Position Statement:

Safe handling of monoclonal antibodies in healthcare settings

Introduction

Monoclonal antibodies (MABs) were introduced into clinical practice in the mid 1980s, with their use in the healthcare setting increasing over the past decade. Their use has become established in the treatment of a variety of disease states including cancer, rheumatoid arthritis, transplanted organ rejection, psoriasis and asthma.

Manufacturers have minimal data on the possible long term risks of handling MABs predominantly because they are not required to provide this information for licensing purposes. Safety data sheets are available, but tend to be geared towards industrial scale handling of raw material and are not easily translated to the clinical setting. Potential levels of occupational exposure are difficult to quantify.

Cytotoxic agents were not considered a handling hazard for many years until their mechanisms of action on genetic material were elucidated and epidemiological evidence emerged linking them to late adverse effects in healthcare workers. With the occupational risks in the handling of cytotoxic agents well established, appropriate guidelines for their workplace handling have been developed.[1,2] However, there are no similar Australian guidelines on the safe handling of MABs in the clinical setting. Many current cytotoxic safe handling guidelines do not assess or provide guidance on how MABs should be handled, particularly during their preparation and administration. To add to the confusion, some authorities include MABs as a subcategory of antineoplastic agents.[3,4]

The National Institute for Occupational Safety and Health (NIOSH) adopted a set of criteria to identify the characteristics of a hazardous drug. MABs have limited data associated with many of these characteristics. Indeed, as they are proteins in nature, MABs are not required to be evaluated for carcinogenicity or genotoxicity, even if their therapeutic effects are directly mediated by antibody binding to target antigens. In 2012 the NIOSH list of antineoplastic and other hazardous drugs in healthcare settings no longer included MABs as hazardous except those MABs conjugated to cytotoxic agents or radio-isotopes.[5]

Arguably, as each MAB is unique and varies considerably in a number of factors such as biological activity, structure, formulation and other characteristics, they need to be evaluated individually rather than as a class. However, there are aspects of their chemistry which allows their safe handling requirements to be considered as one class.

What are the risks?

From the experience with cytotoxic agents, the risks to healthcare workers in the preparation and administration of MABs arise from three distinct mechanisms; dermal exposure, the inhalation of aerosols, and oral intake.

- **Dermal exposure**

The skin is an effective barrier to absorption of high molecular weight proteins. The upper limit for dermal absorption of compounds is around 500 Daltons to allow penetration of the stratum corneum.[6] Given that MABs have a much higher molecular weight (usually greater than 140kDa) the potential for dermal uptake of intact skin of unconjugated MABs or intact conjugates in the occupational setting is unlikely.[7] As MABs are immunoglobulin based they would also have restricted access across diffusional barriers unless transport is facilitated by specific mechanisms.[8] However, skin conditions such as dermatitis and other damage to the skin may facilitate the dermal uptake of monoclonal antibodies.[7]

- **Inhalation exposure**

The greatest risk of exposure during the preparation of MABs is through inhalation. However, even this risk is low. Aerosolized cetuximab in a mouse model has shown that the airway barriers are permeable to MABs, but its passage into the bloodstream is limited.[9] Estimates on the bioavailability of high molecular weight substances have been at 5% by inhalation.[7] However, given the high molecular weights of MABs, the absorption rates could be considered lower. In areas where MABs may be administered to patients via inhalation, the potential for exposure to the worker may be increased.[10]

- **Oral exposure**

Oral exposure of MABs through hand-to-mouth transmission may occur. MABs are intricately folded proteins that are easily susceptible to denaturation from environmental conditions.[11] If ingested, MABs are rapidly broken down by gut enzymes and acids resulting in denaturing of the protein and loss of biological activity. Exposure via this route would be minimal.[7] However, there may be a theoretical risk from resultant lower molecular weight agents from conjugates which may be absorbed systemically.

In the absence of occupational health studies, occupational risks from MABs have also been extrapolated from the side effects of therapeutic doses, and recommendations published.[7, 12] One publication prepared a risk assessment tool based on the antigenic properties and the toxic potential of MABs.[12] The other evaluated the reproductive and developmental toxicity and effects on fertility of several MABs.[7] While the evidence was lacking, the authors concluded that all of the MABs evaluated had the potential for some level of reproductive toxicity.

Both these reviews were based on the extrapolation of occupational related toxicity from data obtained in therapeutic situations. This information alone may be misleading. Potential exposure pathways as discussed above were either not considered or authors concluded that exposure via these pathways would be very minimal. Any data extrapolated in this setting should be critically analysed factoring in aspects of routes of potential exposure.

Recommendations

1. These recommendations do not replace clinical guidelines for the safe prescribing, dispensing and administration of cancer chemotherapy.[13]
2. The information available on the occupational toxicity of MABs is limited. Each institution should review their handling procedures and be guided by professional bodies as new information becomes available. This is especially important when handling newer MABs or MABs used in clinical trial.
3. Staff preparing and administering MABS should be competent in aseptic transfer techniques. Some MABs require complex dosing calculations or complex reconstitution techniques. Proteins are easily broken down with excessive shaking, and may froth when reconstituted. Staff must be offered extra training in the preparation of these agents.
4. It is preferable that the task of preparation be performed by a centralised service. Centralising preparation may also minimise expenditure. Where MABs are prepared by a centralised service, they should be prepared according to accepted standards.[14]
5. Simple precautions taken during the preparation and administration of MABs, such as hand washing, wearing gloves and face masks, backed up with robust surface cleaning of handling areas are likely to reduce potential risks further.[15] Preparation should occur in a dedicated area away from patients and carers.
6. Where MABs are prepared by a centralised service in the same safety cabinets as cytotoxic agents, appropriate cleaning and decontamination should occur between preparations of cytotoxic agents and MABs. If this is not possible, a closed-system drug transfer device should be used for the preparation of all cytotoxic items to minimise surface contamination of the end product.[16] In all other situations the use of such devices should not be considered mandatory.
7. Disposal of waste products associated with MABs should be in accordance with the disposal of clinical waste. This applies to waste production during preparation and administration, as well as patient waste.
8. Any MABs conjugated to a cytotoxic agent must be considered hazardous. Preparation and administration of these agents should follow accepted cytotoxic safe handling precautions.
9. Any MABs conjugated to a radio-isotope must be considered hazardous. Preparation and administration must be in accordance with regulations in regards handling of radiopharmaceuticals.
10. Similar consideration should be given to other complex proteins, such as fusion proteins.

About COSA and the CPG

The **Clinical Oncology Society of Australia** (COSA) is Australia's peak multidisciplinary society for health professionals working in cancer research, treatment, rehabilitation and palliative care with over 1600 members. COSA is an advocacy organisation whose views are valued in all aspects of cancer care. COSA provides high-level clinical advice to Cancer Council Australia.

The **Cancer Pharmacists Group** (CPG) is a group of COSA comprised of pharmacists practising in a variety of settings including medical oncology, haematology, palliative care and cytotoxic preparation services. The CPG provides the only national multidisciplinary forum for pharmacists working in cancer services.

Governance

The COSA CPG appointed a project officer to prepare the guidelines. A comprehensive literature search was undertaken to identify published information in the area of safe handling of monoclonal antibodies. The information was retrieved in June 2013 using the following electronic databases: Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Pubmed. Comment on the draft recommendations was sought from the CPG, COSA and Cancer Nurses Society of Australia (CNSA) members, and incorporated in the final document.

This position statement was approved by the COSA Council on 11 November 2013.

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