Brian Cooper from Mediscript sent the following message:

Mark, Adrian,

These are comments which I made following the meeting of 30 May. Many apologies if they have been acted upon in the meantime:

1. For PCNSL, the PEL section, there is a recommendation: We suggest that first line of PEL in HIV individuals includes CHOP like regimens. No comparative studies have been performed and there is no optimal gold standard therapy. You have graded this 2C, and yet I thought the meeting decided 1C?

[THIS NOW APPLIES IN SECTION 5.6, RECOMMENDATIONS, WHERE THE RECOMMENDATION IS MARKED 'IIA, B?' AND 'TBC'.]

2. For Kaposi sarcoma, please check all entries in the box at the end. For instance, the third and fourth recommendations may not have been discussed at the meeting? You say: We recommend that patients with T1 advanced stage KS, should receive chemotherapy along with HAART (Level of evidence Grade 1B). And yet earlier in the document (with different wording) it seems to be 1A, as confirmed at the meeting. You say: We recommend that liposomal anthracyclines (either Daunoxome 40mg/m2 q14d or Caelyx 20mg/m2 q21d) are first-line chemotherapy for advanced KS (Level of evidence Grade 1A), and yet I thought the meeting decided 1B? And you say: We recommend paclitaxel chemotherapy for second-line treatment of anthracycline refractory KS (Level of evidence 1C). And yet I thought the meeting decided 2C?

[THIS NOW APPLIES TO THE RECOMMENDATIONS IN SECTION 2.3]

For opportunistic infection I thought there should have been reference to the Immunization guidelines as well?

[I NOW NOTE THAT REFERENCE 55, THE IMMUNIZATION GUIDELINE, IS INVOKED, AND SO THIS MAY ANSWER THE QUESTION]

For Non-AIDS defining, section 5.3, third bullet, you say: We recommend that all potential interactions between HAART, opportunistic infection prophylaxis and cancer therapy should be considered (Level of evidence 1C). I thought the meeting decided 1B?

[THIS NOW APPLIES TO SECTION 11.5.3, SUMMARY]

fiona burns from UCL sent the following message:

I know I am a member of the writing group but missed the meeting providing the opportunity to feed this back. I do not think a push button response of BHIVA conference attendees is a suitable level evidence to include in what is otherwise a systemic review of evidence. Or that it should be the basis for a specific recommendation "We suggest that a minimum of 50 patients per year should be required for service designation (level of evidence 2D)."

Kate Templeton from NHS Lothian sent the following message:

These guidelines are quite vague. It reads like a review article rather than a document to help you manage your patient.

I get the impression that different people wrote the different sections as there is not any consistency in the document eg KSHV in one bit and HHV8 in another. The Castleman's section has a good bit about testing for HHV8 but the KS and PEL bits don't have very good detail.

The last bit has a very vague bit about prophylaxis against HSV if the patient has a history of HSV infection. It doesn't make it clear whether this means HSV serology testing and any details about the prophylaxis.

I many looked at the virology bits and accept this document is meant of clinicians.

Noel Connolly from Central Manchester NHS Foundation Trust sent the following message:

1. Is it worth specifically mentioning that irradiated blood products should be used in those with Hodgkin lymphoma

2. Tamoxifen use in Breast cancer
• Oestrogen receptor (ER) antagonist
• Early and advanced ER+ breast cancer in both pre and post menopausal ♀
• A Pro-drug that is metabolized to its active moieties (hydroxytamoxifen) via CYP450 isoenzymes, in particular CYP2D6
• RTV is an inhibitor of both CYP3A4 and CYP2D6
• Unsure how much of an effect the low booster dose has
• Sub-therapeutic levels possible so avoid use with a PI/r

3. Mention Irinotecan as in the BHIVA ART 2012 Guidelines
• Topoisomerase 1 inhibitor (ie. prevents DNA unwinding)
• mCRC (+ 5-FU + LV)
• Active metabolite: SN-38 (x1000 more active)
• SN-38 inactivated by glucuronidation by UGT1A1
• 10% of Caucasians have a variant of UGT1A1 which leads to poor metabolization of Irinotecan predicts Irinotecan toxicity
• Diarrhoea (Loperamide ++++)
• Myelosuppression (neutropenia)
• Therefore avoid ATV use with Irinotecan

Robin Grant from Association of British neurologists sent the following message:

suggest you see the section in the British Neuro-Oncology Society Rare Tumours (PCNSL) guidelines (page 17 HIV associated PCNSL).

It largely agrees with the BHIVA guidelines - just for information

The link to BNOS guidelines

http://www.bnos.org.uk/documents/rare_tumours_guidelines/CNS%20Lymphoma%20Guidelines.pdf

Lindsay Short from North and West Yorkshire HIV Network sent the following message:

The North and West Yorkshire HIV Network would like to make the following comments;

1. 50 patients /year
a. Is this new or mixture of new and follow up patients?
b. If all new unlikely that any centre outside of London will have that case load
c. Does this include cervical abnormalities CIN?
d. Does it include malignancies in people who happen to have HIV as a co-morbidity

2. With respect to CIN in the presence of HIV will this no longer be able to be managed in the general colposcopy clinic?

3. Increasingly cancer care is happening in smaller local centres within a wider clinical network

From Arvind Arumainathan by email to Mark Bower

Dear Prof Bower,

Thanks for sending me the document for comment.
I feel slightly embarrassed seeing my name on the GWG, as I don't believe I've made any meaningful contribution.

I do have one comment though, which is for section 9.7 (management of relapsed Hodgkin lymphoma):

Although there are no data for the use of Brentuximab in patients with HIV and Hodgkin lymphoma, this does seem a reasonable treatment modality in patients unfit for salvage chemotherapy and HDT/ASCT, as the data for Brentuximab in relapsed/refractory Hodgkin lymphoma in the non-HIV setting are compelling.
I understand that there is an front-line NCI trial currently in the early stages of recruitment.
Would it be reasonable to include Brentuximab as a paragraph in section 9.7, though not as a recommendation?

Many thanks

Arvind

Arvind Arumainathan
Cons Haem
Royal Liverpool University Hospital

Alastair Miller from Royal Liverpool sent the following message:

1. I wonder if the requirement to treat >50 cases of HIV related malignancy pa is going to mean that very few centres are able to achieve this? It would be interesting to know how many centres manage that number.

2. On page 14 you refer to "adriamycin" - this presumably should be called doxorubicin in line with the other use of non proprietary names.

3. It is useful to have specific drug regimens/doses for liposomal anthracyclines in the KS summary. It would als be helpful to have a line here about how many cycles should be given and how long one would wait for response and what would be the indication to repeat cycles of anthracycline or switch to taxol.

4. It would be helpful to have specific doses regimens, duration etc for taxol.

Generally excellent well writetn useful document. Thank you

Josie Shew from Association of British Neurologists sent the following message:

Thank you for asking for comments on the Guidance from BHIVA on HIV Associated malignancies. We have confined the comments of the ABN Neuro-Oncology Section to Primary CNS Lymphoma associated with HIV.

There is guidance produced by the British Neuro-Oncology Society/ National Cancer Action Team Guidelines on Primary CNS Lymphoma (1), which includes a section on PCNSL in HIV. Their recommendation: (Grade C Level lII) is that “HIV positive patients presenting with PCNS lymphoma should undergo the same investigations and as those with HIV negative disease. Patients should receive optimal HAART therapy and then receive the same therapy as non- HIV positive patients in similar prognostic groups and with similar performance status”
This BNOS/NCAT Guideline would be worth referencing in the text, but we would suggest an acknowledgement that “full investigation may not be justified when a palliative approach is the only clinically appropriate option”.

The lack of randomized controlled trial data with chemotherapy in PCNSL should be emphasised, but it would be worth referencing the Cochrane Review on the role of chemotherapy

in PCNSL (2)

Presentation does not seem to mention the common sub-acute presentation of focal neurological signs which occurs in one third of cases in most series (3) J Neurosurg 1990 23: 206 – 211). It is more correct also to say neuro-cognitive disturbance, including neuro-psychiatric, as most have problems with memory, verbal fluency or even delirium, rather than psychiatric symptoms.

The description of fundal and slit lamp exam should be more closely associated with the explanation of why and of what is being sought in the text. Currently, these are separated by several sentences.

Thallium SPECT and PET scanning are not particularly specific or sensitive in PCNSL in HIV and may just introduce delay in management. Biopsy can be directed perfectly well using MRI scan and does not require PET. It should be emphasized that MRI with gadolinium, as close to the time of planned surgery as possible, is key.

The risk of performing an LP in the presence of mass lesion (coning) should be emphasized. Where safe, a CSF examination should be done.

It should be emphasized that steroids should only be used in cases where there is raised intracranial pressure, prior to surgery, as these tumours may "disappear" on scanning following steroids, and the neuro-pathologist may struggle to give an accurate diagnosis. There is no need for steroids pre-operatively in the absence of raised intracranial pressure.

Symptomatic or palliative management should be mentioned as an appropriate route based on co-morbidity and when therapeutic response to chemotherapy or radiotherapy is not likely to improve quality of life or survival. Cross reference to guidelines on the management of palliation in brain tumours (4) (http://guidance.nice.org.uk/CSGBraincns/Guidance/pdf/English)

References

1. Guidelines on the diagnosis and management of primary CNS and intra-ocular Lymphoma (PCNSL)
http://www.bnos.org.uk/documents/rare_tumours_guidelines/CNS%20Lymphoma%20Guidelines.pdf

2. Bergner N, Monsef I, Illerhaus, G, Engert A, Skoetz N. Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL). Cochrane Database Syst Rev. 2012 Nov 14;11:CD009355. doi: 10.1002/14651858.CD009355.pub2.

3. Baumgartner JE, Rachlin JR, Beckstead JH, Meeker TC, Levy RM, Wara WM, Rosenblum ML. Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. J Neurosurg. 1990 Aug;73(2):206–211.

4. Improving outcomes for people with brain and other CNS tumours - the manual
http://guidance.nice.org.uk/CSGBraincns/Guidance/pdf/English

Email from Simon Collins:

Hi Mark

Sorry for not asking this earlier - or if it is a stupid question - but the required reading on GRADE standards prior to working on these guidelines - and the general move by BHIVA towards GRADE methods is not mentioned in the Introduction.

The process itself was also very different to the structure that the GRADE system requires - ie drafting questions and outcomes before the literature review and then access each of the questions.

Will this have limitations later or was this deliberate due to the amount of work it would have involved?

thanks

Simon