C, Macro M, Caillot D, Chaleteix C, Roussel M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016 ;127(21):2569-74.
16. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al .Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010 ;11(1):29-37..
17. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017 ;376(14):1311-1320..
18. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-17.
19. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol. 2010;28(34):5101-9.

20. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-17.
21. Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017 ;389(10068):519-527.
22. Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. J Clin Oncol. 2015;33(33):3921-9.
23. Hulin C, Belch A, Shustik C, Petrucci MT, Dührsen U, Lu J, et al. Updated Outcomes and Impact of Age With Lenalidomide and Low-Dose Dexamethasone or Melphalan, Prednisone, and Thalidomide in the Randomized, Phase III FIRST Trial. J Clin Oncol. 2016 ;34(30):3609-3617 .
24. Gay F, Oliva S, Petrucci MT, Conticello C, Catalano L, Corradini P, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015 ;16(16):1617-29.
25. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018 ;378(6):518-528.
26. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007 ;357(21):2123-32.
27. San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 ;14(11):1055-66.

28. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016 ;17(1):27-38.
29. San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014 ;15(11):1195-206.
30. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 ;375(14):1319-1331.
31. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 ;375(8):754-66.
32. Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA. Risks,severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy. Br J Haematol. 2015 ;171(1):100-8.
33. Teh BW, Harrison SJ, Slavin MA, Worth LJ. Epidemiology of bloodstream infections in patients with myeloma receiving current era therapy. Eur J Haematol. 2017 ;98(2):149-153.
34. Hyun SY, Han SH, Kim SJ, Jang JE, Kim Y, Cho H, et al. Pretreatment Lymphopenia, Poor Performance Status, and Early Courses of Therapy Are Risk Factors for Severe Bacterial Infection in Patients with Multiple Myeloma during Treatment with Bortezomib-based Regimens. J Korean Med Sci. 2016;31(4):510-8.
35. Jung, S.H., Bae, S.Y., Ahn, J.S., Kang, S.J., Yang, D.H., Kim, Y.K. et al. Lymphocytopenia is associated with an increased risk of severe infections in patients with multiple myeloma treated with bortezomib-based regimens. Int J Hematol. 2013; 97: 382–387.
36. Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica. 2013 ;98(12):1836-47.

37. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013 ;98(12):1826-35.

38. Martino M, Lemoli RM, Girmenia C, Castagna L, Bruno B, Cavallo F, et al. Italian consensus conference for the outpatient autologous stem cell transplantation management in multiple myeloma. Bone Marrow Transplant. 2016 ;51(8):1032-40.

39. Girmenia C, Viscoli C, Piciocchi A, Cudillo L, Botti S, Errico A, et al. Management of carbapenem resistant Klebsiella pneumoniae infections in stem cell transplant recipients: an Italian multidisciplinary consensus statement. Haematologica. 2015 ;100(9):e373-6.

40. Girmenia C, Rossolini GM, Piciocchi A, Bertaina A, Pisapia G, Pastore D, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant. 2015;50(2):282-8.

41. Girmenia C, Bertaina A, Piciocchi A, K.Perruccio, A.Algarotti, A.Busca et al Incidence, Risk Factors and Outcome of Pre-engraftment Gram-Negative Bacteremia After Allogeneic and Autologous Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey. Clin Infect Dis. 2017 ;65(11):1884-1896.

42. Ahn, J.S., Rew, S.Y., Yang, D.H., Jung, S.H., Kang, S.J., Kim, M.Y. et al. Poor prognostic significance of *Mycobacterium tuberculosis* infection during bortezomib-containing chemotherapy in patients with multiple myeloma. *Blood Res*. 2013; 48: 35–39

43. Kim K, Kim SJ, Maeng CH. Relationship between bortezomib-containing regimens and the incidence of tuberculosis in patients with myeloma. Blood Res. 2013 ;48(3):233-4.

44. Teh BW, Worth LJ, Harrison SJ, Thursky KA, Slavin MA. Risks and burden of viral respiratory tract infections in patients with multiple myeloma in the era of immunomodulatory drugs and bortezomib: experience at an Australian Cancer Hospital. Support Care Cancer. 2015 ;23(7):1901-6.

45. Hioki T, Takama H, Makita S, Watanabe K, Watanabe D, Akiyama M. Cytomegalovirus reactivation accompanied by varicella zoster virus reactivation or reinfection in an adult patient of multiple myeloma during bortezomib therapy. J Dermatol. 2018 ;45(1):108-109.

46. Kim JW, Min CK, Mun YC, Park Y, Kim BS, Nam SH, Koh Y, et al. Varicella-zoster virus-specific cell-mediated immunity and herpes zoster development in multiple myeloma patients receiving bortezomib- or thalidomide-based chemotherapy. J Clin Virol. 2015 ;73:64-69.

47. Sahu KK, Varma SC. Herpes zoster complicating bortezomib therapy. Indian J Med Res. 2015 ;141(2):247-8.
48. Kamber C, Zimmerli S, Suter-Riniker F, Mueller BU, Taleghani BM, Betticher D, et al. Varicella zoster virus reactivation after autologous SCT is a frequent event and associated with favorable outcome in myeloma patients. Bone Marrow Transplant. 2015 ;50(4):573-8.
49. König C, Kleber M, Reinhardt H, Knop S, Wäsch R, Engelhardt M. Incidence, risk factors, and implemented prophylaxis of varicella zoster virus infection, including complicated varicella zoster virus and herpes simplex virus infections,in lenalidomide-treated multiple myeloma patients. Ann Hematol. 2014 ;93(3):479-84.
50. Moreau P, van de Donk NW, San Miguel J, Lokhorst H, Nahi H, Ben-Yehuda D, et al. Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma. Drugs. 2016 ;76(8):853-67.
51. Johnsrud A, Susanibar S, Jo Kamimoto J, Johnsrud J, Kothari A, Burgess M, et al Infectious Complications of Daratumumab-Containing Therapy for Multiple Myeloma Blood 2017; 130:3148;
52. Hasegawa T, Aisa Y, Shimazaki K, Ito C, Nakazato T. Cytomegalovirus reactivation in patients with multiple myeloma. Eur J Haematol. 2016 ;96(1):78-82.
53. Teh BW, Khot AS, Harrison SJ, Prince HM, Slavin MA. A messenger at the door: cytomegalovirus retinitis in myeloma patients with progressive disease. Transpl Infect Dis. 2013 ;15(4):E134-8.
54. Lim HY, Francis D, Yeoh J, Lim LL. Cytomegalovirus retinitis after treatment with lenalidomide for multiple myeloma. Retin Cases Brief Rep. 2013;7(2):172-5.
55. Marchesi F, Pimpinelli F, Dessanti ML, Gumenyuk S, Palombi F, Pisani F, et al. Evaluation of risk of symptomatic cytomegalovirus reactivation in myeloma patients treated with tandem autologous stem cell transplantation and novel agents: a single-institution study. Transpl Infect Dis. 2014;16(6):1032-8.
56. Mallet V, van Bömmel F, Doerig C, Pischke S, Hermine O, Locasciulli A, et al. Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5). Lancet Infect Dis. 2016 ;16(5):606-617.

57. Gentile G, Andreoni M, Antonelli G, Sarmati L. Screening, monitoring, prevention, prophylaxis and therapy for hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation: a systematic review. Clin Microbiol Infect. 2017 ;23(12):916-923.

58. Sarmati L, Andreoni M, Antonelli G, Arcese W, Bruno R, Coppola N, et al. Recommendations for screening, monitoring, prevention, prophylaxis and therapy of hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation-a position paper. Clin Microbiol Infect. 2017 ;23(12):935-940.

59. Li J, Huang B, Li Y, Zheng D, Zhou Z, Liu J. Hepatitis B virus reactivation in patients with multiple myeloma receiving bortezomib-containing regimens followed by autologous stem cell transplant. Leuk Lymphoma. 2015 ;56(6):1710-7.

60. Tsukune Y, Sasaki M, Odajima T, Sunami K, Takei T, Moriuchi Y, et al. Incidence and risk factors of hepatitis B virus reactivation in patients with multiple myeloma in an era with novel agents: a nationwide retrospective study in Japan. Blood Cancer J. 2017 ;7(12):631.

61. Varma A, Biritxinaga L, Saliba RM, Stich M, Jauch SF, Afrough A, et al. Impact of Hepatitis B Core Antibody Seropositivity on the Outcome of Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma. Biol Blood Marrow Transplant. 2017 ;23(4):581-587.

62. Teh BW, Teng JC, Urbancic K, Grigg A, Harrison SJ, Worth LJ, et al. Invasive fungal infections in patients with multiple myeloma: a multi-center study in the era of novel myeloma therapies. Haematologica. 2015;100(1):e28–31.

63. Liu J, Huang H, Li Y, Liu L, Li J, Liu Z, et al. Epidemiology and treatment of invasive fungal diseases in patients with multiple myeloma: findings from a multicenter prospective study from China. Tumour Biol. 2016 ;37(6):7893-900.

64. Wondergem MJ, Gru¨nberg K, Wittgen BP, Wittgen BP, Sonneveld P, Zweegman S. Interstitial pneumonitis caused by Pneumocystis jirovecii pneumonia (PCP) during bortezomib treatment. Histopathology 2009;54:631–3.

65. Swan CD, Reid AB. Three cases of presumed pneumocystis pneumonia in patients receiving bortezomib therapy for multiple myeloma. IDCases. 2014 ;1(3):32

66. http://www.who.int/tb/publications/global_report/en/ (10 August 2018)

67. Offidani M, Corvatta L, Polloni C, Gentili S, Brioni A, Visani G, et al. Infectious complications in patients with multiple myeloma treated with new drug combinations containing thalidomide. Leuk Lymphoma. 2011 ;52(5):776-85.

68. Caravita T, Offidani M, Siniscalchi A, Gentili S, Caraffa P, Perrotti A, et al. Infection complications in an unselected cohort of patients with multiple myeloma treated with lenalidomide combinations. Eur J Haematol. 2012;89(3):276-7.

69. Vesole DH, Oken MM, Heckler C, Greipp PR, Katz MS, Jacobus S, Morrow GR; University of Rochester Cancer Center and the Eastern Cooperative Oncology Group. Oral antibiotic prophylaxis of early infection in multiple myeloma: a URCC/ECOG randomized phase III study. Leukemia. 2012 26(12):2517-20.

70. Jung SH, Kang SJ, Jang HC, Ahn JS, Yang DH, Lee SS, et al. Effect of levofloxacin prophylaxis for prevention of severe infections in multiple myeloma patients receiving bortezomib-containing regimens. Int J Hematol. 2014 ;100(5):473-7.

71. Drayson MT, Bowcock S, Planche T, Iqbal G, Wood J, Raynes K, et al. Tackling Early Morbidity and Mortality in Myeloma (TEAMM): Assessing the Benefit of Antibiotic Prophylaxis and Its Effect on Healthcare Associated Infections in 977 Patients. Blood 2017; 130:903;

72. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, et al Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect. 2018 ;76(1):20-37.

73. Jereb JA. Progressing toward tuberculosis elimination in low-incidence areas of the United States. Recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR Recomm Rep. 2002;51(RR-5):1-14.

74. Cheng MP, Abou Chakra CN, Yansouni CP, Cnossen S, Shrier I, Menzies D, et al. Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2017 ;64(5):635-644..

75. Mya DH, Han ST, Linn YC, Hwang WY, Goh YT, Tan DC. Risk of hepatitis B reactivation and the role of novel agents and stem-cell transplantation in multiple myeloma patients with hepatitis B virus (HBV) infection. Ann Oncol. ;23(2):421-6.

76. Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med. 2008;148(7):519-28. Erratum in: Ann Intern Med. 2009 ;150(9):657-8.

77. Teng CJ, Liu HT, Liu CY, Hsih CH, Pai JT, Gau JP, et al. Chronic hepatitis virus infection in patients with multiple myeloma: clinical characteristics and outcomes. Clinics (Sao Paulo). 2011;66(12):2055-61.

78. Uhm JE, Kim K, Lim TK, Park BB, Park S, Hong YS, et al. Changes in serologic markers of hepatitis B following autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2007 ;13(4):463-8.
79. Salmon SE, Samal BA, Hayes DM, Hosley H, Miller SP, Schilling A. Role of gamma globulin for immunoprophylaxis in multiple myeloma. N Engl J Med. 1967 ;277(25):1336-40
80. Musto P, Brugiatelli M, Carotenuto M. Prophylaxis against infections with intravenous immunoglobulins in multiple myeloma. Br J Haematol. 1995 ;89(4):945-6
81. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma. 2009 ;50(5):764-72
82. Blombery P, Prince HM, Worth LJ, Main J, Yang M, Wood EM, et al. Prophylactic intravenous immunoglobulin during autologous haemopoietic stem cell transplantation for multiple myeloma is not associated with reduced infectious complications. Ann Hematol. 2011 ;90(10):1167-72
83. Park S, Jung CW, Jang JH, Kim SJ, Kim WS, Kim K. Incidence of infection according to intravenous immunoglobulin use in autologous hematopoietic stem cell transplant recipients with multiple myeloma. Transpl Infect Dis. 2015 ;17(5):679-87.
84. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014 ;58(3):e44-100.
85. Backhaus E, Berg S, Andersson R, Ockborn G, Malmström P, Dahl M, et al. Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors. BMC Infect Dis. 2016 ;16:367.
86. Hinge M, Ingels HA, Slotved HC, Mølle I. Serologic response to a 23-valent pneumococcal vaccine administered prior to autologous stem cell transplantation in patients with multiple myeloma. APMIS. 2012;120:935–940
87. Locke FL, Menges M, Nishihori T, Nwoga C, Alsina M, Anasetti C. Boosting humoral and cellular immunity to pneumococcus by vaccination before and just after autologous transplant for myeloma. Bone Marrow Transplant. 2016 ;51(2):291-4.

88. Palazzo M, Shah GL, Copelan O, Seier K, Devlin SM, Maloy M, et al. Revaccination after Autologous Hematopoietic Stem Cell Transplantation Is Safe and Effective in Patients with Multiple Myeloma Receiving Lenalidomide Maintenance. Biol Blood Marrow Transplant. 2017 : S1083-8791(17)31825-6.
89. Musto P, Carotenuto M. Vaccination against influenza in multiple myeloma. Br J Haematol. 1997 ;97(2):505-6.
90. Robertson JD, Nagesh K, Jowitt SN, Dougal M, Anderson H, Mutton K, et al. Immunogenicity of vaccination against influenza, Streptococcus pneumoniae and Haemophilus influenzae type B in patients with multiple myeloma. Br J Cancer. 2000 ;82(7):1261-5
91. Hahn M, Schnitzler P, Schweiger B, Kunz C, Ho AD, Goldschmidt H, et al. Efficacy of single versus boost vaccination against influenza virus in patients with multiple myeloma. Haematologica. 2015 ;100(7):e285-8
92. Branagan AR, Duffy E, Albrecht RA, Cooper DL, Seropian S, Parker TL, et al. Clinical and Serologic Responses After a Two-dose Series of High-dose Influenza Vaccine in Plasma Cell Disorders: A Prospective, Single-arm Trial. Clin Lymphoma Myeloma Leuk. 2017 ;17(5):296-304.e2.
93. Branagan A, Duffy E, Foster C, Verma R, Zhang L, Gan G, Li F, Dhodapkar MV. Two Dose Series of High-Dose Influenza Vaccine Is Associated with Longer Duration of Serologic Immunity in Patients with Plasma Cell Disorders. Blood 2017; 130:438;
94. Alemu A, Richards JO, Oaks MK, Thompson MA. Vaccination in Multiple Myeloma: Review of Current Literature. Clin Lymphoma Myeloma Leuk. 2016 ;16(9):495-502.
95. Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, Kastritis E, et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. Haematologica. 2015 ;100(10):1254-66.
96. Rafei H, Haroun F, Tabbara IA. Novel Immunotherapeutic Agents for the Treatment of Multiple Myeloma. Am J Clin Oncol. 2018 Dec 14. doi: 10.1097/COC.0000000000000506. [Epub ahead of print] PubMed PMID: 30557165.
97. Oliva S, Troia R, D'Agostino M, Boccadoro M, Gay F. Promises and Pitfalls in the Use of PD-1/PD-L1 Inhibitors in Multiple Myeloma. Front Immunol. 2018;9:2749. doi: 10.3389/fimmu.2018.02749. eCollection 2018.
98. Goldschmidt H, Ashcroft J, Szabo Z, Garderet L. Navigating the treatment landscape in multiple myeloma: which combinations to use and when? Ann Hematol.2018 Nov 23. doi: 10.1007/s00277-018-3546-8. [Epub ahead of print]

99. Cornell RF, Costa LJ. The Future of Chimeric Antigen Receptor T Cell Therapy for the Treatment of Multiple Myeloma. Biol Blood Marrow Transplant. 2018 Nov 16. pii: S1083-8791(18)30719-5. doi: 10.1016/j.bbmt.2018.11.009. [Epub ahead of print].

Table 1. Rate of grade 3 or higher infections from phase 3 randomised clinical trials in MM patients treated according to the current strategies.

Author, year (n.reference)	Type of treatment	N. of patients	Rate of infections, %	Comments
Studies in newly diagnosed ASCT-eligible patients				
Rosinol, 2012 [10]	Chemotherapy 4 induction cycles + bortezomib 2 induction cycles , followed by ASCT	129	15	The rate of infections refers to the induction therapy.
	TD 6 induction cyles, followed by ASCT	127	16	
	VTD 6 induction cycles, followed by ASCT	130	21	
Cavo, 2010 [11]	VTD 3 induction cycles, followed by ASCT	236	3	The rate of infections refers to the induction therapy. All grade 3-4 infections were considered with the exclusion of H.zoster. Aciclovir prophylaxis to prevent reactivation of varicella zoster virus infection was recommended for patients receiving VTD.
	TD 3 induction cycles, followed by ASCT	238	5	
Moreau, 2011 [12]	vTD 4 cycles induction, followed by ASCT	100	10	The rate of infections refers to the induction therapy.
	VD 4 cycles induction, followed by ASCT	99	14	
Palumbo 2014 [13]	RD, induction	399	6	Consolidation therapy with high-dose melphalan plus ASCT and lenalidomide maintenance significantly prolonged progression-free survival among patients with multiple myeloma who were 65 years of age or younger, although at a cost of increased infectious risk.
	HDM+ASCT, consolidation	141	13.3	
	MPR, consolidation	132	0.8	
	Lenalidomide, maintenance	116	6.0	
	No maintenance	115	1.7	
Mai, 2015 [14]	VCD induction, followed by ASCT	250	10.8	The rate of infections regarded only the induction phase. Infectious death occurred in 2 patients in the VDD group and one in the VCD group

	VDD induction, followed by ASCT	248	12.9	
Moreau, 2016 [15]	VTD induction, followed by ASCT	169	7.7	Hematologic toxicity was higher in the VCD arm,with significantly increased rates of grade 3 and 4 neutropenia. This higher rate of neutropenia in the VCD arm was not associated with a higher rate of grade 3 and 4 infections. Two patients in both arms died due to infection during consolidation
	VCD induction, followed by ASCT	169	10.1	
Rajkumar 2010 [16]	RD four induction cycles, followed by same therapy until disease progression or ASCT or other treatment options	223	16	Toxicities were most common with high-dose dexamethasone particularly in the first 4 months and in elderly patients.
	Rd four induction cycles, followed by same therapy until disease progression or ASCT or other treatment options	220	9	
Attal, 2017 [17]	VRD 3 induction cycles, followed by VRD 5 consolidation cycles	350	8.9	In both groups respiratory tract infections (4.0% and 6.6%) and sepsis (1.7% and 5.1%) were the most frequent infections. VRD therapy plus transplantation was associated with significantly longer progression-free survival than VRD therapy alone, but infections were more frequent in the transplantation group and overall survival did not differ significantly between the two approaches.
	VRD 3 induction cycles, followed by HDM+ASCT consolidation	350	20.3	
Studies in newly diagnosed ASCT not-eligible patients				
San Miguel, 2008 [18]	VMP 9 cycles	340	10	Any grade H.zoster occurred in 13% and 4% of patients in TMP and MP groups, respectively. The incidence of H.zoster was reduced to 3% in patients in the VMP group who were receiving antiviral prophylaxis
	MP 9 cycles	337	7	
Palumbo 2010 [19]	VMPT 9 induction cycles, followed by maintenance VT	253	13	The incidence of severe infections was similar in both groups and mainly due to pneumonia and neutropenic fever; grade 3 to 4 herpes zoster was_1% in both groups.
	VMP 9 induction cycles	250	9	
Benboubker, 2014 [20]	RD continuous induction	535	29	Most cases of infection in the continuous lenalidomide–dexamethasone group occurred in the absence of neutropenia (80%) and the rate of infections remained stable over time.
	RD 18 cycles induction,	541	22	

	MPT induction,	547	17	
Durie, 2017 [21]	RD induction,	226	13.7	
	VRD induction,	244	14.1	
Niesvizky, 2015 [22]	VD 8 induction cycles, followed by bortezomib 5 maintenance cycles	165	21	Pneumonia and H.zoster were the most frequent infections. Grade > 3 sepsis was reported in 3% (5 of 165),3%(5 of 158), and 2% (3 of 163) of patients, respectively. Almost all grade 3-4 infections occurred during the 8 induction cycles
	VTD 8 induction cycles, followed by bortezomib 5 maintenance cycles	158	16	
	VMP 8 induction cycles, followed by bortezomib 5 maintenance cycles	163	18	
Hulin, 2016 [23]	Rd continuous, ≤75 y	347	30	Infections were the most common grade 3 to 4 non-hematologic treatment emergent adverse events and were more frequently reported in the Rd arms in both age groups.
	Rd for 18 cycles, ≤75 y	348	21	
	MPT, ≤75 y	357	16	
	Rd continuous, >75 y	185	29	
	Rd for 18 cycles, >75 y	192	23	
	MPT, >75 y	184	20	
Gay, 2015 [24]	RD induction	387	7.0	As expected, fewer adverse events were reported with chemotherapy plus lenalidomide than with high-dose melphalan and ASCT consolidation. In the maintenance groups lenalidomide dose reduction due to infections was required in 0% and 4% of patients who received lenalidomide plus prednisone and lenalidomide alone, respectively
	RCD, consolidation	129	5.0	
	HDM+ASCT, consolidation	127	19.0	
	Lenalidomide plus prednisone, maintenance	117	7.0	
	Lenalidomide alone, maintenance	106	5.0	
Mateos 2018 [25]	DaraVMP	346	23.1	The most common grade 3-4 infection was pneumonia, with a higher rate in the daratumumab group than in the control group (11.3% vs. 4.0%).
	VMP	354	14.7	
Studies in relapsed-refractory MM patients				
Dimopoulos 2007 [26]	RD	176	11.3	grade 3 or 4 febrile neutropenia was rare (occurring in 3.4% of the patients in the lenalidomide group and in none of those in the placebo group).
	Placebo-Dexamethasone	175	6.2	

San Miguel [27]	Poma-d	300	34	Most infections occurred in the absence of neutropenia. In the Poma-d group the incidence of grade 3 or worse febrile neutropenia (10%) was fairly low. The rate of pomalidomide discontinuation due to infection was low.
	Poma-D	150	33	
Dimopoulos, 2016 [28]	KD	463	7	Percentages refer only to patients with pneumonia
	RD	456	8	
San Miguel, 2014 [29]	PanVD	381	13	Percentages refer only to patients with pneumonia
	Placebo- VD	377	11	
Dimopoulos 2016 [30]	DaraRD	283	28.3	The most common infection of grade 3 or 4 was pneumonia, which occurred at similar rates in the two groups (7.8% vs 8.2%).
	RD	281	22.8	
Palumbo 2016 [31]	DaraVD	243	21.4	The most common infection of grade 3 or 4 was pneumonia, which occurred at similar rates in the two groups (8.2% vs 9.7%).
	VD	237	19	

ASCT= autologous stem cell transplant;
DaraRD= daratumumab-lenalidomide-dexamethasone
DaraVD= daratumumab- bortezomib- dexamethasone
DaraVMP=daratumomab bortezomib, melphalan, prednisone
HDM= high-dose melphalan
KD= carfilzomib- dexamethasone
MPR=melphalan–prednisone–lenalidomide;
MP= melphalan- prednisone
MPT=melphalan-prednisone-thalidomide
PanVD= panobinostat-bortezomib-dexamethasone
Poma-D= pomalidomide-high-dose dexamethasone
Poma-d= pomalidomide-low-dose dexamethasone
RD= Lenalidomide–Dexamethasone high dose
Rd=Lenalidomide–Dexamethasone low dose;
TD= thalidomide dexamethasone
VCD=bortezomib/cyclophosphamide/dexamethasone;
VD= bortezomib-dexamethasone
VDD=bortezomib-doxorubicin/dexamethasone;
VMP= bortezomib, melphalan, prednisone
VMPT= Bortezomib-Melphalan-Prednisone-Thalidomide
VRD= bortezomib lenalidomide dexamethasone;
VT= bortezomib thalidomide
VTD= bortezomib thalidomide dexamethasone

vTD= bortezomib thalidomide dexamethasone with reduced doses of bortezomib

Table 2. Potential drug-drug Interactions of drugs used in the treatment of multiple myeloma and antimicrobials.

Drug	**Metabolism and potential of drug-drug interactions**	**Precautions of co-administration with certain antimicrobial drugs**
Melphalan	It is not actively metabolized by CYP enzymes, it spontaneously degrades to mono and dihydroxy products.	No precaution is required with any antibacterial, antifungal and antiviral drugs co-administration
Cyclophosphamide	Metabolism and activation occurs at the liver. 75% of the drug is activated mainly by the enzymes CYP2B6, CYP2C9 and CYP3A4. Cyclophosphamide is a pro-drug and undergoes activation to eventually form active metabolites, phosphoramide mustard and acrolein.	Concomitant use of cyclophosphamide with other drugs that are inhibitors or inducers of CYP2B6, CYP2C9, or CYP3A4 enzymes could cause interactions. Inhibition of cyclophosphamide metabolism determines reduced toxicity and, presumably, reduced efficacy. Co-administration with ciprofloxacin, and triazoles (in particular fluconazole which inhibits both CYP2C9 and CYP3A4) should be avoided.
Thalidomide	Thalidomide is a substrate of human CYP450 enzymes but is not subjected to clinically significant pharmacokinetic drug–drug interactions when co-administered with CYP inhibitors, inducers, or substrates.	No precaution is required with any antibacterial, antifungal and antiviral drugs co-administration
Lenalidomide	Lenalidomide is not a substrate of human CYP450 enzymes and is not subjected to direct conjugative metabolism. Hence, lenalidomide is not anticipated to be subjected to pharmacokinetic drug–drug interactions when coadministered with CYP and P-gp inhibitors, inducers, or substrates.	No precaution is required with any antibacterial, antifungal and antiviral drugs co-administration
Pomalidomide	Pomalidomide is neither an inducer nor inhibitor of CYP450 and P-gp.	Co-administration with ciprofloxacin (a strong

	Oxidative metabolism of pomalidomide is predominately mediated by CYP1A2 and CYP3A4, and pomalidomide is a P-gp substrate. Coadministration of pomalidomide with strong CYP1A2 inhibitors significantly increases pomalidomide exposure.	CYP1A2 inhibitor) should be avoided or pomalidomide reduced by 50%. There is no interaction with Levofloxacin. No significant interaction with triazoles.
Bortezomib	Bortezomib is a substrate of the enzymes CYP1A2, CYP2C9 and CYP3A4 and a mild inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Coadministration of bortezomib with strong CYP3A4 inhibitors increases bortezomib exposure by 35%.	Serum concentration can be increased when combined with clarithromycin, fluconazole, itraconazole, posaconazole, voriconazole. Combination with these drugs should be possibly avoided.
Carlfizomib	Carlfizomib is not a substrate of the CYP enzymes. It is a substrate of the P-gp, however, being an intravenous drug this interaction does not seem to be clinically relevant.	No precaution is required with any antibacterial, antifungal and antiviral drugs co-administration
Ixazomib	Ixazomib is not a substrate of human CYP450 enzymes and is not subjected to direct conjugative metabolism. Hence, ixazomib is not anticipated to be subjected to pharmacokinetic drug–drug interactions when coadministered with CYP and P-gp inhibitors, inducers, or substrates.	No precaution is required with any antibacterial, antifungal and antiviral drugs co-administration
Elotuzumab and daratumumab	There are no studies on interactive pharmacokinetic. Presumably, monoclonal antibodies do not interact with CYP or other enzymes	No precaution is required with any antibacterial, antifungal and antiviral drugs co-administration
Panobinostat	Approximately 40% of the hepatic elimination of panobinostat occurs through the CYP3A4 enzyme pathway.	Co-administration with clarithromycin, itraconazole, voriconazole and posaconazole (strong/moderate CYP3A4 inhibitors) should be avoided or panobinostat reduced by 50%.