Date: October 15, 2008

Topic: CTCAE v3.0 Help Desk Tickets: WG #1: SOC: Blood and lymphatic system disorders

From: Ann Setser

Suggestion for addition to CTCAE v4.0: Oncologic emergencies:

* MedDRA: Leukocytosis -- SOC Blood and lymphatic system disorders
* MedDRA: Hyperviscosity syndrome -- SOC Blood and lymphatic system disorders
* MedDRA: LLT & PT Coagulopathy

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**Bone marrow cellularity**, grades 2

Grade 2, change to: >25 - >50% reduction from normal cellularity for age

Grade 3, change to: >50 - >75% reduction from normal cellularity for age

Date: October 15, 2008

Topic: CTCAE v3.0 Help Desk Tickets - SOC: Immune system disorders

From: Ann Setser

Issue: Cytokine release syndrome

Thank you again for your help on 'diarrhea' definition in CTCAEv3 last

month. We included your consideration into my presentation for introduction of CTCAEv3 in a several scientific meetings here.

Today, I am writing to ask you another issue.

At the review of Japanese version of CTCAEv3 by JCOG Committee, one of the committee member (Dr. Yasuhiro Matsumura MD/PhD , a specialist of research on Drug Delivery System) raised a question and comment on 'Cytokine Release Syndrome/Acute Infusion Reaction' in the original CTCAEv3 as well as its Japanese translation.

I am not familiar with 'infusion reaction' and could not understand the

discussion points enough, so I asked Dr. Matsumura to make a detailed document with evidence. He send me the attached file as response upon my request.

Dr. Nagahiro Saijio (JCOG Chair) and I (JCOG Data Center Director) on behalf of JCOG have agreed with Dr. Matsumura's opinion, and we would much appreciate it if you could take his opinion into consideration by CTCAE Development Team.

We, JCOG, have just released Japanese version of CTCAEv3 on our website last month, and it will be hopefully used in the most of cancer clinical trials conducted in Japan, both in investigator-initiated trials and industry-sponsored trials. We hope it would be helpful to increase comparability and availability of Japanese data for cancer

patients not only in Japan but also patients in the world.

CTEP Response: Thanks to all for the very insightful comments.

This AE was one of the most difficult for us to revise for CTCAE v3.

At the time of drafting of the version 3, some thought that infusion

reaction should be separated in the CTCAE from cytokine release, some did

not, and nobody was entirety happy with the label of the AE. We kept

cytokine release part of the title primarily for the antibody therapies.

While there is some wiggle room in the grade 2 description, I agree that we

could better state the fact that interruptions with resolution without any

intervention should be included in grade 2, and we will keep this in mind

when we revise again.

I'll ask that the addition of liposomal products be discussed at next

revision, but I am not sure this is necessary. In the future, we are going

to have many vehicles and polymeric preps that might be relevant and we

don't intend to include an exhaustive list.

Again, thanks. It is this sort of thoughtful follow- up from the oncology

community that will make the CTC a progressively improved document.

Pease add this email and the attached PDF to the file of issues to be examined at next revision.

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Questions regarding cytokine release syndrome/acute infusion reaction in SYNDROMES of

CTCAEv3.0

Indication 1

This syndrome is generally termed “infusion-related reactions”. Although given classes of cytokines

and complements are considered to be pathogenic factors, its precise etiologies still remain

undefined. Therefore, it is questionable to give a term “cytokine release syndrome”. After all, we

consider that the term should be integrated to “infusion-related reactions” (1,2,3).

Indication 2

The description of grade 2 involves an obvious contrariety. This syndrome makes a clear distinction

from allergy (2,4). A gross suspicion is elicited about antihistaminic activity. We consider that no

definite treatment is available for this syndrome (A package insert from ALZA corporation). The

only undubious fact is that symptoms disappear after the interruption of treatment There is no

evidence that an anit-histamine is effective for the infusion related reaction.. Therefore, we consider

that the acceptable description of grade 2 is “Moderate reactions require the interruption of

treatment.”

Indication 3

Liposomal drug preparations should be added to biological products, e.g., monoclonal antibodies,

which are mentioned as examples.

Reference

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Y. Barenholz, C.R. Alving. Role of complement activation in hypersensitivity reactions to doxil

and hynic peg liposomes : experimental and clinical studies. Journal of Liposome Research. 12 :

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2)A. Chanan-Khan, J. Szebeni, S. Savay, L. Liebes, N. M. Rafique, C. R. Alving, and F. M. Muggia.

Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil®):

possible role in hypersensitivity reactions. Ann. Onc., 14: 1430 – 1437 2003.

3) Skubitz, K. M., Skubitz, A. P. Mechanism of transient dyspnea induced by pegylated-liposomal

doxorubicin (Doxil). Anti-Cancer Drugs. 9 : 45-50, 1998.

4) Susan J. Edwards. Prevention and treatment of adverse effects related to chemotherapy for

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Date: October 15, 2008

Topic: CTCAE Help Desk Tickets – SOC Infections

From: Ann Setser

Consider adding to CTCAE v4.0:

* Gastroenteritis MedDRA LLT & PT
* Sepsis MedDRA LLT & PT
* thrush=candidiasis
  + LLT Thrush for PT Candidiasis