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Safe handling of oral antineoplastic medications: Focus on targeted therapeutics in the home setting

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Abstract

Introduction: With the growing number of oral targeted therapies being approved for use in cancer therapy, the potential for long-term administration of these drugs to cancer patients is expanding. The use of these drugs in the home setting has the potential to expose family members and caregivers to them either through direct contact with the drugs or indirectly by exposure to the parent compounds and/or their active metabolites in contaminated patients' waste.

Methods: A systematic literature review was performed and the known adverse health effect of 32 oral targeted therapeutics is summarized. In particular, the carcinogenicity, genotoxicity, and embryo-fetal toxicity, along with the route of excretion were evaluated.

Results: Carcinogenicity testing has not been performed on most of the oral targeted therapeutics and the genotoxicity data are mixed. However, the majority of these drugs exhibit adverse reproductive effects, some of which are severe. Currently, available data does not permit the possibility of a health hazard from inappropriate handling of drugs and contaminated patients waste to be ignored, especially in a long-term home setting. Further research is needed to understand these issues.

Conclusions: With the expanding use of targeted therapies in the home setting, family members and caregivers, especially those of reproductive risk age, are, potentially at risk. Overall basic education and related precautions should be taken to protect family members and caregivers from indirect or direct exposure from these drugs. Further investigations and discussion on this subject are warranted.

Keywords

Oral antineoplastic medications, safe handling, targeted therapies, home setting

Introduction

The last two decades have witnessed significant changes in the general landscape of the cancer chemotherapy armamentarium. There has been a rapid development of targeted cancer therapies consequent to advanced specific monoclonal antibodies and low-molecular weight signal transduction inhibitors targeted to specific receptors or specific molecular pathways up-regulated in certain cancers.[1–4] Regulatory authorities have approved a wide range of oral targeted antineoplastic medications since the beginning of the 21st century.[5]

Consequently, there has been a simultaneous movement away from conventional chemotherapy to targeted therapeutics with an increased number of available oral antineoplastic agents. At this time, approximately 30–35% of all chemotherapy drugs (conventional and non-conventional) may now be found as oral formulations (apart from hormonal agents).[6]

This phenomenon has brought about changes in attitudes and regulations concerning certain aspects of the

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safe handling of antineoplastic drugs. The occupational hazards of conventional antineoplastic (cytotoxic) drugs consequent to inappropriate handling, dispensing, and administration of antineoplastic drugs (direct contact) have been well documented.[7–10] Simultaneously, there exists the problem of indirect contact from various sources. These include contact with patient waste: urine and/or feces containing either parent drugs or their active metabolites. This indirect source of exposure can affect health care workers, as well as family members and other non-medical caregivers.[11–13] In addition, the drugs and/or their metabolites may be found in other body fluids such as: saliva, sweat, vomit, ascetic fluid, and semen.[14–18]

Guidelines exist on the safe handling of antineoplastics as well as handling of excreta from patients receiving conventional parenteral chemotherapy.[19–24] With the proliferation of oral antineoplastic therapies, guidelines have been issued specifically to address the use of oral agents as well as safe handling procedures.[25] An International Group of Pharmacy Practitioners developed recommendations covering a wide range of subjects including recommendations for manufacturers, distributors, health care providers, as well as for patients and their caregivers.[26] However, in these recommendations of January 2011, small molecular weight oral targeted therapeutics were not addressed as a separate group. The direct and indirect aspects of safe handling of oral targeted therapeutics in the home setting need to be more fully considered taking into account some of the issues which give rise for concern such as:

1. The rapidly expanding inventory of targeted therapies, even more so in recent years.[27,28]
2. The large percentage of targeted cancer drugs now available as oral agents, causing a shifting of treatment from the hospital setting into the home scenario.
3. Conventional parenteral chemotherapy treatment regimens are designed to treat patients in hospital wards, day care outpatient clinics, office, or, in some countries, home settings. Cytotoxic agents are administered over a fairly short period of time (generally using the maximum tolerated dose) followed by a period of rest from therapy. Generally speaking, this on/off cycle applies equally to oral conventional chemotherapy drugs (such as cyclophosphamide, lomustine, topotecan, and so on). Even when the patient receives ''maintenance therapy'' with oral chemotherapy drugs using a more prolonged schedule, this still takes place over a relatively restricted period of time.
4. In contrast, current treatment plans for most oral targeted therapeutics state that ''treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.'' Consequently, the majority of these agents are administered in a continuous fashion for many months and even years.[29,30] This increases the probability of direct contact by family members and/or caregivers with targeted therapeutics as well as the hazard of indirect exposure to them from excreta contaminated with the parent drug and/or its active metabolites.

Thus, it seems prudent to reconsider general aspects of potential health hazards to the health care provider, patients, and their caregivers from long-term use of oral targeted exposure in the home setting.

General aspects of potential health hazards to the health care provider, patients, and their caregivers from oral targeted agents should be considered. These include reviewing issues such as carcinogenicity, mutagenicity, genotoxicity, and embryo-fetal toxicity together with data relating to excretion of these agents as a part of their pharmacokinetic parameters.

The overview presents the currently available data on these topics for further discussion.

Methods

Current guidelines from the NIOSH,[20] the American Society of Health-System Pharmacists (ASHP),[21] and the International Society of Oncology Pharmacy Practitioners (ISOPP)[22] were consulted. A systematic English-language literature search was conducted using standard electronic databases (such as PubMed, International Pharmaceutical Abstracts, and Google Scholar) for papers from 1990 to 30 September 2015. Relevant conference abstracts were also considered. The following search terms were combined: *carcinogenicity, clastogenicity*, *embryo-fetal toxicity, genotoxicity, occupational hazards of antineoplastic/cytotoxic drugs, pharmacokinetic parameters (metabolism and excretion) of oral targeted antineoplastics*, *safe handling of antineoplastic/cytotoxic drugs, secondary neoplasms, targeted cancer therapy, teratogenicity*. In addition, a manual review of the bibliographies of the available literature (based on ''The Berman Medical Library,'' Hebrew University-Hadassah Medical Centre School, Ein Kerem, Jerusalem) was performed with relevant information included. Results of the literature search were independently reviewed by the authors for their relevance to the review and identify other pertinent articles.

Overview

Oral targeted therapeutics in cancer treatment

Table 1 lists currently used oral targeted cancer therapeutics and their approved indications. The table bears

Table 1. Currently approved oral targeted antineoplastic medications: General indications.[a,b]

No.	International non-proprietary names	Trade names	Initial approval	General indications[c]
1	Afatinib[d]	GILOTRIF®	2013[a] 2013[b]	U.S./EU Approval: NSCLC
2	Axitinib[d]	INLYTA®	2012[a] 2012[b]	U.S./EU Approval: RCC
3	Bosutinib[d]	BOSULIF®	2012[a] 2013[b]	U.S./EU Approval: Ph + CML
4	Cabozantinib[d]	COMETRIQ®	2012[a] 2014[b]	U.S./EU Approval: MTC
5	Ceritinib	ZYKADIA®	2014[a]	U.S. Approval: NSCLC
6	Cobimetinib	COTELLIC ®	2015[a]	U.S. Approval: melanoma (in combination with vemurafenib)
7	Crizotinib[e]	XALKORI®	2011[a] 2012[b]	U.S./EU Approval: NSCLC
8	Dabrafenib[d]	TAFINLAR®	2013[a] 2013[b]	U.S./EU Approval: melanoma
9	Dasatinib[e]	SPRYCEL®	2006[a] 2006[b]	U.S./EU Approval: Ph + CML; Ph + ALL
10	Erlotinib[e]	TARCEVA®	2004[a] 2005[b]	U.S./EU Approval: NSCLC; pancreatic cancer
12	Everolimus[e]	AFINITOR®	2009[a] 2009[b]	U.S. Approval: BC; pNET; RCC; renal angiomyolipoma with TSC; SEGA with TSC EU Approval: BC; PNET; RCC
13	Gefitinib	IRESSA®	2003/2015[a] 2009[b]	U.S./EU Approval: NSCLC
14	Ibrutinib	IMBRUVICA®	2013[a] 2014[b]	U.S. Approval: MCL; CLL;WM EU Approval: MCL; CLL
15	Idelalisib	ZYDELIG®	2014[a] 2014[b]	U.S. Approval: CLL; FL; SLL EU Approval: CLL; FL
16	Imatinib[e]	GLEEVEC® GLIVEC®	2001[a] 2001[b]	U.S./EU Approval: Ph + CML; Ph + ALL; MDS/ MPD; ASM; HES/CEL; DFSP; GIST
15	Lapatinib	TYKERB® TYVERB®	2007[a] 2008[b]	U.S./EU Approval: BC
17	Lenvatinib	LENVIMA®	2015[a]	U.S./EU Approval: radioactive iodine-refractory DTC
18	Nilotinib[e]	TASIGNA®	2007[a] 2007[b]	U.S./EU Approval: Ph + CML
19	Nintedanib	OFEV® VARGATEF®	2014[a] 2014[b]	U.S. Approval: IPF EU Approval: NSCLC
20	Olaparib	LYNPARZA®	2014[a] 2014[b]	U.S. Approval: ovarian cancer EU Approval: ovarian neoplasms
21	Palbociclib	IBRANCE®	2015[a]	U.S. Approval: BC
22	Pazopanib[e]	VOTRIENT®	2009[a] 2010[b]	U.S./EU Approval: RCC; STS

(continued)

Table 1. Continued

No.	International non-proprietary names	Trade names	Initial approval	General indications[c]
23	Ponatinib[e]	ICLUSIG®	2012[a]	U.S./EU Approval: Ph + CML; Ph + ALL
			2013[b]	
24	Regorafenib[e]	STIVARGA®	2012[a]	U.S./EU Approval: CRC; GIST
			2013[b]	
25	Ruxolitinib	JAKAFI®	2011[a]	U.S./EU Approval; myelofibrosis, polycythaemia vera
			2012[b]	
26	Sonidegib	ODOZO ®	2015[a]	U.S./EU Approval: BCC
			2015[b]	
27	Sorafenib[e]	NEXAVAR®	2005[a]	U.S./EU Approval: HCC; RCC; DTC (refractory to radioactive iodine)
			2006[b]	
28	Sunitinib[e]	SUTENT®	2006[a]	U.S./EU Approval: RCC; GIST; pNET
			2006[b]	
29	Trametinib[e]	MEKINIST®	2013[a]	U.S./EU Approval: melanoma
			2014[b]	
30	Vandetanib[e]	CAPRELSA®	2011[a]	U.S./EU Approval: MTC
			2012[b]	
31	Vemurafenib[e]	ZELBORAF®	2011[a]	U.S./EU Approval: melanoma
			2012[b]	
32	Vismodegib[e]	ERIVEDGE®	2012[a]	U.S./EU Approval: BCC
			2013[b]	

ASM: aggressive systemic mastocytosis; BC: breast cancer; BCC: basal cell carcinoma; CLL: chronic lymphocytic leukemia; CRC: colorectal cancer; DFSP: dermatofibrosarcoma protuberans; DTC: differentiated thyroid carcinoma; FL: follicular B-cell non-Hodgkin lymphoma; GIST: gastrointestinal stromal tumors; HCC: hepatocellular carcinoma; HES/CEL: hypereosinophilic syndrome/chronic eosinophilic leukemia; IPF: idiopathic pulmonary fibrosis, MCL: mantle cell lymphoma; MDS/MPD: myelodysplastic/ myeloproliferative diseases; MTC: medullary thyroid cancer; MM: multiple myeloma; NSCLC: non-small cell lung cancer; pNET: pancreatic neuroendocrine tumor's; Ph + ALL: Philadelphia chromosome positive acute lymphoblastic leukemia; Ph + CML: Philadelphia chromosome positive chronic myeloid leukemia; RCC: renal cell carcinoma; SEGA: subependymal giant cell astrocytoma; SLL: small lymphocytic lymphoma; STS: soft tissue sarcoma; TSC: tuberous sclerosis complex, WM: Waldenström's macroglobulinemia.
[a]Retrieved from: US FDA http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
[b]Retrieved from: European medicines agency http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp
[c]For further details, see full prescribing information.
[d]NIOSH 2014 list of hazardous drugs.[41]
[e]NIOSH proposed 2016 list of hazardous drugs (http://www.regulations.gov/#!documentDetail;D = CDC-2015-0034-0002)

witness to both the rapid increase in the quantity and number of these agents as well as their broad spectrum of clinical activity. It is noteworthy that approximately 70% of the currently used targeted oral antineoplastics were approved by the regulatory authorities in the United States and/or Europe since January 2011. The broad clinical spectrum of currently available targeted agents now includes not only treatment of hematological malignancies but also solid tumors such as breast cancer, lung cancer, and colorectal cancer.[31]

Along with the increasing number of oral targeted therapeutics, the emergence of new drugs with differing molecular mechanisms of action is noteworthy. For example, olaparib is a first-in-class, orally active, small molecule, poly (ADP-ribose) polymerase (PARP) inhibitor which capitalizes on the "Achilles' heel" of BRCA1/2-mutated cells whose DNA repair mechanisms are already impaired.[32,33]

Usually, oral targeted agents are used as first-line treatment, or in cases of failure of prior chemotherapy. A case in point is imatinib mesylate. After a decade, imatinib still remains the first-line treatment of patients with Kit (CD117) positive unresectable and/or metastatic gastrointestinal stromal tumors (GIST). The recent European Society of Medical Oncology and National Comprehensive Cancer Network guidelines mention use of adjuvant imatinib for $\geq$1 year in patients with KIT positive, resectable GIST at high-risk of recurrence. Moreover, the guidelines support the use of neoadjuvant imatinib in cases of limited disease if it would facilitate less extensive surgery and be organ sparing.[34]

In addition, oral targeted agents are used to overcome primary and acquired drug-resistance of first-generation targeted agents. For example, second- and third-generation tyrosine kinase inhibitors (TKIs) are used for the treatment of patients with Ph-positive chronic myeloid leukemia (CML) with resistance or intolerance to prior targeted therapy.[35] In addition, crizotinib and ceritinib are used as first- and second-line therapy, respectively, for the treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC).[36,37]

A novel and significant use of oral targeted agents is in combination with other antineoplastics, including monoclonal antibodies. Thus, idelalisib, a first-in-class orally bio-available, reversible, p110 delta isoform-specific phosphoinositide-3 kinase (PI3K) inhibitor is currently indicated in combination with rituximab, an anti-CD20 monoclonal antibody, for the treatment of adult patients with chronic lymphocytic leukemia (CLL). This combination significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.[38] In addition, the combination of ibrutinib, a first-in-class orally administered inhibitor of Bruton tyrosine kinase (BTK), and of atumumab, an anti-CD20 monoclonal antibody that binds to an epitope distinct from that for rituximab, exhibited clinical activity in heavily pre-treated patients with relapsed/refractory CLL/small lymphocytic lymphoma (SLL).[39]

These are just some of the examples of significant changes in the role of oral targeted therapeutics in treatment of cancer patients over recent years.

Oral targeted therapeutics as hazardous substances

A number of conventional antineoplastic (cytotoxic) agents (such as alkylating agents, antimetabolites, antineoplastic antibiotics, microtubule inhibitors, etc.) are classified as hazardous substances based on the ASHP definition that was originally developed in 1990.[40] This initial definition was revised by the NIOSH Working Group on Hazardous Drugs.[20,41] Drugs currently considered hazardous include those that exhibit one or more of the following basic characteristics in humans or animals:

1. Genotoxicity (i.e. mutagenicity and clastogenicity in short-term test systems).
2. Carcinogenicity in animal models, in the patient population, or both.
3. Teratogenicity or fertility impairment in animal studies or in treated patients.
4. Reproductive toxicity.
5. Evidence of serious organ or other toxicity at low doses in animal models or treated patients.
6. Structure and toxicity profiles of new drugs that mimic existing hazardous drugs.

An evaluation of these parameters was made in order to determine if the currently used oral targeted agents should be categorized as hazardous substances. The assessment was based on information gleaned mainly from non-clinical toxicology sections printed on the Patient Information Leaflets (PILs), as supplied by the drug companies. The data are outlined in Table 2 with a focus on (a) carcinogenicity, (b) genotoxicity, and (c) embryo-fetal toxicity.

Carcinogenicity. As can be seen from Table 2, carcinogenicity studies have not been conducted with the majority of currently used oral targeted antineoplastics (22 out of 32). This is acceptable according to the guideline ICH S9 on Non Clinical Evaluation for Anticancer Pharmaceuticals: ''Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.''[42] However, standard animal two-year carcinogenicity studies were negative for the following drugs: bosutinib, erlotinib, everolimus, nilotinib, nintedanib. Five drugs: dasatinib, gefitinib, imatinib, lapatinib, and sunitinib, were positive or weakly positive but the clinical relevance of these findings is unknown.

Additionally, it is noteworthy that the results of some clinical trials suggest that certain targeted antineoplastics are potentially carcinogenic. Thus, small-molecule BRAF inhibitors, such as vemurafenib and dabrafenib, for which formal animal carcinogenicity studies have not been conducted, cause a multitude of treatment-related cutaneous adverse events, including squamoproliferative lesions. The most common related malignant lesions of the skin include keratoacanthomas (KA), cutaneous squamous cell carcinoma (cuSCC), and new primary melanomas. Clinical trials report that cuSCCs and KAs were diagnosed in up to 31%, and 11% of patients receiving vemurafenib and dabrafenib monotherapy, respectively.[43] This, however, may vary with trial duration, dosage, and length of follow up. A notable property of vemurafenib and other selective RAF inhibitors is that they inhibit RAF activation of extracellular signal-regulated kinase (ERK) only in tumors expressing mutant BRAF. In BRAF wild-type tumors as well as normal cells, they activate this pathway.[44] This paradoxical activation of RAF signaling by the BRAF inhibitor likely accounts for its unique toxicity profile including squamoproliferative lesions. Moreover, histologic characterization of these secondary malignant lesions suggested that they are generally more aggressive than those arising

Table 2. Oral targeted antineoplastic medications: Non-clinical toxicology.[a,b]

No.	International non-proprietary name /trade name	Carcinogenesis	Mutagenesis	Embryo-fetal toxicity
1	Afatinib (GILOTRIF®)	Carcinogenicity studies have not been conducted	Afatinib showed no genotoxic potential in a standard test battery of genotoxicity assays	Administration of afatinib to pregnant rabbits at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose) or greater during the period of organogenesis caused increased post-implantation loss and, in animals showing maternal toxicity, abortion at late gestational stages. In an embryo-fetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg.
2	Axitinib (INLYTA®)	Carcinogenicity studies have not been conducted	Axitinib was not mutagenic or clastogenic in conventional assays in vitro. Axitinib was genotoxic in the in vivo mouse bone marrow micronucleus assay.	Axitinib was teratogenic, embryo-toxic, and fetotoxic in animal reproductive studies. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformation (cleft palate) at 1.5 mg/kg/dose (approximately 0.5 times the AUC in patients at the recommended starting dose) and variation in skeletal ossification at $\geq$0.5 mg/kg/dose (approximately 0.15 times the AUC in patients at the recommended starting dose).
3	Bosutinib (BOSULIF®)	A two-year rat carcinogenicity study was negative for carcinogenic findings	Bosutinib was not mutagenic or clastogenic in a standard test battery of genotoxicity assays	In a study conducted in rabbits, at the maternally-toxic dose of 30 mg/kg/day of bosutinib, there were fetal anomalies (fused sternebrae, and two fetuses had various visceral observations).The dose of 30 mg/kg/day resulted in exposures (AUC) approximately four times greater than the clinical exposure at the recommended bosutinib dose.
4	Cabozantinib (COMETRIQ®)	Carcinogenicity studies have not been conducted	Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	Cabozantinib was embryo-lethal in rats at exposures below the recommended human dose, with increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.
5	Ceritinib (ZYKADIA®)	Carcinogenicity studies have not been conducted	Ceritinib was not mutagenic when tested in an in vitro bacterial cell assay. Ceritinib was aneugenic in the in vitro cytogenetic assays	In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits.
6	Cobimetinib (COTELLIC®)	Carcinogenicity studies with cobimetinib have not been conducted.	Cobimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in bone marrow of rats.	Administration of cobimetinib to pregnant rats during the period of organogenesis resulted in increased post-implantation loss, including total litter loss, at exposures (AUC) of 0.9–1.4 times those in humans at the recommended dose. Fetal malformations of the great vessels and skull (eye sockets) occurred at the same exposures.
7	Crizotinib (XALKORI®)	Carcinogenicity studies have not been conducted	Crizotinib was not mutagenic when tested in an in vitro bacterial cell assay.Crizotinib was aneugenic in the in vitro cytogenetic assays.	In animal reproduction studies, oral administration of crizotinib in pregnant rats during organogenesis at exposures similar to those observed with the maximum recommended human dose resulted in embryo-toxicity and fetotoxicity.
8	Dabrafenib (TAFINLAR®)	Carcinogenicity studies have not been conducted.	Dabrafenib was not mutagenic and clastogenic in a standard test battery of genotoxicity assays	Dabrafenib was teratogenic and embryo-toxic in rats at doses three times greater than the human exposure at the recommended clinical dose. At doses of 20 mg/kg/day or greater (equivalent to the human exposure at the recommended dose), rats demonstrated delays in skeletal development and reduced fetal body weight.

(continued)

Table 2. Continued

No.	International non-proprietary name /trade name	Carcinogenesis	Mutagenesis	Embryo-fetal toxicity
9	Dasatinib (SPRYCEL®)	The two-year carcinogenicity study was positive for carcinogenic findings	Dasatinib was not mutagenic when tested in an in vitro bacterial cell assay. Dasatinib was clastogenic when tested in vitro in Chinese hamster ovary cells	In non-clinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities were observed in rats and rabbits. Embryo-fetal toxicities included skeletal malformations at multiple sites, reduced ossification, edema, and microhepatia.
10	Erlotinib (TARCEVA®)	The two-year carcinogenicity study was negative for carcinogenic findings	There was no evidence for a genotoxic potential of erlotinib when studied in a standard battery of genotoxicity assays	Erlotinib has been shown to cause maternal toxicity resulting in embryo-fetal lethality and abortion in rabbits when given during the period of organogenesis at doses that result in plasma drug concentrations approximately three times those achieved at the recommended dose in humans.
11	Everolimus (AFINITOR®)	A two-year carcinogenicity study was negative for carcinogenic findings	Everolimus showed no genotoxic potential in a standard test battery of genotoxicity assays	In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g. sternal cleft), and retarded skeletal development.
12	Gefitinib (IRESSA®)	In a two-year carcinogenicity study in rats, administration of gefitinib at 60 mg/m^2/ day (approximately 0.4 times the recommended daily clinical dose on a mg/m^2 basis) caused hepatocellular adenomas and hemangiomas/hemagiosarcomas of the mesenteric lymph nodes in female rats.	Gefitinib has been tested for genotoxicity in a series of in vitro (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an in vivo rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage.	A single-dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 0.2 times the recommended human dose on a mg/m^2 basis). In animal reproductive studies, when pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning there was a reduction in the number of off spring born alive. This effect was more severe at 20 mg/kg (approximate the human clinical dose) and was accompanied by high neonatal mortality soon after parturition.
13	Ibrutinib (IMBRUVICA®)	Carcinogenicity studies have not been conducted	Ibrutinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	In pregnant rats, ibrutinib at a dose of 80 mg/kg/day was associated with increased post-implantation loss and increased visceral (heart and major vessels) malformations and skeletal variations with an exposure margin 14 times the AUC found in patients at a daily dose of 560 mg.
14	Idelalisib (ZYDELIG®)	Carcinogenicity studies have not been conducted	Idelalisib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	In an embryo-fetal development study in rats, increased post-implantation loss, malformations (absence of caudal vertebrae and in some cases also of sacral vertebrae), skeletal variations, and lower fetal body weights were observed. Malformations were observed at exposures from 12 times the human exposure based on AUC.
15	Imatinib (GLEEVEC®)	In the two-year rat carcinogenicity study administration of imatinib at clinically relevant doses resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/ day and females at	Imatinib showed no genotoxic potential in a standard test battery of genotoxicity assays. Positive genotoxic effects were obtained for imatinib for	Imatinib was teratogenic in rats when administered during organogenesis at doses equal to the maximum clinical dose of 800 mg/day. Placental transfer of imatinib to the fetus has been documented

(continued)

Table 2. Continued

No.	International non-proprietary name /trade name	Carcinogenesis	Mutagenesis	Embryo-fetal toxicity
		≥30 mg/kg/day. Target organs for neoplastic changes were the kidneys (renal tubule and renal pelvis), urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands, and non-glandular stomach.	clastogenicity in the presence of metabolic activation	
16	Lapatinib (TYKERB®)	In carcinogenicity studies performed in rats and mice, lapatinib was administered orally for up to 104 weeks at clinically relevant doses. There was no evidence of carcinogenicity in mice. In male rats, there was an increased incidence of whole body combined hemangiomas and hemangiosarcomas.	Lapatinib showed no genotoxic potential in a standard test battery.	Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first four days after birth. When administered to pregnant animals during the period of organogenesis, lapatinib caused fetal anomalies (rats) or abortions (rabbits) at maternally toxic doses.
17	Lenvatinib (LENVIMA®)	Carcinogenicity studies have not been conducted	Lenvatinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	In an embryo-fetal development study, daily oral administration of lenvatinib at doses greater than or equal to 0.3 mg/kg (approximately 0.14 times the recommended human dose) to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies.
18	Nilotinib (TASIGNA®)	A two-year carcinogenicity study was negative for carcinogenic findings	Nilotinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	Nilotinib did not induce teratogenicity, but did show embryo- and fetotoxicity. In rats, nilotinib at doses ≥30 mg/kg/day (approximately two times the AUC in patients at the dose of 400 mg twice-daily the recommended daily dose [RDD]) resulted in embryo-fetal toxicity as shown by increased resorption and post-implantation loss. When pregnant rats were dosed with nilotinib during organogenesis and through lactation, the adverse effects included a longer gestational period, lower pup body weights until weaning, and decreased fertility indices in the pups when they reached maturity, all at a maternal dose of 360 mg/m^2 (approximately 0.7 times at the RDD).
19	Nintedanib (VARGATEF®)	A two-year carcinogenicity study was negative for carcinogenic findings	Nintedanib showed no genotoxic potential in a standard test battery of genotoxicity assays	In animal reproduction studies, nintedanib caused embryo-fetal lethality and teratogenic effects at exposure levels below human exposure at the maximum recommended human dose. Effects on the development of the axial skeleton and on the

(continued)

Table 2. Continued

No.	International non-proprietary name /trade name	Carcinogenesis	Mutagenesis	Embryo-fetal toxicity
				development of the great arteries were also noted at sub therapeutic exposure levels.
20	Olaparib (LYNPARZA®)	Carcinogenicity studies have not been conducted with olaparib	Olaparib was clastogenic in an in vitro and an in vivo genotoxicity assays.	In animal reproduction study, embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia) were observed in pregnant rats received oral dose 0.5 mg/kg/day olaparib (approximately 0.3% of human exposure at the recommended dose).
21	Palbociclib (IBRANCE®)	Carcinogenicity studies have not been conducted with palbociclib	Palbociclib was aneugenic in an in vitro and an in vivo genotoxicity assays	In animal reproduction studies, palbociclib was teratogenic and fetotoxic at maternal exposures that were greater than or equal to four times the human clinical exposure
22	Pazopanib (VOTRIENT®)	Carcinogenicity studies with pazopanib have not been conducted	Pazopanib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	In animal reproduction studies, pazopanib was teratogenic, embryo-toxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of $\geq$3 mg/kg/day (approximately 0.1 times the human clinical exposure) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch), and incomplete or absent ossification.
23	Ponatinib (ICLUSIG®)	Carcinogenicity studies have not been performed with ponatinib	Ponatinib did not exhibit genotoxic properties when evaluated in the standard in vitro and in vivo systems	In animal reproduction studies, ponatinib caused embryo-fetal toxicity at exposures lower than human exposures at the recommended human dose. Embryo-fetal toxicities were observed at 1 mg/kg/day (approximately 24% the AUC in patients receiving the recommended dose) and involved multiple fetal soft tissue and skeletal alterations, including reduced ossification.
24	Regorafenib (STIVARGA®)	Carcinogenicity studies have not been performed with regorafenib	Regorafenib itself did not demonstrate genotoxicity in in vitro or in vivo assays; however, a major human active metabolite of regorafenib, (M-2), was positive for clastogenicity	Regorafenib was embryo-lethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardio-vascular, genitourinary, and skeletal malformations.
25	Ruxolitinib (JAKAFI®)	Ruxolitinib was not carcinogenic in carcinogenicity studies.	Ruxolitinib has shown no mutagenic or clastogenic potential in a	Ruxolitinib decreased fetal weight and increased post-implantation loss in animal studies. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day.

(continued)

Table 2. Continued

No.	International non-proprietary name /trade name	Carcinogenesis	Mutagenesis	Embryo-fetal toxicity
			standard battery of genotoxicity assays	This dose is approximately 7% the clinical exposure at the maximum recommended dose. There was no evidence of a teratogenic effect in rats and rabbits.
26	Sonidegib (ODOMZO®)	Carcinogenicity studies with sonidegib have not been performed	Sonidegib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	In animal reproduction studies, oral administration of sonidegib during organogenesis at doses below the recommended human dose of 200 mg resulted in embryotoxicity, fetotoxicity, and teratogenicity. Teratogenic effects observed included severe midline defects, missing digits, and other irreversible malformations. Sonidegib can cause fetal harm when administered to a pregnant female based on its mechanism of action. This represents a black-box warning
27	Sorafenib (NEXAVAR®)	Carcinogenicity studies have not been performed with sorafenib	Sorafenib was clastogenic when tested in an in vitro assay in the presence of metabolic activation	When administered to rats and rabbits during the period of organogenesis, sorafenib was teratogenic and induced embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose
28	Sunitinib (SUTENT®)	The two-year rat carcinogenicity study was positive for carcinogenic findings	Sunitinib did not exhibit genotoxic potential in a standard battery of genotoxicity assays	Sunitinib was evaluated in pregnant rats and rabbits for effects on the embryo. Significant increases in the incidence of embryo-lethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryo-lethality was observed in rabbits at 5 mg/kg/day, while developmental effects were observed at $\geq$1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day).
29	Trametinib (MEKINIST®)	Carcinogenicity studies with trametinib have not been conducted	Trametinib did not exhibit genotoxic potential in a standard battery of genotoxicity assays	In reproductive toxicity studies, administration of trametinib to rats during the period of organogenesis resulted in decreased fetal weights at doses greater than or equal to 0.031 mg/kg/day (approximately 0.3 times the human exposure based on AUC at the recommended dose). In pregnant rabbits, administration of trametinib during the period of organogenesis resulted in decreased fetal body weight and increased incidence of variations in ossification at doses greater than or equal to 0.039 mg/kg/ day (approximately 0.08 times the human exposure at the recommended dose based on AUC)
30	Vandetanib (CAPRELSA®)	Carcinogenicity studies have not been conducted with vandetanib.	Vandetanib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	When vandetanib was administered to female rats prior to mating and through the first week of pregnancy at a dose of 25 mg/kg/day (approximately equal to the human exposure at the recommended dose), there were increases in pre-implantation loss and post-implantation loss resulting in a reduction in the number of live embryos. During organogenesis, a vandetanib dose of 25 mg/kg administered

(continued)

Table 2. Continued

No.	International non-proprietary name /trade name	Carcinogenesis	Mutagenesis	Embryo-fetal toxicity
				to rats caused an increase in post-implantation loss, including occasional total litter loss
31	Vemurafenib (ZELBORAF®)	Carcinogenicity studies have not been conducted with vemurafenib.	Vemurafenib did not exhibit genotoxic potential in a standard battery of genotoxicity assays	Vemurafenib revealed no evidence of teratogenicity in rat embryo/fetuses at doses up to 250 mg/kg/day (approximately 1.3 times the human clinical exposure based on AUC) or rabbit embryo/fetuses at doses up to 450 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC). Fetal drug levels were 3–5% of maternal levels, indicating that vemurafenib has the potential to be transmitted from the mother to the developing fetus.
32	Vismodegib (ERIVEDGE®)	Carcinogenicity studies with vismodegib have not been conducted. Pilomatricoma (a benign cutaneous neoplasm) was observed in rats administered oral vismodegib at exposures approximately 0.8 times the systemic exposure (AUC) in patients at the recommended human dose	Vismodegib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays	In animal reproductive studies, vismodegib was teratogenic, embryo-toxic, and fetotoxic. A dose of 10 mg/kg/day (approximately 0.2 times the AUC in patients at the recommended dose) resulted in malformations (including missing and/or fused digits, open perineum and craniofacial anomalies) and retardations or variations (including dilated renal pelvis, dilated ureter, and incompletely or unossified sternal elements, centra of vertebrae, or proximal phalanges and claws). Vismodegib can cause fetal harm when administered to a pregnant female based on its mechanism of action. This represents a black-box warning

[a]Retrieved from: US FDA http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
[b]Retrieved from: European Medicines Agency http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp

sporadically.[45] The combination of these data formed the basis for limitation of clinical use BRAF inhibitors. Thus, according to current prescribing information, vemurafenib and dabrafenib should not be used in patients with wild-type BRAF melanoma.

There are a handful of reports suggesting a potential relationship between the occurrence of cuSCC in patients with basal cell carcinoma (BCC) and treatment with vismodegib, a first-in-class, orally active, small molecule, Hedgehog (Hh) pathway inhibitor. However, this is a difficult issue to analyze because (i) these patients are at risk of developing both BCC and SCC, and (ii) some BCCs can have squamous features, such as basosquamous carcinoma.[46] Further studies are needed to critically address this issue.

In a recent study, Brown et al.[47] described a worrying frequency (in 11 of 30 patients) of secondary malignancies, including skin cancer, ovarian cancer, lung cancer, and thyroid neoplasm observed in the triple-combination of bendamustine, rituximab, and ibrutinib in relapsed/ refractory CLL. Trial participants received bendamustine and rituximab for up to six cycles (repeated every 28 days) with daily ibrutinib until progressive disease or unacceptable toxicity and followed up over a three-year period, including an extension phase. The risk of second malignancies in CLL patients is higher at baseline, so the relationships to study treatments are unclear.[48] These findings merit further investigation in subsequent larger trials evaluating this combination treatment.

Additionally, cases of secondary myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been reported in a small number of patients with germline BRCA-mutated (gBRCAm) status who received olaparib monotherapy. These data formed the basis for inclusion of this life-threatening side effect in the "WARNINGS AND PRECAUTIONS" section of the current prescribing information. However, all MDS/AML patients had previously received platinum-based chemotherapy and/or other DNA damaging agents.[49] Further epidemiologic research is needed to understand the baseline risk of developing therapy-related MDS/AML.

In summary, there is no complete picture allowing an accurate estimate of the carcinogenic potential of oral targeted antineoplastics. A justified concern with the use of targeted therapies is the possibility that abrogation of one pathway may lead to activation of another. Hopefully, future studies will assess more data, including post-marketing experience, with currently approved preparations as well as from non-clinical investigation of new targeted oral therapeutics.

Genotoxicity. A more predictable situation exists with respect to the evaluation of genotoxicity in short-term test systems of currently used oral targeted antineoplastic drugs. Conventional cytotoxic drugs affect universally vital targets, firstly DNA, while most of the targeted agents function as signal transduction inhibitors, not directly affecting DNA structure. Data presented in Table 2 shows that most drugs do not have mutagenic or clastogenic activity in a standard battery of genotoxicity assays with the exception of olaparib, a potent, oral poly (ADPribose) polymerase (PARP) inhibitor, which was clastogenic in in vitro and in vivo assays. Simultaneously, a dose-dependent increase in the frequency of sister chromatid exchange (SCEs) arising from short-term, low-dose (typically greater than 90% cell viability) olaparib exposure of normal human cells was seen.[50] As expected, in this study, olaparib resulted in marked hypersensitivity, greater than a 200-fold increased sensitivity, for BRCA1-deficient cells as compared to wild type.

PARP are a family of nuclear protein enzymes involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. PARP-1 and PARP-2 are the best characterized members of the PARP family and play a key role in the DNA damage response and repair of single-stranded breaks (SSB) through base excisional repair (BER).[51] PARP inhibitors are pharmacologic agents which primarily inhibit the PARP-1 and PARP-2 enzymes within the cell. Inhibition of PARP results in failure of BER to correct single-stranded breaks in DNA. This failure results in double-stranded breaks (DSBs) that are subsequently repaired either by homologous recombination (HR) repair, which is error-free, or by non-homologous end joining (NHEJ), which is an error-prone process.[52] Clinically, PARP inhibitors demonstrate activity in tumors which lack a functional HR system (i.e. BRCA1 and BRCA2 mutations). This phenomenon known as "synthetic lethality," a term to describe the combined lethal effect of two genetic variations that are otherwise non-lethal when occurring in isolation.[53,54] Thus, clastogenicity and related genomic instability were consistent with the known pharmacology of olaparib as a PARP inhibitor, likely through interfering with the BER pathway. Although the adverse genomic consequences of PARP inhibitors therapy in clinical practice have not yet been fully investigated, the potential genotoxic risk from clinical use of PARP inhibitors should be considered, especially for patients with early stage cancers. Simultaneously, given the mechanism of action and, as discussed above, increased rates of MDS/AML seen in the olaparib clinical trials, there exists a clear safety signal that this compound may increase the risk of this potentially fatal complications.

Embryo-fetal toxicity. A clearer picture exists in regard to the embryo-fetal toxicity of oral targeted medications

which demonstrate reproductive toxicities in animal studies often at exposures below or similar to the recommended human dose. Based on these data, all oral targeted therapeutics in clinical use are categorized with a FDA pregnancy risk category "D" at the time of their approval, as well as conventional (cytotoxic) drugs. These letter-based FDA pregnancy categories have recently been replaced with new nomenclature, but the older categories will be in place until they are phased out over time.[55]

The majority of conventional chemotherapy drugs cross the placenta and reach the fetus due to their relatively small molecular weight and, therefore, realize their fetotoxic and/or teratogenic potential affect universally vital cellular targets (DNA, RNA, microtubuli, etc.) and interrupt cell functions during different phases of the cell cycle.[56] Almost all conventional antineoplastics are teratogenic in animals. The teratogenic properties of these drugs in clinical practice depend on the type, amount, and threshold dose.[57,58] Conventional chemotherapy should be avoided during the first trimester. This is the period of organogenesis and the vulnerability to drugs at this time is high with the possible occurrence of both major congenital malformations and miscarriages.[59,60]

Currently used oral targeted antineoplastics which are small molecules similar to many cytotoxic drugs can cross the placenta throughout the pregnancy period. Targeted therapeutics are aimed to hit one or a comparatively limited number of key cellular targets and therefore can inhibit tumor-related molecular aberrations (on-target effect) and as well as affecting a variety of unintended signal transduction pathways (off-target effect).[61] Related "on-target toxicities" are usually regarded as the "class effects," while "off-target toxicities" are generally observed when therapeutic agents affect the unintended targets.[62] They can, in some instances, affect fetal development. At the same time, oral targeted medications do not represent a homogenous group of drugs. Hence, each group of agents with specific "targets" could have specific pregnancy-related adverse events secondary to their "on-target" and "off-target" effects. In contrast to conventional cytotoxics, oral targeted therapeutics act as "embryo-selective teratogens," which specifically target embryonic pathways.[63]

The embryo-toxic and teratogenic potential of selected groups of oral targeted antineoplastics is presented below.

TKIs *in the treatment of CML.* The first-generation TKI, imatinib was found to induce embryo-toxicity and teratogenicity when administered during organogenesis. When administered to female rats at doses similar to those used in humans it can induce significant post-implantation fetal loss and a reduced number of live fetuses.[64] When imatinib was administered during organogenesis at doses ≥ 100 mg/kg, equivalent to a dose in adults of 800 mg/day based on body surface area, it induced teratogenic effects including exencephaly or encephalocele, absent or reduced frontal bones and absent parietal bones.[64] In more recent animal studies, imatinib was seen to be teratogenic when given orally to pregnant rats causing direct maternal or developmental toxicity such as exencephaly and encephalocele in addition to skeletal growth retardation and this effect was proportional to the drug dose.[65]

To date, there are five TKIs approved for clinical use in CML by the regulatory authorities in the United States and Europe.[66] As can be seen from Table 2, all these medications are associated with significant maternal and embryo-fetal toxicity in animal studies. Thus, dasatinib was teratogenic in rats and rabbits at sub therapeutic exposures. Embryo-fetal toxicities included skeletal malformations, reduced ossification, edema, and microhepatia.[67,68] Simultaneously, considerable fetal exposure was shown in pregnant rats treated with radiolabeled dasatinib.[69] The peak level of radioactivity in fetal blood was approximately 39% of that in maternal blood, but the overall AUC exposures were similar between fetus and mother. The data from this study in rats would predict a significant exposure to the fetuses of pregnant women undergoing dasatinib treatment.

The first- and second-generation TKIs such as imatinib, dasatinib, and nilotinib have revolutionized the treatment of CML.[70] Simultaneously, each agent targets tyrosine kinases within the cell uniquely to cause the desired anti-proliferative effect. Thus, although nilotinib and imatinib exhibit great selectivity for Bcr-Abl, stem cell factor (SCF) receptor (c-Kit), and platelet-derived growth factor receptors (PDGFR), these agents bind these kinases with different affinities. The ranking of imatinib affinities is PDGFR > c-Kit > Bcr-Abl, whereas for nilotinib this is Bcr-Abl > PDGFR > c-Kit.[71,72] Dasatinib was originally described as a dual kinase inhibitor of SFKs (Src family kinases) and BCR/ABL but was later found to be a multiple kinase inhibitor of c-Kit, PDGFR-alpha and beta, c-fms, and the Eph receptor family members.[73]

A number of listed proteins are relevant to gonadal development, embryonic implantation, and fetal maturation. Thus, PDGFR-alpha and PDGF ligands are key regulators for embryonic development. As demonstrated by Xu et al.,[74] disruption of PDGFR-alpha signaling disturbs the growth of dental cusp and interferes with the critical extension of palatal shelf during craniofacial development in mice. Additional data from animal studies suggest that PDGFR-alpha also plays a role in lung maturation, and inhibition of PDGFR-alpha may lead to lung hypoplasia.[75]

Many TKIs have activity against c-Kit receptor-associated tyrosine kinase involved in the differentiation and growth of a variety of mammalian cell types including hematopoietic stem cells, neuroblasts, melanoblasts, and primordial germ cells.[76,77] SCF and its cognate receptor c-Kit are known to be related to reproduction. As demonstrated by Mitsunari et al.,[78] SCF derived from endometrial cells and the implanting embryo exerts paracrine and/or autocrine action on the process of implantation by stimulating trophoblast outgrowth through its receptor c-Kit and, therefore, may have a significant role during mouse embryo implantation.

Multi-targeted antiangiogenic *TKIs*. Compelling evidence indicates that the interactions between vascular endothelial growth factor (VEGF) ligands and VEGF receptors (VEGFR) act as a fundamental regulator of normal and abnormal angiogenesis. VEGF blocking by interfering with the post-receptor signaling pathways by multi-targeted antiangiogenic TKIs provides the rational anticancer treatment option.[79] Data obtained in animal models indicate a major role for VEGFs and their receptors during organogenesis, particularly in embryonic mouse lung morphogenesis.[80,81] In a recent animal study, sunitinib, a potent oral multi-targeted TKI exhibited antitumor and antiangiogenic activities, was associated with embryo-fetal toxicity and malformation such as thoracic/lumbar vertebral alterations in rats and cleft lip/palate in rabbits at clinically relevant dose levels.[82] The observed embryo-toxic effects and skeletal abnormalities associated with sunitinib suggest the predictive critical role of VEGF-mediated angiogenesis in embryo-fetal development, including endochondral bone formation.

Hedgehog (Hh) pathway inhibitors. A special mention is worthy on the embryo-fetal toxicity activity of the Hedgehog (Hh) pathway inhibitors sonidegib and vismodegib representing the first class of targeted drugs approved for use in advanced and metastatic BCC. According to the printed "WARNINGS AND PRECAUTIONS" on the patient information leaflet, these compounds must not be used during pregnancy because of their teratogenic, embryo-toxic, and fetotoxic effects. Specific pregnancy prevention measures must be used during sonidegib and vismodegib treatment for at least 20 and 7 months after the final dose in women of childbearing age and for 8 and 3 months in men (due to their presence in semen), respectively (based on FDA recommendations). Patients must not donate blood until 20 months after their last dose of sonidegib and 7 months after their last dose of vismodegib to avoid their blood or blood products being given to a female of reproductive potential. To support marketing applications, an embryo-fetal development study was completed in which a number of pregnant rats were administered vismodegib by oral gavage on gestation days 6 to 17.[83] When vismodegib was administered at $\geq$60 mg/kg/day, doses associated with evidence of pharmacologic activity in previous rat toxicity studies, all concept uses were resorbed at an early embryonic stage in the absence of significant maternal toxicity. At the low dose of 10 mg/kg/day, corresponding to an exposure (AUC_{0-24h}) approximately 15% of the median in patients at steady state, morphologic examination of 70 fetuses revealed 21 fetuses with abnormalities classified as frank malformations among four of five examined litters. In contrast, no malformations were observed in the six control group litters. The findings in this study confirmed the embryo-toxic potential of vismodegib at clinically relevant exposures.

The crucial developmental function of Hh signaling at the developmental stage is also illustrated by the dramatic consequences in human fetuses of defects in the signaling pathways, such as holoprosencephaly associated with Sonic Hedgehog (SHH) mutations.[84] Therefore, teratogenicity and embryo-fetal toxicity can be regarded as a potential class effect of Hedgehog (Hh) pathway inhibitors.

Oral targeted agents for cancer treatment during pregnancy. The clinical relevance in humans of non-clinical studies remains to be determined. Owing to the relatively restricted experience of the use of oral targeted therapies in pregnant women, there is very limited information on the side effects of oral targeted agents on fertility and/or pregnancy. It is recommended to avoid these drugs during pregnancy, but single patient case reports suggest that inadvertent pregnancies may have a contradictory outcome. Thus, in the first trimester, dasatinib has been reported to cause fetal hydrops and severe fetal bicytopenia,[85] but normal pregnancies have also been reported.[86] Therefore, a lack of fetal toxicity in single reported cases does not indicate the safety of these drugs in pregnancy.

A case in point is imatinib mesylate. In 2008, Pye et al.[87] reported data on a series of 180 women who were exposed to imatinib during pregnancy, with available data for 125 pregnancies. In this cohort, 63 pregnancies (50.4%) resulted in normal live births, 18 (14.4%) ended in spontaneous abortion and 35 women underwent elective termination of pregnancy (three following identification of fetal abnormalities). Congenital malformations occurred in 12 (9.6%) of these pregnancies (eight live births, one stillbirth, and the three elective terminations). A total of 10 of the 12 infants with abnormalities have been exposed to imatinib during the first trimester. The congenital malformations

observed after exposure to imatinib in early pregnancy were relatively unusual. These include premature closure of skull sutures (craniosynostosis), hypoplastic lungs, and duplex kidney, absent kidney, shoulder anomaly, exomphalos, renal agenesis, hemivertebrae, and scoliosis.

More recently, Abruzzese et al.[88] summarized the outcome of 167 pregnancies among women exposed to imatinib: 128 were uneventful (77%), 24 ended in spontaneous abortion (14%), and 15 (9%) presented with abnormalities, including one referred to a concomitant drug (warfarin syndrome). All patients in this group were exposed to imatinib during organogenesis (>5-week gestation).

Based on the published data, approximately 20–25% of maternal exposure during the 1st trimester to TKIs ends in fetal problems or spontaneous abortion. The problems consist mainly of skeletal malformations and soft tissue abnormalities (especially involving the vessels and organ formation), and to a certain extent such abnormalities seem similar to those observed in preclinical studies (exencephaly, encephalopathy, and abnormalities of the skull bones observed in the rodent studies).

In summary, given the pre-clinical and clinical data set, there exists a clear signal that oral targeted therapeutics have some teratogenic potential and possibly some abortifacient potential as well.

Excretion of oral targeted therapeutics

There is a possible hazard of indirect exposure to health care providers, as well as family members and other non-medical caregivers from oral antineoplastic drugs. This exposure is primarily caused by contact with unchanged drug and/or its active metabolites present in urine, feces, and/or other body fluids excreted by patients receiving these drugs. Complete information on the actual amounts of unchanged drug and /or its active metabolites present in urine or feces is difficult to ascertain from the information presented in the manufacturer's Drug Package Inserts. In some cases, these contain only common data on excretion of isotope-labeled material in feces and urine without a detailed description of the relative contents of the unchanged parent compound and/or its active metabolites. Table 3 provides a framework for analyzing and interpreting data from other available sources. These data indicate that the elimination of most oral targeted therapeutics is primarily hepatic via feces or combined fecal and urinary routes of elimination. In the concentration profile of parent compounds and their metabolites in feces and urine, there are marked differences between the enumerated oral targeted antineoplastics.

Drugs such as cobimetinib, erlotinib, everolimus, ibrutinib, lenvatinib, palbociclib, and ruxolitinib are extensively metabolized and characterized by low or negligible levels of unchanged parent compound and/or active metabolites in excreta. Inactive metabolites are primary excreted in feces and urine. The possible hazard of indirect exposure associated with these compounds is probably minimal.

In contrast, drugs such as afatinib, bosutinib, ceritinib, nilotinib, pazopanib, regorafenib, sonidegib, sorafenib, and vemurafenib are not only excreted primarily via the feces (≥60%) but simultaneously are characterized by a relatively high content (≥40%) of unchanged excreted parent drug alone or in combination with active metabolites in the feces.

It is important to consider that the data may not precisely reflect the real situation. Most of the pharmacokinetic and mass balance data are based on single dose experiments with isotope-labeled parent compounds, performed in both healthy volunteers as well as patients. It is known that in some cases, after continuous daily dosing, pharmacokinetic parameters may change, possibly substantially. Thus, in a clinical study on the pharmacokinetic effects of prolonged imatinib treatment in gastrointestinal stromal tumors (GIST) patients, it was found that after long-term treatment the typical apparent imatinib clearance increased by 33% with a concomitant decrease in systemic exposure of about 42%.[160] The impact of these pharmacokinetic changes on the contents of the unchanged parent compound in excreta is unknown.

A case in point are single-dose experiments with [14C]-vemurafenib.[156] In the first 48 h, ≥94% of all recovered radioactivity in feces was associated with the parent compound, with total metabolites accounting for ≤6% of the total administered dose. Between 48 and 96 h, total metabolites accounted for a considerably higher proportion of radioactivity, with mean values of 55.5 % for the parent compound and 18.8%, 13.7%, and 11.9% for M6, M3, and M8, metabolites, respectively. The predominant metabolites in feces seem to be glucuronidated (M8) and glycosylated (M6) species that might be substrates for gut flora, allowing for reconversion to the parent molecule in the intestine for subsequent reabsorption into the systemic circulation. It is possible that the predominance of the parent molecule found in the 48-h pooled sample partially represents unabsorbed drug, whereas the parent molecule found in the second pooled fraction from 48 to 96 h represent parent drug generated through hepatobiliary recirculation. In this case, it can be assumed that after continuous daily dosing there is combined excretion of the parent compound as unabsorbed drug as well as drug generated through hepatobiliary recirculation. A similar situation can be predicted for

Table 3. Selected pharmacokinetic prameters oral targeted antineoplastic drugs.

No.	Generic/trade name	Elimination half-life	The median excretion of drug-related material (parent compound and/or metabolites)		Notes	Sources of information 1
			Feces	Urine		
1	Afatinib dimaleate (GILOTRIF®)	34 h	85.4%	4.3%	The main route of elimination after a single oral dose of 14C-labeled afatinib is excretion of unchanged drug in the feces (~ 90% of the recovered radioactivity). Only small amounts of metabolites were observed in excreta.	89–91
2	Axitinib (INLYTA®)	4.5 h	37%	22.7%	Following administration of a single dose [14C]-axitinib, the drug-related products identified in feces were unchanged axitinib, comprising 12% of the dose and pharmacologically inactive metabolites. The recovery of radioactivity from feces was variable (2.5%–60.2%) and warranted further investigation. Unchanged axitinib was not detected in urine.	92,93
3	Bosutinib (BOSULIF®)	22.5 h	91.3%	3.3%	Following administration of a single dose [14C]-bosutinib in a mass balance study, the major components in feces were unchanged bosutinib (~ 40% of dose) and N-desmethyl-bosutinib (M5), while in urine bosutinib and oxydechlorinated-bosutinib (M2) were the major components. The two major bosutinib metabolites M5 and M2 were pharmacologically inactive	94,95
4	Cabozantinib (S)-malate (COMETRIQ®)	~120 h	53.8%	27.3%	Following administration of a single dose [14C]-cabozantinib, the major components in feces were cabozantinib and pharmocologically inactive metabolites. Unchanged cabozantinib was not detected in urine.	96,97
5	Ceritinib (ZYKADIA®)	41 h	92.3%	1.30%	Following a single dose of [14C]-ceritinib the mean percentage of the dose eliminated in the feces as unchanged ceritinib was 68.0%.	98,99
6	Cobimetinib (COTELLIC®)	44 h	76.00%	17.80%	Metabolite profiling indicated that cobimetinib had been extensively metabolized with only 1.6% and 6.6% of the dose remaining as unchanged drug in urine and feces, respectively.	100,101

(continued)

Table 3. Continued

No.	Generic/trade name	Elimination half-life	The median excretion of drug-related material (parent compound and/or metabolites)		Notes	Sources of information 1
			Feces	Urine		
7	Crizotinib (XALKORI®)	42 h	63%	22%	A mass balance trial with a single dose of [14C]-crizotinib suggested that approximately 53% and 2.3% of crizotinib are excreted as unchanged drug in the feces and urine, respectively. Renal excretion of unchanged crizotinib is a minor route of elimination; however, the kidney appears to play an important role in the elimination of the main lactam metabolite (PF-06260182) which exhibits inhibitory activity in vitro against ALK and c-Met/HGFR.	102–104
8	Dabrafenib mesylate (TAFINLAR®)	8 h for parent compound. Hydroxy- dabrafenib and desmethyl-dabrafenib – 10 and 21 h, respectively	71. 1%	22.7%	Following a single oral administration of [14C]-dabrafenib, the parent compound was predominant component in feces, accounting for 21.8% of the dose, whereas desmethyl-dabrafenib, and hydroxy-dabrafenib accounted for 14.4%, and 4.5% of the recovered dose, respectively. Hydroxy- and desmethyl- metabolites may contribute to clinical activity. Unchanged dabrafenib was not detected in urine	105,106
9	Dasatinib monohydrate (SPRYCEL®)	4 h	85%	<4%	Following administration of a single dose [14C]-dasatinib unchanged parent drug accounted for <1 and 19% of the dose in urine and feces, respectively.	107
10	Erlotinib hydrochloride (TARCEVA®)	36 h	83%	8%	Following administration of a single oral dose of [14C]-erlotinib less than 2% of the administered dose was excreted as unchanged drug in urine and faces	108,109
11	Everolimus (AFINITOR®)	~30 h	80%	5%	The parent substance was not detected in urine or feces.	110,111
12	Gefitinib (IRESSA®)	41 h in cancer patients	86.3%	3.4%	Following administration of a single dose of [14C]-gefitinib unchanged parent drug accounted for 12.1% of the radio-labeled excretion product in feces. The most abundant component accounted for 26% of the faecal radioactivity consist of two components: O-desmethyl gefitinib (~14-fold less potent than the parent substance) and an unidentified pharmacologically inactive metabolite.	112,113

(continued)

Table 3. Continued

No.	Generic/trade name	Elimination half-life	The median excretion of drug-related material (parent compound and/or metabolites)		Notes	Sources of information 1
			Feces	Urine		
13	Ibrutinib (IMBRUVICA®)	4–8 h	80.6%	7.8%	Ibrutinib was extensively metabolized after a single dose of [14C]-ibrutinib. Only oxidative metabolites and very limited parent compound (0.77% of the administered dose) were detected in feces. The small percentage of radioactivity recovered and the negligible amount of unchanged drug present in urine.	114,115
14	Idelalisib (ZYDELIG®)	8 h	78%	14%	Following administration of a single dose [14C]-idelalisib in a mass balance study, unchanged idelalisib accounted for 23% of total radioactivity recovered in urine over 48 h and 12% of total radioactivity recovered in feces over 144 h	116–118
15	Imatinib mesylate (GLEEVEC®)	The parent compound: ~18 h CGP74588: ~40 h	67.8%	13.2%	Following administration of a single dose [14C]-imatinib in a mass balance study, unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces). 11% of the total radioactivity recovered in feces were identified as *N*-des-methyl metabolite (CGP74588) shows comparable pharmaco-logical activity to the parent drug.	119,120
16	Lapatinib ditosylate (TYKERB®)	14 h (after a single dose); 24 h (after continuous daily dosing)	91.8%	1.16%	Following administration of a single dose [14C]-lapatinib faecal elimination being the predominant pathway with parent drug as the largest component accounts for a median of 27% (range 2.7% to 66.9%) of the dose.	121,122
17	Lenvatinib mesylate (LENVIMA ®)	28 h	63.6%	24.7%	Following administration of a single dose [14C]-lenvatinib unchanged parent drug in feces and urine accounted for 2,5 % of the administered dose, indicating a major role of metabolism in the elimination of lenvatinib.	123,124
18	Nilotinib mono-hydrochloride, monohydrate (TASIGNA®)	17 h	93.5%	4.4%	Fiscal excretion is the predominant route of nilotinib elimination. In an open-label study, four healthy volunteers received 400 mg PO of 14C-labeled nilotinib over a seven-day collection period. Complete recovery (97.9%) was achieved, with 93.5% in the	125,126

(continued)

Table 3. Continued

No.	Generic/trade name	Elimination half-life	The median excretion of drug-related material (parent compound and/or metabolites)		Notes	Sources of information 1
			Feces	Urine		
					feces and 4.4% in urine.. Parent drug accounted for 69% of the dose.	
19	Nintedanib (VARGATEF®)	10–15 h	94.1%	0,6%	Following administration of a single dose [14C]-nintedanib in a mass balance study,19.9% of the total radioactivity recovered in feces were identified as unchanged parent drug	127,128
20	Olaparib (LYNPARZA®)	12 h	42%	44%	After administration of a single [14C]-olaparib dose unchanged drug accounting for 15% and 6% of radioactivity in urine and feces, respectively	129,130
21	Palbociclib (IBRANCE®)	29 h	74.1%	17.5%	Following administration of a single dose of [14C]-palbociclib 2.3% and 6.9% of radioactivity in feces and urine, respectively, were identified as unchanged parent drug.	131,132
22	Pazopanib hydrochloride (VOTRIENT®)	30 h	82.2%	2.6%	Following administration of a single dose of [14C]-pazopanib the primarily excreted drug-related product identified in feces were unchanged parent drug (≥67%)	133,134
23	Ponatinib hydrochloride (ICLUSIG®)	24 h	87%	5%	In the human mass balance study, 23.7% and <1% of the dosed material were identified as unchanged parent drug in the feces and urine, respectively.	135,136
24	Regorafenib monohydrate (STIVARGA®)	The parent compound 28 h; two active metabolites M2 ((N-oxide) – 25 h and M5 (N-oxide and N-des-methyl) – 51 h	71%	19%	Studies using a radiolabeled oral solution of regorafenib (120 mg) showed that approximately 90 % of the radioactive dose was reco-vered within 12 days of administration, with about 71% of the dose excreted in feces (47% as parent compound, 24% as metabolites), and about 19% of the dose excreted in urine (17% as glucuronides).	137,138
25	Ruxolitinib phosphate (JAKAFI®)	The parent compound −3 h; ruxolitinib +	22%	74%	After administration of a single dose of [14C]-ruxolitinib less than 1% of the dose was excreted as unchanged drug	139,140

(continued)

Table 3. Continued

No.	Generic/trade name	Elimination half-life	The median excretion of drug-related material (parent compound and/or metabolites)		Notes	Sources of information 1
			Feces	Urine		
		metabolites – ~5.8 h				
26	Sonidegib (ODOMZO®)	~28 days	93.4%	1.95%	After administration of a single dose of [14C]-sonidegib, unchanged parent compound in feces represented 88.7% of the administered dose and was not detectable in urine.	141,142
27	Sorafenib tosylate (NEXAVAR®)	24–36 h	77%	19%	Following administration of of a single dose [14C]-sorafenib, unchanged parent compound, which accounted for 51% of the dose, was found in feces but not in urine.	143–145
28	Sunitinib malate (SUTENT®)	The parent compound: 40–60 h. N-desethyl sunitinib (SU12662): 80–100 h	61%	16%	Following administration of a single dose of [14C]-sunitinib, unchanged parent compound (13.6%) and its primary active metabolite N-desethyl sunitinib (25%) were the major drug-related compounds identified in feces	146–148
29	Trametinib dimethyl sulfoxide (MEKINIST®)	127 h after single dose administration	81%	19.00%	Two male subjects (A and B) with solid tumor malignancies received a single oral dose of [14C]-trametinib as an oral suspension. Unchanged trametinib together with M1 and M3 accounted for 81% of the administered dose recovered in feces from subject A. Unchanged trametinib accounted for 17% of the administered dose recovered in feces from subject B. The Phase I metabolites M1 and M3 demonstrated approximately equal or 10-fold less potent activity compared to the parent compound	149–151
30	Vandetanib (CAPRELSA®)	~19 days	44%	25%	The elimination has not been fully elucidated in the human mass balance study. Qualitative measurements identified unchanged vandetanib, N-desmethyl-vandetanib, and vandetanib-N-oxide in urine and feces. Thin layer chromatography analysis of fecal extracts	152–154

(continued)

Table 3. Continued

No.	Generic/trade name	Elimination half-life	The median excretion of drug-related material (parent compound and/or metabolites)		Notes	Sources of information 1
			Feces	Urine		
					confirmed the presence of vandetanib and N-desmethyl metabolite, in the ratio of 5:1. *N*-desmethyl vandetanib has equivalent potency to vandetanib, whereas the *N*-oxide metabolite is at least 50-fold less active than the parent compound based on in vitro cellular assays.	
31	Vemurafenib (ZELBORAF®)	~57 h	94%	<1%	Following administration of a single dose of [14C]-vemurafenib, when calculated as mean of the total radioactive dose in pooled faecal samples, ~55% of the total radioactive dose was found as a parent molecule, and 6.0%, 3.4%, and 4.1% as a main metabolites, within the first 96 h post dose.	155,156
32	Vismodegib (ERIVEDGE®)	12 days (after a single dose); 4 days (after continuous daily dosing)	82%	4.4%	Following administration of a single dose of [14C]-vismodegib, unchanged parent molecule was dominant, representing 21.7% of the dose in fecal samples over 0 to 72 h post dose	157–159

preparations with a prolonged terminal half-life. In all cases, these are assumptions in need of experimental verification. Additionally, changes in pharmacokinetic parameters may depend on individual patient-associated factors such as hepatic impairment since many of the oral targeted agents are substrates for cytochrome P450 (mainly CYP3A4).[161,162] Thus, following a single oral dose of bosutinib in patients with hepatic impairment, the elimination half-life was increased from 55 h in healthy subjects to 86 h in Child-Pugh class A, 113 h in Child-Pugh class B, and 111 h in Child-Pugh C class patients. In addition, the metabolism of bosutinib to the major circulating metabolites of bosutinib in humans (M2 and M5) was decreased among patients with hepatic impairment when compared with subjects with normal hepatic function.[163] Further research is needed to understand the impact of these pharmacokinetic changes on the contents of the unchanged parent compound in excreta.

Currently, available data provide only general information in regard to the levels of unchanged drug and/or its active metabolites excreted from patients receiving oral targeted agents. Moreover, in some cases, these data may reflect only the lower limit of contamination. An unequivocal position as to the hazard of exposure from excreta contaminated by oral antineoplastic agents with a primarily hepatic via the faecal route of elimination is difficult to make but a hazard of indirect exposure with most oral targeted agents in this group cannot be excluded.

Discussion

Summarizing the above data, one may conclude that the question at hand revolves around the potential hazard of oral targeted antineoplastic agents predominantly for the patients' family members and other non-medical caregivers from direct and indirect long-term exposure to these agents in the home setting. This overview has been presented as a basis for further discussion on this subject. While on the one hand, conventional antineoplastic drugs as well as excreta from patients receiving them can be defined as hazardous; the situation with oral targeted antineoplastic agents is more complex. With a cursory glance it appears that in comparison with conventional antineoplastic (cytotoxic) drugs, targeted cancer therapeutics would seem to pose a less hazardous risk. However, the development of a large number of antineoplastic targeted therapies in the past decade has led to new mechanism-based adverse effects which can manifest themselves in a wide variety of tissues and organs.[62] There are already a number of selected targeted oral drugs appearing on the 2014 NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings albeit that only 11 compounds of 32 currently approved targeted therapies appear.[41] In addition, nine targeted oral drugs have been proposed to be added to the list in 2016 (http://www.regulations.gov/#!documentDetail;D = CDC-2015-0034-0002).

Qualitative and quantitative levels of the biological hazard from direct and/or indirect contamination by targeted oral antineoplastics are currently almost impossible to determine. It seems reasonable to err on the side of caution without going to inappropriate extremes.

As noted previously, oral targeted therapies are customarily given to ambulatory patients in a home location over a relatively long time frame, months, or even years. Certain patients, such as pediatric, geriatric, and psychiatric, often require that their tablets be crushed before delivery leading to potential direct exposure to the family members or caregivers. Thus, the exhaustive recommendations for safe handling procedures to avoid direct contamination from oral antineoplastics developed by the International Group of Pharmacy Practitioners could realistically be applied to oral targeted therapeutics (Table 3. "Specific Recommendations for Patients and Their Caregivers: Dos and Don'ts").[26]

The lifetime probability of being diagnosed with an invasive cancer, and subsequent initiation of treatment with antineoplastics, rises with age, peaking at age 65 years or older.[164] It seems reasonable to envisage a future scenario of elderly patients receiving long-term treatment with oral targeted therapies spending the majority of their treatment time at home. Many elderly patients require assistance with their daily living functions. However, in the case of these sick and elderly patients, the situation is aggravated not only due to their basic illness but also consequent to common adverse events of the oral targeted therapeutics such as fatigue and diarrhea. Patients receiving epidermal growth factor receptor (EGFR)-TKIs have a relatively high incidence of diarrhea: up to 50–60%, including 6–9% grade 3–4.[165] The combination of these factors in the home setting can lead to increased risk of indirect exposure to family members and caregivers from the parent drugs and/or its active metabolites. This is especially important with oral targeted antineoplastics characterized by high levels of excretion of such potentially harmful substances.

There are some limited current recommendations on how to deal with this issue such as to wash the patient's clothes and bed linen separately from other items and double flushing the toilet after use, during the use of oral chemotherapy.[26] Several recent publications have addressed concerns about the administration of oral chemotherapy drugs from a nursing standpoint.[166–168]

More complete suggested recommendations may include these:

- Minimize the number of individuals coming in contact with the contaminated excreta.
- Avoid all direct contact (including contaminated patient's clothes and bed linen) with feces and urine and/or body fluids (vomitus, ascitic fluid, or pleural fluid) excreted from patients receiving oral targeted therapies.
- Wear gloves at all times while handling contaminated items in order to minimize risk of exposure.
- Wash hands thoroughly before and after glove application.
- Advise patients to use either personal toilet facilities or, if not available, double-flush the toilet after use, during use of and four to seven days after discontinuing oral targeted chemotherapy.
- Wash the patient's clothes and bed linens separately from other items.

We believe that the stated position can be the basis for further critical discussion. The information related to health risks to fetuses due to the handling of conventional chemotherapeutic agents by health care professionals during pregnancy is incomplete; however, recently proposed recommendations based on current evidence can reduce any potential risk.[169] The similar hazard of handling oral targeted antineoplastic drugs, or excreta contaminated by them by pregnant health care providers, caregivers, and family members requires careful consideration. The potential hazard appears to be linked to the existing risk factors such as teratogenic potential of the drug, the first trimester of pregnancy and pharmacokinetic parameters. There is currently no consensus on this issue but the introduction into clinical practice of Hedgehog (Hh) signaling pathway inhibitors possessing high embryo-toxic, fetotoxic, and teratogenic potential increases the importance of a re-evaluation of this approach in view of the possible risk of congenital anomalies.

Health care professionals play a critical role in counseling patients regarding all aspects of the safe use of oral cancer chemotherapy including targeted antineoplastic medications. As oral, small-molecule targeted therapies become routinely available, the community pharmacist will of necessity, be more involved in the care of cancer patients.[170,171] Patients and their caregivers expect their pharmacists to provide counseling regarding the safe use of oral cancer chemotherapy as an important component of optimal patient care. Therefore, pharmacists need to understand not only pharmacology, indications, side effects, and drug interactions of these agents but also pharmacokinetic aspects of drug metabolism with emphasis on excretion. This expectation was not borne out by the recent results in a Canadian study which showed that only 24% of responding community pharmacists were familiar with the common doses of oral anticancer agents, including targeted therapy, and only 9% felt comfortable educating patients on these medications.[172] We believe that the proposed strict guidelines pertaining to prescription writing, patient follow-up, and toxicity management for patients treated with oral anticancer agents, predominantly targeted medications, may be supplemented by sections dedicated to the basic education patients, caregivers, and family members to minimize the risk of direct and/or indirect exposure to these agents in the home setting.

There still remain a number of issues for further discussion. It is our intention increase awareness of this issue with the intention to reach a consensus on the appropriate future actions to be taken. Nevertheless, the number of approved oral targeted antineoplastics with a broad spectrum of the clinical activity is increasing progressively which makes the potential biological hazard of direct or indirect exposure a reality to be contended with.

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