Meeting report
UK BMT Pharmacists' Group Educational meeting, London, 12th July 2019

The fifth meeting of the UK BMT Pharmacists' Group took place at the UCLH Education Centre, London on Friday 12th July 2019. Over 30 pharmacists from a cross section of UK transplant centres attended. Sponsorship was very kindly provided by Incyte, Jazz and Pfizer. The following sessions took place……

Invasive fungal infections – Diagnostic challenges

Dr P. Lewis White, Head of the PHW Mycology Reference Laboratory, University Hospital of Wales, Cardiff

Dr White provided a comprehensive overview of current challenges in the diagnosis of IFIs in haematology patients. He talked about the fact that empirical therapy is still widely used for the following reasons - Infection is associated with significant morbidity and mortality, signs and symptoms of systemic infection are nonspecific, conventional diagnostic techniques are suboptimal and delays in treatment are associated with poorer outcome. He then discussed the role of different diagnostic techniques, focusing on serological tests such as β-D-Glucan and galactomannan (GM) assays and molecular PCR testing for both aspergillus and PJP. All tests have high negative predictive values and are therefore of value as surveillance tools. PCR testing has excellent specificity (i.e. low rate of false positives) in BAL samples and is therefore useful for confirming disease in symptomatic patients. Dr White described the use of combined antigen and PCR testing in Cardiff as a tool for reducing the use of empirical antifungals (*Barnes RA, Stocking K, Bowden S, Poynton MH, White PL.. Prevention and diagnosis of invasive fungal disease in high-risk patients within an integrative care pathway. J Infect. 2013; 67:206-14*) and explained how antifungal expenditure had fallen sharply since this strategy was introduced. In his experience, the negative predictive value of both PCR and GM detection is high and enables empirical therapy to be safely withheld; when used together, the positive predictive value is high and enables the diagnosis to be confirmed. Interestingly, biomarker positivity precedes radiological signs in 85% of cases, demonstrating the potential to detect infection before disease develops.

EHA feedback

Dav Manku, Principal Pharmacist Cancer Services. Dudley Group of Hospitals NHS Foundation Trust

Dav Manku provided a summary of some of the key sessions that she attended at the recent European Haematology Association (EHA) conference in Amsterdam. One of the CLL education sessions focused on the role of allogeneic SCT in this disease. Factors predicting for a poorer outcome include older age, poorer PS, an unrelated donor, female donor for male recipient and active disease at the time of transplant. She then summarised the results of a recent trial from Seattle of CAR-T for refractory CLL, focusing on the role of concurrent ibrutinib and its potential to reduce the risk of CRS and increase the efficacy of the CAR-T product in this setting. A follow-up phase I/II trial based on these encouraging findings is ongoing. Finally, Dav discussed a CML case study that had been presented during one of the CML educational sessions that had elegantly demonstrated the challenge of managing key adverse events associated with the various TKIs that are available for the treatment of CML.

Results of a National Antifungal Survey

Nick Duncan, Consultant haematology pharmacist, University Hospitals Birmingham

Nick Duncan presented the results of a recently completed survey of UK BMT centres, (both Adult and paediatric) that aimed to investigate antifungal practice in a number of clinical settings – ALL and AML induction, autologous SCT and allogeneic SCT. This was a follow-up to an earlier survey undertaken in 2010. The principal conclusion was that practice is still extremely variable and recent ECIL guidelines in this area do not appear to have led to any noticeable standardisation. Results are summarised in the EHA poster PDF at the end of the report.

The role of transplantation in management of lymphoma: current approaches and future strategies

Dr Will Townsend, Consultant haematologist, University College London Hospitals

Dr Townsend presented an overview of treatment of specific types of lymphoma and what kind of transplant options each patient group has in the current climate.

Currently, in relapsed Hodgkin lymphoma, an autograft is considered in those who obtain a PET negative remission (Complete metabolic response [CMR]). In those who are PET positive they will go on to receive further chemotherapy of which treatment with immunotherapy is an emerging option. 75% of patients respond, however only 15% of patients obtain a sustainable CR. This group of patients may be considered for treatment with an allograft after immunotherapy but we need to be aware of an increased risk of GvHD. Do clinicians need to consider a washout period (~ 6 weeks) after treatment? Dr Townsend also discussed the The Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) for response assessment post immunotherapy.

In follicular lymphoma the current practice is to consider an autograft in second remission. Follicular lymphoma would be ideal to treat with CAR-T transplants. However trials are unlikely to be considered due to the long follow up period and the cost implications associated with it. A relatively new end-point of POD24 (Progression of disease within 2 years) is being evaluated as a potential useful early end point to help overcome this.

CAR-T and the clinical pharmacist

Jackie Chappell, Consultant pharmacist, Kings College Hospital, London

Sumantha Gabriel, Lead Clinical Pharmacist - Specialist Haematology, Freeman Hospital, Newcastle

Sumi Gabriel introduced her talk by describing the development of the Advanced Therapy Treatment Centre (ATCC) network before moving on to the evolution of the CAR-T clinical pharmacist group which is a subgroup of the Pan UK Pharmacy ATMP Working Group. She discussed the aims of the group and presented key outcomes from the group's recent meeting in London. Finally, she summarised the experience to date with CAR-T in Newcastle before outlining some next steps in terms of developing the role of the clinical pharmacist in this field. Following on from this, Jackie Chappell delivered a

comprehensive case study of a DLBCL patient receiving Yescarta® who developed CRS, failed to respond to tocilizumab and was then successfully treated with Anakinra. The patient also developed neurotoxicity (ICANS) that was treated with IV dexamethasone. She finished by summarising key aspects of the clinical pharmacist's role when looking after CAR-T patients.

Update on BMT Pharmacists' Group – BOPA affiliation, training passport, e-learning
Group discussion

BOPA-affiliation

Nick Duncan confirmed that the group is now officially affiliated with BOPA as a special interest group and it will have its own page on the new-look BOPA website which is due to go live soon. For the moment, the Yahoo email discussion forum will continue but there may be potential for the BOPA website to provide a better email platform for the group in the future. Nick Duncan and Simon Cheesman will co-chair the group initially but will be looking for volunteers to take over this role in the next 12-18 months. Terms of reference for the group are currently being drafted.

Training passport

Following on from a presentation by Vivek Soni at the June 2018 meeting, a group of pharmacists, led by Nadjoua Maouche from Oxford have been developing a generic BMT/CAR-T training passport that could be used across the UK. Nadjoua provided an overview of the content of the passport. After going through a number of draft versions, the passport is now nearly complete and it is hoped to be able to launch it in the autumn.

e-learning

Charlotte Clark from Addenbrookes is leading on a project to prepare a series of e-learning modules on BMT (working with the BOPA E&T group and the BMT Pharmacists' Group), that are designed to dovetail with the clinical sections of the training passport and will be available through the BOPA website. There will potentially be 5-6 modules in total and the first modules should be available later in the year.

Future plans

It is hoped to hold our next meeting towards the end of 2019. Further details will be emailed out and will also be available via the group page on the BOPA website shortly.

Report written by Nick Duncan, Amrit Atwal and Nicky Marchant, July 2019

Building healthier lives

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A survey of practice relating to the prevention and treatment of invasive fungal infections in UK haematology centres

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Background

Invasive fungal infections (IFIs), particularly due to Aspergillus species, are an important cause of morbidity and mortality in patients with haematological malignancies. In 2017 and 2018 the European Conference on Infections in Leukaemia (ECIL) published updated guidelines for both prophylaxis and treatment of IFIs in haematology patients.[1,2] A previous survey of UK practice undertaken in 2010 demonstrated marked variability in practice in relation to the prevention and treatment of IFIs in this patient group[3], similar to what had been reported in earlier Europe-wide surveys. The aim of the current study was to investigate whether variability in practice still exists in the UK or whether recently published guidelines have helped to standardise practice.

Methods

A short questionnaire was sent electronically to all members of the UK BMT pharmacists' group. The majority of questions focused on prophylaxis and treatment of fungal infection in four specific clinical areas – AML induction, ALL induction, autologous stem cell transplantation (SCT) and allogeneic SCT. Further questions related to uptake of the newer azole, isavuconazole, and the use of therapeutic drug monitoring (TDM) for azoles. Responses were collated and analysed using Microsoft Excel.

Results

Responses were received from 29 centres. All centres treated autologous SCT and AML/ALL patients and 25 treated allogeneic SCT patients. Seventeen centres treated adult patients only, seven were paediatric centres and five treated both adults and children.

The most common prophylactic strategies for the four indications are shown in table 1:

Table 1: Antifungal prophylaxis

Indication	Most common strategy	% centres	2nd most common strategy	% centres
Autograft	Fluconazole	59	No prophylaxis	17
Allograft	Posaconazole	44	Lipid amphotericin	28
AML Induction	Posaconazole	45	Lipid amphotericin	21
ALL Induction	Lipid amphotericin	69	No prophylaxis	21

There was marked variability in dosing schedules for fluconazole (50mg-400mg/day) and lipid amphotericin [12 different schedules ranging from 50mg thrice weekly (TTW) up to 3mg/kg TTW]. Only 69% of centres gave prophylaxis routinely to all 4 patient groups. Compared with the previous survey, itraconazole use had fallen sharply and was only used prophylactically by 38% of centres (previously 76%). There was also variability seen in the duration of prophylaxis: in the autograft setting the majority of centres (67%) stopped prophylaxis at the time of engraftment. However, in allograft patients, only 32% of centres stopped at engraftment with the majority continuing for 3-6 months post transplant.

Empirical therapy was recommended by 79% of centres – see figure 1 for individual drugs. The criteria for starting an antifungal empirically (i.e. duration of fever unresponsive to broad spectrum antibiotics) varied from 48-120 hours. As in the previous survey, Ambisome® (at doses ranging from 1-3mg/kg/day) was the most common empirical antifungal agent, followed by caspofungin. However, voriconazole had replaced Ambisome® as the most widely recommended first line drug for the management of invasive aspergillosis. Caspofungin, micafungin, posaconazole and IV itraconazole were only recommended in a minority of policies – see figure 2 for further details.

Figure 1 - 1st line Antifungals - Empirical

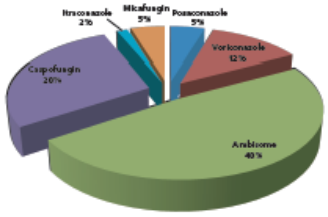
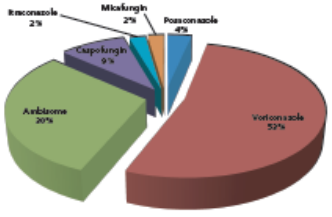


Figure 2 - 1st line Antifungals - Treatment



Ambisome® was the most popular second line agent, being recommended in 62% of policies, followed by caspofungin (24%) and isavuconazole (17%). Twenty one centres (72%) would consider giving dual therapy.

In terms of uptake of new agents, Isavuconazole was included in the antifungal policy in 34% of centres, had been used on an adhoc basis in a further 28% but had not yet been used in 38% of centres.

For those centres that included the following azoles in their antifungal policies, the use of TDM was inconsistent – 76% of centres undertook TDM for voriconazole, 71% for itraconazole and 55% for posaconazole.

Conclusions

Similar to the previous survey undertaken in 2010, this study showed significant variations in practice between UK haematology centres with respect to both preventing and treating invasive fungal infections. Recent guidelines in this area do not appear to have resulted in a noticeable standardisation of practice.

References

1. Tissot F *et al.* ECIL-6 Guidelines For The Treatment Of Invasive Candidiasis, Aspergillosis And Mucormycosis In Leukemia And Hematopoietic Stem Cell Transplant Patients. Haematologica 2017; 102: 433-444

2. Maertens JA *et al.* European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrobial Chemother 2018; 73: 3221-3230.

3. Duncan N *et al.* A survey of practice relating to the prevention and treatment of invasive fungal infections in UK transplant centres. Annual Meeting of the EBMT 2011; p781