Regulatory Toxicology and Pharmacology 70 (2014) 46–53

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Functional differentiation of cytotoxic cancer drugs and targeted cancer therapeutics

Gian C. Winkler [a,*], Ester Lovsin Barle [b], Giuseppe Galati [c,1], William M. Kluwe [d]

[a] Novartis Pharma AG NIBR, Postfach, CH-4002 Basel, Switzerland
[b] Novartis Pharma AG, Postfach, CH-4002 Basel, Switzerland
[c] Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada
[d] Novartis Pharmaceuticals Corporation, NIBR, One Health Plaza, East Hanover, NJ 07936-1080, USA

ARTICLE INFO

Article history:
Received 2 April 2014
Available online 20 June 2014

Keywords:
Cytotoxic cancer drugs
Antineoplastic drugs
Selective oncology drugs
Targeted therapeutics
Functional definition
Occupational health
Pharmaceutical manufacturing
Drug development

ABSTRACT

There is no nationally or internationally binding definition of the term "cytotoxic drug" although this term is used in a variety of regulations for pharmaceutical development and manufacturing of drugs as well as in regulations for protecting medical personnel from occupational exposure in pharmacy, hospital, and other healthcare settings. The term "cytotoxic drug" is frequently used as a synonym for any and all oncology or antineoplastic drugs. Pharmaceutical companies generate and receive requests for assessments of the potential hazards of drugs regularly – including cytotoxicity. This publication is intended to provide functional definitions that help to differentiate between generically-cytotoxic cancer drugs of significant risk to normal human tissues, and targeted cancer therapeutics that pose much lesser risks. Together with specific assessments, it provides comprehensible guidance on how to assess the relevant properties of cancer drugs, and how targeted therapeutics discriminate between cancer and normal cells. The position of several regulatory agencies in the long-term is clearly to regulate all drugs regardless of classification, according to scientific risk based data. Despite ongoing discussions on how to replace the term "cytotoxic drugs" in current regulations, it is expected that its use will continue for the near future.

1. Introduction

There is no nationally or internationally binding definition of the term "cytotoxic drug". Understanding of cytotoxicity as a property of oncology drugs has evolved with increased appreciation of the molecular mechanism of generally toxic nitrogen mustard beginning in the 1940s. Later development of therapies based on administration of mono- and bifunctional alkylating agents, natural *Vinca* alkaloids and anthracyclines took advantage of the preferential susceptibility of cancerous tissues to the toxic effects of agents that impaired cellular replication. Such selective susceptibility was based on the high rate of cell division and poorly-regulated growth in malignant tumors. Therapeutic use of these agents in oncology depends on careful selection of dose and regimen since selectivity is a relative concept considering the adverse effect profiles of many chemotherapeutics. By the end of the century, so-called targeted cancer therapy with reduced side effects was made possible by advances such as specific monoclonal antibodies that bound to unique epitopes on the surface of cancerous cells and by small molecules such as selective tyrosine kinase inhibitors that affected specific molecular pathways up-regulated in certain cancers (Gottesman, 2002). More recently, targeted monoclonal antibodies linked to a variety of microtubule-active compounds (e.g. auristatins and maytansinoids) (ADC antibody drug conjugates) have been developed conferring specificity for cancer cells to non-selective anti-mitotic drugs (Chari, 2008).

Unfortunately, by common use, the term "cytotoxic drug" is frequently used as a synonym for any and all oncology or antineoplastic drugs. It is formally a part of many regulations for pharmaceutical development and manufacturing of oncology drugs (ICH, 2000; ANVISA, 2010; WHO, 2010; EMA, 2012a,b). On the other hand, the pharmaceutical manufacturers and regulatory agencies are moving to clearly regulate all drugs based on scientific data and risk assessment and not based on terms lacking a specific definition. Respective guidances have been published (ISPE, 2010; Bercu et al., 2013). In a draft of the European Medicine Agency

* Corresponding author.
E-mail addresses: gian_christian.winkler@novartis.com (G.C. Winkler), ester.lovsin_barle@novartis.com (E.L. Barle), joe.galati@patheon.com (G. Galati), william.kluwe@novartis.com (W.M. Kluwe).
[1] Fax: +1 905 816 3953.

http://dx.doi.org/10.1016/j.yrtph.2014.06.012
0273-2300/

guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA, 2012a), reference is made to establishing safe exposure values based on scientific data. Oncology hospitals, pharmacies and caregiver organizations often have their own regulations (e.g. OSHA, 1999; NIOSH, 2004; ASHP, 2006; Green et al., 2009; HSE, 2003; HSE/MCA, 2003; Ziegler et al., 2013) for administering oncology drugs, designed to protect personnel from occupational exposure and safely dispose of contaminated waste. Adequate interpretation of monitoring results of exposed hospital personnel should take into account the actual hazard of oncology drugs dispensed. Finally, cytotoxic drugs are also a category of special concern mentioned in the recent publication for pharmaceutical quality and safety, especially as it concerns potentially genotoxic contaminants in medicinal products (ISPE, 2010; Bercu et al., 2013).

Pharmaceutical companies frequently receive requests from internal (good manufacturing practices [GMP] quality assurance; local production sites, medical safety departments and country organizations) and external (health authorities, contract manufacturers, hospitals) organizations for assessing the hazards of a variety of products – and a number of these concern whether a pharmaceutical agent could be defined as cytotoxic cancer drug for research, manufacturing, or other uses. The background is usually concern for determining and managing risk either for potential occupational exposure of employees in manufacturing, exposure of hospital and nursing staff or compliance with GMP guidance. Lacking a well-recognized and standard definition of "cytotoxic drug" makes very difficult the tasks of providing consistent advice and ensuring easily understood communications. The terms "non-specific" or "non-selective" cancer drugs have been used to describe generically-cytotoxic anticancer drugs in previous publications (Blagosklonny, 2004; Broxterman and Georgopapadakou, 2004). However, the authors also discussed the fact that "non-specific" or "non-selective" cytotoxic cancer drug drugs focus on targets such as DNA, microtubules or histone deacetylases, selectively. Specifically, these targets are not unique to cancer cells, but are also part of normally replicating cells. We have chosen to use the term "cytotoxic cancer drugs" in this manuscript for the sake of clarity. Other agents used in oncology form part of a broad group of "targeted cancer therapies".

The purpose of this publication is to provide functional definitions that discriminate between cytotoxic cancer drugs and targeted cancer therapeutics for the purpose of guiding safe handling practice and some product quality decisions. The definition is used in Novartis and Patheon and in a similar format in other companies contacted.

Together with example assessments, the publication may be used to differentiate cytotoxic cancer drugs and targeted cancer therapeutic in a consistent way. The publication is intended to provide a comprehensible guidance for those involved in answering specific requests for relevant safety information from internal and external organizations.

2. Methods

Database searches were initiated in Embase, Medline and Biosis (OvidSP provided by Wolters Kluwer, Alphen aan den Rijn NL), by combinations of the keywords "cytotox*", "oncology", "regulation", "definition" "properties", "histopathology" and "mitosis" covering the span 1996–2013. Resulting hits were reviewed and integrated into this publication.

Besides the authors' own experience with addressing requests concerning drug hazards, we contacted a number of pharmaceutical companies and contract manufacturers and conducted a survey on how similar requests regarding the cytotoxic properties of drugs are handled.

Additional data base searches in Embase, Medline and Biosis (OvidSP provided by Wolters Kluwer, Alphen aan den Rijn NL) were initiated combining the individual "drug name" with "pharmacology" and "mode of action" of select targeted cancer drugs. Resulting hits were reviewed and integrated into the individual assessments.

3. Results

3.1. Functional differentiation of cytotoxic cancer drugs

From database searches, a single scientific definition of the term "cytotoxicity" was retrieved: (OECD, 2010): "The adverse effects resulting from interference with structures and/or processes essential for cell survival, proliferation, and/or function. For most chemicals/substances, toxicity is a consequence of non-specific alterations in "basal cell functions" (i.e. via mitochondria, plasma membrane integrity, etc.), which may then lead to effects on organ-specific functions and/or death of the organism. These effects may involve the integrity of membranes and the cytoskeleton, cellular metabolism, the synthesis and degradation or release of cellular constituents or products, ion regulation, and cell division." This OECD monograph is intended as guidance on using cytotoxicity tests to estimate starting doses of chemicals/substances in acute oral systemic toxicity tests in rodents. Although the term cytotoxic is mentioned in several other regulations, no definition is provided. A number of internet sites provide practical descriptions of cytotoxic cancer drugs.

Based on our collective experience and review of the literature, we have compiled an alternate definition of cytotoxic cancer drugs for the purposes of assessing safety risks: a therapeutic agent, whose primary activity is to indiscriminately and directly kill both healthy and cancerous cells in an effort to control the spread of cancer in the human body is considered to be cytotoxic if:

- the mechanism of action is to directly disrupt DNA structure or mitotic function (e.g., intercalation, clastogenicity, spindle destruction) causing cell death; and
- the above mechanism of action does not selectively target tumor cells or differentiate in susceptibility between tumor and non-tumor cells; and
- results of cell culture assays, genotoxicity and experimental animal studies or human clinical studies demonstrate that the drug's toxicity is not specific to nor displays substantially different susceptibility to tumor cells in comparison to non-tumor cells in living tissue.

To meet the definition, all three elements have to be present.

Cytotoxic cancer drugs are usually of high acute toxicity. In preclinical studies, corroborative evidence can be provided by histopathology. Tubulin-binding cytotoxic cancer drugs such as maytansine, colchicine, DM1 and others are known to cause specific radiomimetic lesions indicative of cytotoxicity in numerous target organs. Lesions consist of mitotic arrest (aberrant mitoses) or apoptosis, which can be seen histologically (Melgoza et al., 2008; Barok et al., 2011; Poon et al., 2013).

Primary toxicity effects in rats between DM1 and maytansine are comparable. Aberrant mitotic figures in target organs e.g. liver have been described at intravenous doses of 1400–1600 μg DM1/m^2 in rats. This corresponds to similar DM1 plasma concentration achieved with therapeutic concentrations of 3.6 mg/kg trastuzumab-DM1 (corresponding to about 2300 μg DM1/m^2) in clinical trials (Poon et al., 2013). Intravenous therapeutic maytansine