The Golden Guide to Oncologic Pharmacy

Carolina Witchmichen Penteado Schmidt
Kaléu Mormino Otoni *Editors*

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Preface

Oncology is an area of high complexity, where more and more specific knowledge is required. The time is short, the area is embracing and deep, and the books for pharmacists are few. *The Golden Guide to Oncologic Pharmacy*, edited by Carolina Witchmichen Penteado Schmidt and Kaléu Mormino Otoni, is a book by oncology pharmacists for oncology pharmacists. We, editors, have years of experience in the daily practice and teaching of oncology in postgraduate courses and publishing scientific knowledge to help professionals have the information we would like to have had when we started, and also years later, for quick search. So, we gathered a team of experienced pharmacists and other healthcare professionals who work in this area of high complexity. This book fills a gap, and it's the first one aimed at oncology pharmacists' daily practice. If you also work with pediatric patients, please check *Pediatric Oncology Pharmacy: A Complete Guide to Practice* as well.

This essential guide will support oncologic pharmacists, clinical pharmacists, and hospital pharmacists in their daily practice with every area that involves chemotherapy, such as oncology, hematology, rheumatology, stem cell transplantation, ICU, and surgery center, as well as approaches without chemotherapy for cancer, such as CAR-T cells. The essential knowledge has been

gathered in this volume, being essential also for postgraduate students, residents, and even undergraduate students.

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The Pharmacist in Oncology and Hematology

1

Carolina Witchmichen Penteado Schmidt

1.1 The Oncology Pharmacist

The history of the oncology pharmacy is relatively new, and we are still building our place and roles in this area. There are different roles the pharmacists play throughout the world and in (adult and pediatric) oncology, hematology, and chemotherapy for other specialized areas, like rheumatology. As cancer knowledge becomes more complex, there are more areas in which specialists are needed. Pharmacists are needed in diverse stages of cancer treatment, from the research, production of chemotherapeutic drugs in the industry, logistics, hospital management, clinical pharmacy with oncologic patients, chemotherapy handling, follow-up and management of side effects, and support drugs even when the patient is at home. Another relatively new area where the pharmacist is essential is stem cell transplantation. Furthermore, for those cases in which all the possibilities of treatment ended, the pharmacist has much work in palliative care, especially the clinical pharmacist. Many countries and many oncology centers only allow pharmacists specialized in oncology to be responsible for chemotherapy handling, since the professional doing this work needs to know drug interaction, han-

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dling, chemistry, microbiology, and, among other areas, especially a deep knowledge in pharmacology that only pharmacists have. The specialization and graduation courses have been modernized to include the new high complexity needs. As well as we cannot imagine another professional administrating chemotherapy but an oncology/hematology nurse, and it is unimaginable another professional defining the protocol and prescribing the chemotherapy but an oncology/hematology physician, it is impossible to imagine nowadays another professional handling chemotherapy but the oncology/hematology pharmacist. Unfortunately, some countries have so many health issues and social problems that barely have cancer treatment, even more pharmacists handling chemotherapy. In the past, when cancer was treated with less complexity than today, nurses were the healthcare professionals who used to handle chemotherapy. In 1979, it was published the first convincing evidence, in a small but controlled study, that mutagenic activity was found in the urine of patients who received chemotherapy as well as in the nurses who administered it. Since then, there was evidence of significant risk by occupational exposure published all around, and the safety of professionals involved in the chemotherapy treatment and also of the patients was improved. The main routes of cytotoxic drug exposure occur through skin contact and absorption, inhalation, ingestion, and sharp injuries. In the 1980s, the USA Occupational Safety and Health Administration (OSHA) was concerned about chemotherapy preparation practices, and the analysis of the procedures showed facilities failing in protecting the pharmacists. A safe handling program was implemented, described in the American Journal of Hospital Pharmacy, and it became the basis for the first American Society of Hospital Pharmacists (ASHP) Technical Assistance Bulletin on Handling Cytotoxic Drugs [1].

1.2 The Roles of an Oncology Pharmacist

The Oncology Pharmacy Team consists of specialty-trained pharmacists and their team of pharmacy technicians, and it is an integral component of the multidisciplinary healthcare team. Involved with all aspects of cancer patient care, this team works to guaran-

tee quality in patient care, safety, and local regulatory compliance. The International Society of Oncology Pharmacy Practitioners (ISOPP) developed a statement to guide five key areas: oncology pharmacy practice as a pharmacy specialty, contributions to patient care, oncology pharmacy practice management, education and training, and contributions to oncology research and quality initiatives to involve this team. Their position statement advocates that the oncology pharmacy team be fully incorporated into the multidisciplinary team to optimize patient care, educational and healthcare institutions develop programs to educate the members of this team continually, and regulatory authorities develop certification programs to recognize the unique contributions of the oncology pharmacy team in cancer patient care [2].

An oncology pharmacist is responsible for evaluating the prescriptions and protocols and if they are appropriate for the patient, evaluating the doses, drug interactions, chemical compatibility, volume, and, if it is not adequate, contact the physician who prescribed it to suggest changes and politely discuss the reasons and mechanisms and work as a team for the well-being of the patient. Before calling the physician, the pharmacist should be sure about what he has to discuss and be open to hear the feedback and analyze the protocol as a team working for the patient. The pharmacist is co-responsible for every drug the patient will receive, so if the therapy is harmful and the physician is not able to identify an error, it is the role of the pharmacist to talk as much as it is necessary with them or contact a preceptor or the rest of the team to discuss the therapy. At the same time that a pharmacist evaluates the appropriateness of the therapy, including pre-chemotherapy and support drugs, the pharmacist should evaluate if he can contribute to this therapy to make it better for that patient. Maybe the patient has a volume restriction, and the protocol can be handled in a more concentrated way. Maybe the patient will benefit from another combination of support drugs due to a reduced drug interaction. Maybe another formula can be better for that patient. If there are ways to improve the therapy, the pharmacist should call the physician who prescribed to suggest that. The pharmacist should have in mind an optimization of the patient's adherence to anticancer therapy and the different formulas and support drugs

that can help this. A clinical pharmacist can monitor drug therapy's adverse effects and pharmacovigilance-related activities. Verifying, reviewing, and recommending strategies for food and drug interactions before and throughout therapy is also essential. Implement patient-specific management of treatment-related adverse effects, and ensure supportive care is planned and implemented is important. Promoting patient and caregiver advocacy is also a pharmacist's role, together with the whole team [2].

It is also the role of an oncology pharmacist to define practices and standards for safe practice and train the team. The oncology pharmacist should develop strategies to mitigate, manage, and prevent medication errors, drug-related problems, and drug-related morbidity. Standard operating procedures (SOP) are necessary and should be written and studied by all the team. It is important to reread the SOPs and do new training to guarantee a safe practice from time to time. The oncology pharmacist needs to guarantee the quality of the drugs, promoting appropriate storage and handling and dispensing of medication. The drugs and the environment should be controlled regarding temperature, microorganisms, and the drugs handled should be sterile. The pharmacist needs to have critical thinking, certify the procedures and the references used, and modernize it according to the advance of science. A good oncology pharmacist is ahead; they do not just follow the legislation and only the minimum standard. A good oncology pharmacist is creative and can adapt and make the best possible with the minimum resources. Education and training are necessary for the pharmacist, and it is also essential that they promote knowledge for their team inside the pharmacy, the multidisciplinary team, and the patients. Good pharmacists learn and teach; they share knowledge always. Moreover, they are humble enough to understand that what they do is always for the patient's health and the community, the collective health. However, they are also strong enough not to be tricked by false knowledge or accept situations that can harm their own health or the patients. The safety of them and their teams is the most critical priority. To take care of the others, you need to take care of yourself first. That story of the oxygen

masks in the airplanes, to put your mask before helping your kid or another person, is the perfect metaphor for the oncology pharmacists. Nobody should accept to work in harmful conditions. The work of an oncology pharmacist can be extended for research. They can conduct and facilitate oncology-related research activities [2].

1.3 Becoming an Oncology Pharmacist

The first thing to have in mind when becoming an oncology pharmacist is to check the local law and what it demands. Then, what the institutions ask. In general, a pharmacist can become an oncology pharmacist completing a post-graduation, residency program, or a structured traineeship in the area. The kind of certification the countries ask in law may vary. Official organizations recognize and certificate pharmacists after a test or validating their own certifications achieved by courses. To become a pediatric oncology pharmacist, knowledge in pediatrics and neonatal is also needed, as well as the knowledge specifically in pediatric oncology, which differs a lot from adult oncology. The most common of childhood cancer types are hematological. Children receive, in general, higher doses of chemotherapy than adults since their cellular renewal is faster. Pediatric oncology is more complex than adult oncology and has much more details. Pediatric oncology books, courses, training, experience, and internship help a lot. Formal training in pediatric oncology is still not standard everywhere, and many pharmacists search for education in oncology in post-graduation courses that include pediatric oncology and focus all their work in pediatric oncology, studying books, making research or their monography or another kind of final course assignment in this area, as well as an internship. Residence programs for pharmacists in pediatric oncology are not standard everywhere, but some countries have it available more commonly. Independent from the method available and chosen, the important is to be qualified to offer high-quality therapy for the patients and be allowed by law to work in this area.

1.4 Resources

It is important that oncology pharmacists surround themselves with trustworthy resources that help them find the correct information quickly, such as books, articles, journals, and protocols. An investment must be made in good resources to guarantee that the oncology pharmacist will have support when they need it. Springer Nature (https://link.springer.com/) has packages for hospitals and universities to sign up for their clinical medicine database and access trustworthy books and journals; it is a great resource that can be available at the pharmacist's workplace, and it can be found out talking to the librarian. National Cancer Institute (https://www.cancer.gov/) has a lot of good material available for free. The International Society of Oncology Pharmacy Practitioners (ISOPP) (https://www.isopp.org/) has many resources available for memberships. American Society of Clinical Oncology (ASCO) (https://beta.asco.org/) has resources to keep informed. There are wonderful books that help pharmacists a lot; one of them, which helps to check doses and concentrations quickly, is the Lexicomp Drug Information Handbook for Oncology. Since the oncology area is all based on protocols, the pharmacist must be present in congresses and events that present the most recent research and be a part of research groups if possible.

1.5 Oncology Pharmacist: A Valuable Resource in the Workforce

The pharmacist is a valuable resource for many different subareas in oncology and hematology, making a difference in the treatment of patients in the most diverse ways.

A study evaluated the incorporation of a clinical oncology pharmacist into an ambulatory care pharmacy in pediatric hematology-oncology and transplant clinic. It published the results of the professional playing an integral role in minimizing the adverse effect and reduction in readmission into the hospital, which was especially important because this study was performed in Pakistan, which is defined by the authors of the study as an

underdeveloped country. This is a relatively new expansion of the pharmacist's role in 2019 and was published in 2020. During the five months analyzed, 1820 visitations were performed for pediatric patients. The clinical oncology pharmacist documented 1665 pharmacist interventions in the 980 direct patient interviews performed. Most of the documented clinical oncology pharmacist interventions were reviews of medication histories (24%) and dose adjustments of deferiprone (24%). Genomic profiling interventions were also among the commonly reported activities by the professional. For beta-thalassemia patients undergoing hydroxyurea therapy, genomic profiling was performed to assess whether the hydroxyurea treatment was clinically effective or not (23%) [3].

A study performed in Japan aimed to demonstrate the differences in clinical pharmacy services provided by oncology and non-oncology pharmacists for patients and physicians. The study also defined the potential impact of these services on medical costs. It concluded that although both oncology pharmacists and non-oncology pharmacists provided a service that contributed greatly to cancer therapy and reduction in medical costs, the service provided by oncology pharmacists was of higher quality. The impact of the service provided by both oncology pharmacists and non-oncology pharmacists may exceed the medical fees currently being charged for their services. Clinical pharmacy service for outpatients who undergo chemotherapy may not only provide better clinical management for patients but also reduce medical costs [4].

A pharmacist-led program open to adult outpatients with refractory chemotherapy-induced nausea and vomiting was implemented at the University of Wisconsin. Pharmacists conducted baseline and follow-up assessments, provided patient education, and started, discontinued, and/or adjusted antiemetic drugs according to the clinical necessary for all enrolled patients. A retrospective chart review described the proportion of patients whose chemotherapy-induced nausea and vomiting improved through the intervention. The effect of the program on antiemetic adherence was analyzed as well and the duration of patient enrollment. Forty-six patients were enrolled in this program. 89.1% had an overall reduction in their nausea and vomiting. 23.9% met the

criteria for non-adherence to prescribed antiemetic drugs at baseline, and all patients were adherent in the end. One hundred eleven interventions were made. The most common intervention was the addition of a breakthrough antiemetic drug. The least common intervention was dose escalation of a previously prescribed antiemetic drug. The average number of interventions made per patient was 2.5. On average, patients were enrolled in the program for 16.6 days and met with a pharmacist three times. The implementation of this program standardized and streamlined pharmacist involvement with refractory chemotherapy-induced nausea and vomiting, resulting in a measurable reduction in nausea and/or vomiting for those patients [5].

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Oncological Diseases

2

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2.1 Breast

2.1.1 Introduction and Epidemiology

This is a malignant tumor that develops due to genetic changes in the breast cells, which undergo an abnormal growth. Most breast cancers begin in the lobules (milk glands) or in the ducts that connect the lobules to the nipple [2]. If diagnosed early and treated in

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a timely manner, the prognosis is positive, and the cure rate is high. Despite being diagnosed in a few cases, men should also be alert to possible symptoms of the disease.

According to the IARC publication, 2,261,419 new cases of breast cancer were estimated in 2020, equivalent to 12.5% of all estimated cancers and 684,996 deaths corresponding to 6.9% of the deaths of all cancers [3].

2.1.2 Risk Factors

There is not only one risk factor for breast cancer; however, the age above 50 years is considered the most important. Other factors that contribute to the increased risk of developing the disease are:

- Genetic factors (*BRCA1* and *BRC2* gene mutations) and hereditary factors
- Late menopause
- Obesity
- Sedentary lifestyle
- Frequent exposure to ionizing radiation [4]

2.1.3 Signs and Symptoms

Breast cancer typically has no symptoms when the tumor is small and most easily treated, and that is why screening is important for early detection [2, 5].

- Changes in the skin that covers the breast (such as redness or retractions).
- On the nipple, an aspect similar to orange peel.
- Spontaneous release of abnormal fluid through the nipples.
- Palpable nodes with or without pain in the breast or armpit.
- Presence of a fixed and generally painless node is the main manifestation of the disease, which is present in about 90% of cases when cancer is noticed by the woman herself.

- Abnormal calcifications and/or structural distortion in routine mammography.

2.1.4 Detection

Breast cancer diagnosis is based on clinical examination combined with imaging studies and confirmed by histopathological evaluation. Anamnesis (with special attention to the menopausal condition and family history of breast and ovarian cancer) and physical examination should be performed, which should include bimanual palpation of the breasts and regional lymph nodes. At the same time, a search should be made for signs and symptoms that may indicate potential sites of metastatic disease.

A minimal blood evaluation (complete blood count, liver and kidney function tests, alkaline phosphatase, and calcium level tests) is recommended prior to surgery and also a definition of the systemic (neo) adjuvant treatment. A bilateral mammography should be performed and, if necessary, complement it with a breast ultrasound scan. Breast magnetic resonance imaging (MRI) is not routinely indicated and can be considered in special situations [6].

2.1.5 Staging

The staging system used for breast cancer is the TNM system of the *American Joint Committee on Cancer* (AJCC) that considers the clinical and pathological staging. In 2018, the staging system was updated to include details about the tumor such as estrogen and progesterone receptor status, HER2 status [7].

- The *pathological stage*, also called surgical stage, is determined by the analysis of the tissue sample removed during surgery.
- If surgery is not possible, the tumor receives the *clinical staging*, which is based on the physical examination, biopsy, and

imaging results. The clinical stage is used in the treatment planning. However, when the disease is disseminated, the clinical stage does not have the same accuracy as the pathological stage to predict prognosis.

In both staging systems, the following prognostic factors were adopted:

- *T:* Indicates the primary tumor size and if it is spread to other areas.
- *N*: Describes if there is disease dissemination to regional lymph nodes.
- *M*: Indicates if metastasis is present in other organs, such as lungs or liver.
- *ER*: The tumor is an estrogen receptor.
- *PR*: The tumor is a progesterone receptor.
- *HER2*: The tumor has HER2 protein.
- *G*: The grade indicates how much cancer cells look like normal cells.

Due to the high complexity of the new staging for breast cancer prognosis, we present the Anatomical Staging (AS) solely based on the anatomical extension as defined by TNM and according to data from clinical history, physical examination, and imaging studies (when indicated) [6].

Definition of the Primary Tumor (T): Clinical and Pathological [6]

- *TX:* Primary tumor cannot be assessed.
- *T0*: No evidence of primary tumor.
- *Tis (DCIS)*: Ductal carcinoma in situ (lobular carcinoma in situ was excluded from the new TNM, and it is characterized as a benign disease).
- *T1*: T $\leq$ 20 mm in the greatest dimension.
- *T1mi* (microinvasion): T $\leq$ 1 mm.
- *T1*: > 1 and $\leq$ 20 mm.
- *T2*: > 20 and $\leq$ 50 mm.
- *T3*: > 50 mm.

- *T4*: Any size, with direct extension to the thoracic wall and/or skin or inflammatory cancer. Dermis invasion alone does not qualify it as T4.

Clinical Definition of Regional Lymph Nodes (cN) [6]
- *cNX*: Regional lymph nodes (LNs) cannot be assessed.
- *cN0*: No regional metastasis (by physical or imaging examination).
- *cN1*: Metastasis to movable ipsilateral axillary LNs levels I and II.
- *cN2*: Metastasis to ipsilateral LNs levels I and II that are clinically fixed or coalescent or metastasis to internal breast LNs in the absence of axillary metastases.
- *cN3*: Metastasis to LNs of the ipsilateral infraclavicular chain (level III), with or without involvement of the axillary chain (level I or II) or clinically apparent metastasis in the ipsilateral internal breast chain, in the presence of clinically positive metastasis in the axillary region or metastasis in the ipsilateral supraclavicular chain, with or without involvement of the axillary or internal breast chain.

Definition of Distant Metastasis (M) [6]
- *M0*: No metastasis by clinical or radiological criterion of distant metastasis.
- *cM1(i+)*: No metastasis by clinical or radiological criteria in the presence of tumor cells or tumor deposits not greater than 0.2 mm detected microscopically or by molecular techniques in the blood, bone marrow, or other non-regional lymph node tissue in a patient with or without symptoms or signs of metastasis.
- *M1*: Distant metastasis detected by clinical or radiological criterion (cM) and/or histological criterion with deposit greater than 0.2 mm (pM).

Stage Grouping [8, 9]
Stage zero (0): Describes disease that is only in the breast tissue ducts and has not spread to the surrounding tissue of the breast. It is also called non-invasive or in situ cancer (Tis, N0, M0).

Invasive breast cancer is classified in the following stages, according to the disease extent:

- *IA:* (T1, N0, M0).
- *IB:*(T0 or T1, N1mi, M0).
- *IIA:* (T0, N1, M0);(T1, N1, M0) or (T2, N0, M0).
- *IIB:*(T2, N1, M0) or (T3, N0, M0).
- *IIIA:*(T0, T1, T2, or T3; N2; M0) or (T3, N1, M0).
- *IIIB:*(T4; N0, N1, or N2; M0).
- *IIIC:* (any T, N3, M0).

Stages *IA*, *IB,* and *IIA* are generally considered early-stage breast cancer and stages *IIIA*, *IIIB,* and *IIIC*, a locally advanced disease. Stage IIB can be classified as initial stage if the tumor is >20 mm, but ≤50 mm, and if it is disseminated to 1–3 axillary lymph nodes (T2 N1 M0), or as a locally advanced disease if the tumor has >50 mm without axillary lymph node involvement (T3 N0 M0) [5].

In general, the new staging system classifies triple-negative breast cancer (estrogen-receptor-negative, progesterone-receptor-negative, and HER2-negative) at a higher stage and classifies most hormone-receptor-positive breast cancer at a lower stage.

Although breast cancer most commonly spreads to nearby lymph nodes, it can also spread further through the body to areas such as the bones, lungs, liver, and brain. This is called metastatic or stage IV breast cancer and is the most advanced type of breast cancer (any T, any N, M1). If breast cancer comes back after initial treatment, it can recur locally, mainly in the same breast and/or regional lymph nodes. It can also recur elsewhere in the body, called a distant recurrence or metastatic recurrence [8].

2.1.6 Histopathological and Molecular Classification [10]

2.1.6.1 Non-invasive Breast Conditions

Also called carcinoma in situ. These are precancerous conditions, where the cells look like cancer cells, but have not invaded nearby tissues.

- *Ductal carcinoma in situ* (DCIS): abnormal cells in the breast ducts may develop into invasive breast cancer.
- *Lobular carcinoma in situ* (LCIS): abnormal cells in the breast lobules increase the risk of developing cancer in either breast.

2.1.6.2 Invasive Breast Cancer

There are two main types of invasive breast cancer. They are named after the area of the breast they start in:

- *Invasive ductal carcinoma* (IDC): starts in the ducts/accounts for about 80% of breast cancers.
- *Invasive lobular carcinoma* (ILC): starts in the lobules/makes up about 10% of breast cancers.

There are other less common types of breast cancer. These include inflammatory breast cancer, Paget's disease of the nipple, medullary carcinoma, mucinous carcinoma, and papillary carcinoma.

2.1.6.3 Molecular Classification

Breast cancer molecular classification can be performed in the histopathological material by genetic analysis and, more commonly, by immunohistochemistry. Different molecular subtypes of breast cancer are described, which differ in their clinical evolution and prognosis. The five molecular subtypes are luminal A, luminal B, luminal HER, receptor of human epidermal growth factor 2 (HER-2), and triple negative; however, in clinical practice, for defining the breast cancer treatment, in addition to the clinical-pathological criteria, the estrogen (ER) and progesterone (PR) hormone receptors status and the HER-2 status evaluation are mainly used.

2.2 Cervix Uteri

2.2.1 Introduction and Epidemiology

Uterine cancer is considered the most common invasive gynecological cancer among American women. Endometrial cancer accounts for approximately 90% of all uterine cancers.