Orofacial Supportive Care in Cancer

A Contemporary Oral Oncology Perspective

Raj Nair
Editor

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I dedicate this book to my grandfather,
Dr (Capt.) K N Pillai and my father,
Dr N G Nair for teaching me,
when I was a boy,
the true meaning of empathy in patient care.

Preface

Cancer has become a global term signifying apprehension, a cause of superfluous concern and a significant diagnosis. As a disease, it is distressing us, affecting someone who is close to our hearts, a friend or a stranger. Cancer diagnosis makes an individual a (cancer) survivor due to the nature and course of the disease process. Supportive care becomes a critical facet in their lives whether during active treatment, remission or palliation.

This book, first of its kind as far as I am aware, intended to deliver contemporary updated knowledge and information in orofacial supportive care of cancer patients. This book is a companion for clinicians, nursing fraternity, allied health professionals, trainees in haematology, oncology, radiation oncology, oral medicine and oral oncology.

I have made a conscious effort with the help of my colleagues—contributing authors—in making this book an easy read. When preparing the topics, I have taken into consideration every aspect of cancer care including the hectic nature of dedicated professionals at a cancer centre. The contributing authors are experts in their respective fields and leaders with a wealth of knowledge and experience in cancer care and many of them are international authorities in clinical consensus and guideline development in supportive care in cancer.

I wish to express my sincere gratitude to all of the contributing authors for their excellent contributions and valuable time dedicated towards creating this book. I also extend my thanks to all at Springer, especially Alison Wolfe for initially contacting me regarding this book, Christobel Gunasekaran and the editors for their patience and support.

I hope you will enjoy this book as I did creating it. This unique book will help you understand the full practice of oral oncology in supportive care in cancer thus abetting to provide better cancer care.

Gold Coast, QLD, Australia — Raj Nair

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Editors and Contributors

About the Editor

Raj Nair is an internationally known academic and clinician in Oral Medicine and Oral Oncology. He was Deputy Head of School (Research) and Higher Degree Research (HDR) Convenor and is the Discipline Head of Oral Medicine, Oral Pathology and Human Diseases at Griffith University, Australia. He is Senior Oral Oncology Consultant, Haematology and Oncology (Cancer Services), Gold Coast University Hospital (GCUH), Queensland Health, Gold Coast, Australia. He is a member of the Menzies Health Institute Queensland with over 100 publications, books and book chapter contributions. He holds honorary faculty position at the University of Queensland, Brisbane, Australia.

He obtained his PhD in Oral Medicine and Microbiology from the University of Hong Kong in 1996. He received his oral medicine/oncology clinical training as a fellow at Harvard and affiliated hospitals, USA and the University of London, England, UK and recipient of research scholarship from Centre for Blood Disorders, Harvard Medical School. He was awarded membership in the special stream of Oral Medicine by the Royal Australasian College of Dental Surgeons (RACDS) in 2008.

His clinical training and interests are in the field of oral medicine, oral oncology, management of orofacial diseases, orofacial manifestations in patients with medically complex diseases, HIV disease and orofacial supportive care in cancer therapy and haematopoietic stem cell transplantation. Raj has established and maintains out-patient oral medicine practices providing much needed care for complex orofacial diseases, biopsy service and cancer screen for patients from northern New South Wales and southern Queensland. He provides out-patient and in-patient care to cancer patients at the GCUH as senior oral oncology consultant.

His current research projects include but not limited to (1) biomarkers for cancers using precision oncology techniques and microbiome studies; (2) photomedicine in cancer therapy-induced complications; and (3) oral mucositis and other complications amongst cancer patients. He maintains external research collaborations with universities in the USA and Europe. He has presented a number of original research papers at international conferences and has given invited lectures worldwide since 1994.

Raj is the convenor of courses in the discipline of oral medicine, oral pathology and human diseases (internal medicine) which are designed and implemented by Raj. He contributes to education of specialist trainees and nurses at the GCUH and lectures at School of Pharmacy, Griffith University.

Raj holds membership in both professional and research bodies including the International Association for Craniofacial Research (IADR since 1994), the American Academy of Oral Medicine (since 1998), the International Society of Oral Oncology (ISOO), Multinational Association of Supportive Care in Cancer (MASCC since 1999) and Harvard Club of Australia.

He has been an invited consultant and member of international consensus bodies such as World Workshop in Oral Medicine, World Workshop in Oral Health and Diseases in AIDS and Oral Mucositis Group of MASCC/ISOO. He is a Founding Member of the Oral Medicine Academy of Australasia (OMAA).

His senior international leadership positions include (1) Immediete-Past President, Oral Medicine/Pathology Group of international peak research body, IADR; formerly Chair of Membership Recruitment Committee, and Fellowship Committee and currently member of Publication Committee of the IADR, (2) Past Vice President, Editor and Director Board Member of the ISOO (re-elected three terms) and (3) founding Board Member of International Group in Light in Oncology-Barcelona (iGLOB). He was the first Australian-Indian in the 50-ear history of RACDS to serve as an elected Director/Councillor (2012–2014).

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Introduction to Modern Cancer Diagnosis and Survivorship

1

Raj Nair, Ramil Nair, and Stephen T. Sonis

There is virtually no one who has not been impacted by cancer. We all have relatives or close friends who have had cancer, many who have died from cancer. And the incidence of the disease is increasing from 13.4 million people in 2006 to 18.1 million in 2018 ([1]; Fig. 1.1). That number is projected to be close to 24 million new cases by 2035 [2]. Despite innovative treatments, cancer caused the deaths of 9.6 million people last year (2018) which is equivalent in number to the total populations of Hungary, Austria, or Switzerland and equal to the sum of the populations of Norway and Ireland or Kuwait and Uruguay. Consider that just cancers of the respiratory tract (trachea, bronchus, and lung) were themselves the sixth leading cause of death globally. All cancer diagnoses were the second leading cause of death. But cancer burden is not equally dispersed around the world. While the number of new cases is increasing in less developed countries, it is decreasing in developed countries, and, conversely, cancer deaths are increasing in less developed countries compared to developed countries. The reasons for these disparities are multifold and have been well described and continue to be studied but include risk factor awareness, diet, tobacco and alcohol use and overall lifestyle, access to care, and quality of care.

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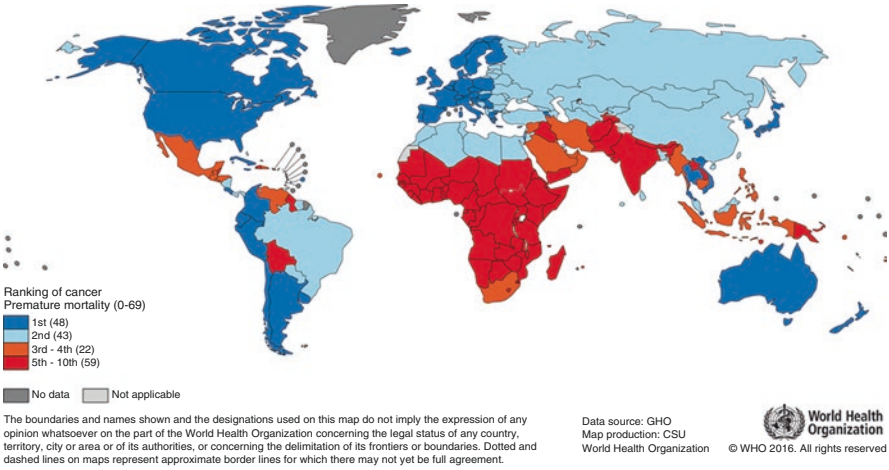

Fig. 1.1 National ranking of cancer as a cause of death at ages below 70 years in 2015 in different countries

The incidence of specific cancers varies geographically, but worldwide lung cancer is both the most common and most deadly accounting for over 2 million new cases in 2018 and more than 1.75 million deaths. Close behind in frequency was breast cancer but with fewer deaths (626,000). Interestingly, new cancers of the head and neck (oral cavity, larynx, nasopharynx, oropharynx, hypopharynx, and salivary glands) impacted almost 1 million patients (907,000) with the same diagnoses associated with more than 450,000 deaths.

Men are more likely (by 20%) than women to develop cancer. Not unexpectedly, given the cancer type distribution by sex, men have a death rate that is 50% higher than women. This is most likely associated with differences in the incidence of lung and liver cancers in men vs. women (Table 1.1).

1.1 Cancer Control

Recognition of many of the environmental and lifestyle cancer risk factors has been known for years. Certainly, tobacco and betel nut use, ultraviolet light exposure, alcohol consumption, excess body weight, air pollution, HPV status, and poor diets have long been associated with increasing the likelihood of an individual developing a malignancy. More recently, the potential importance of the microbiome has been implicated [3], particularly with respect to its contribution to the metabolism of carcinogens. In aggregate, Islami et al. [4] estimated that for patients aged 30 or older in the United States, 42% of diagnosed cancers and 45% of cancer deaths were associated with modifiable risk factors.

Given the breadth of our understanding of identifiable causes of cancer, progress in the development and implementation of programs designed to control risk would

Table 1.1 New cases and deaths for 36 cancers and all cancers combined in 2018

Cancer site	No. of new cases (% of all sites)	No. of deaths (% of all sites)
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Nonmelanoma of skin	1,042,056 (5.8)	65,155 (0.7)
Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Esophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Thyroid	567,233 (3.1)	41,071 (0.4)
Bladder	549,393 (3.0)	199,922 (2.1)
Non-Hodgkin lymphoma	509,590 (2.8)	248,724 (2.6)
Pancreas	458,918 (2.5)	432,242 (4.5)
Leukemia	437,033 (2.4)	309,006 (3.2)
Kidney	403,262 (2.2)	175,098 (1.8)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Lip, oral cavity	354,864 (2.0)	177,384 (1.9)
Brain, nervous system	296,851 (1.6)	241,037 (2.5)
Ovary	295,414 (1.6)	184,799 (1.9)
Melanoma of skin	287,723 (1.6)	60,712 (0.6)
Gallbladder	219,420 (1.2)	165,087 (1.7)
Larynx	177,422 (1.0)	94,771 (1.0)
Multiple myeloma	159,985 (0.9)	106,105 (1.1)
Nasopharynx	129,079 (0.7)	72,987 (0.8)
Oropharynx	92,887 (0.5)	51,005 (0.5)
Hypopharynx	80,608 (0.4)	34,984 (0.4)
Hodgkin lymphoma	79,990 (0.4)	26,167 (0.3)
Testis	71,105 (0.4)	9507 (0.1)
Salivary glands	52,799 (0.3)	22,176 (0.2)
Anus	48,541 (0.3)	19,129 (0.2)
Vulva	44,235 (0.2)	15,222 (0.2)
Kaposi sarcoma	41,799 (0.2)	19,902 (0.2)
Penis	34,475 (0.2)	15,138 (0.2%)
Mesothelioma	30,443 (0.2)	25,576 (0.3)
Vagina	17,600 (0.1)	8062 (0.1)
All sites excluding skin	17,036,901	9,489,872
All sites	18,078,957	9,555,027

Source: GLOBOCAN 2018

be expected to have a marked and favorable impact on cancer statistics. Recognizing the value of cancer control programs, the WHO's developed a Global Action Plan for the Prevention and Control of Noncommunicable Diseases (2013–2020) [5], which has served as a guidance in the United States for programmatic development and implementation.

Cancer control strategies have historically focused on modifying lifestyle behaviors and environmental factors known to impact cancer risk. Probably the most notable have been programs to reduce and eliminate tobacco use. Importantly, the success of these programs is illustrative of the importance of integration of and

support between policy makers and lawmakers that effectively influence outcomes. As a measure of effectiveness, smoking prevalence in the United States has declined from 55% of adult men in 1955 to 17.5% in 2016 and 35% of adult women in 1965 to 13.5% in 2016 [6]. Among tactics that have been effective are the levying of high taxes on tobacco products, mandates for smoke-free environments (workplace, restaurants, hotels, etc.), public information programs, restrictions on advertising tobacco products on television, and black box warnings on tobacco product packaging [5]. Other prevention/control programs focused on cessation have also been helpful. Nonetheless, it is important to acknowledge that cancer control programs' effectiveness has varied depending on the demographics of the target population. For example, with respect to smoking, the impact of cancer control programs has been markedly more impressive among patients with higher level education compared to those with less. Thus, like treatment, it is unlikely that a "one-size-fits-all" approach to cancer control programs is realistic. Rather, directed approaches seem likely of having the most utility.

Likewise, initiatives to reduce pollutants associated with cancer risk have had success. One of the most visible programs is associated with radon, the leading cause of lung cancer among US nonsmokers [7]. Increased awareness, home testing, and remediation coupled with policy and legal initiatives have demonstrated efficacy. In addition to radon, the US National Cancer Institute lists 26 other environmental carcinogens as part of their effort to increase awareness and mitigate risk.

An alternative strategy for cancer control has focused on the development of vaccines which target known etiologic agents. Among the most successful of these have been vaccines directed against HPV and hepatitis B (HBV). HPV is a known cause of cervical, vaginal, vulvar, anal, and oropharyngeal cancers, and Gardasil, a 9-valent HPV vaccine, has been approved by the US FDA as a preventive intervention. HBV has been associated with liver cancer risk. Consequently, anti-HBV vaccination mitigates that risk.

1.2 Screening and Early Diagnosis

Screening for cancer and cancer survivors are equally important. Considering the varied types of cancer and their early clinical and biological presentations, it is difficult to come up with a common general screening process for all cancers. In an ideal situation, screening for cancer must be at a primary care setup though that is not the case due to known reasons. When it comes to early diagnosis, those cancers with a known early clinical presentation or a molecular marker have the advantage.

At present, breast and cervical cancer among females and prostate cancer in males and colon cancer screening for those above the age of 50 years in certain parts of the developed world are probably the only cancers with funded screening process. Even though there is a month—April—dedicated to oral cancer screening and awareness internationally, not much has been done to make it mandatory for high-risk individuals.

The gold standard for many cancer screenings still relies upon clinical evaluation by trained individuals, followed by qualitative or quantitative evaluation of additional molecular markers either in the blood or from tissue sampling such as smears or biopsies and imaging techniques. If one were to take oral cancer as an example, dentifying high risks such as (1) high-risk individual based on history or family history of cancer; (2) high-risk activities such as habits, diet, and others; and, finally, (3) high-risk areas, for example, the nonkeratinized oral mucosae in general and floor of the mouth or posterior-lateral borders of the tongue for oral squamous cell carcinomas. The other major hurdle for early cancer screening, indeed, is the financial burden, especially in developing or underdeveloped countries. The best tackle is still prevention and early detection especially when it comes to overall survival.

In recent years, there are several articles on a broader term "liquid biopsy" in the detection of cancer. This method simply refers to detection of tumor cells in body fluids like blood in which free-circulating nucleic acids (cftDNA or cftRNA) originating from tumor cells are to be detected [8]. The basic principle of these noninvasive laboratory-based techniques is with the use of biosensors that can detect cancer biomarkers. It is evident that there are several biomarkers specific to various cancers which are in different phases of refinement and commercialization. For example, inhibitor of apoptosis proteins (IAP) such as surviving has become an important prognostic biomarker for a number of cancers [9].

Broadly, the applications of liquid biopsy are (1) **early detection** of tumor-specific genetic alterations, (2) **forecasting** absence of cftDNA after surgery with a better prognosis and quantification of cftDNA on tumor burden, (3) **prediction** of therapeutically relevant target structures, and (4) **monitoring** of patients using quantification of cftDNA toward tumor burden under therapy, quantification of therapy response, and early identification of resistance mutations [8].

These analyses are expected to provide minimally invasive information about certain properties of the tumor and its metastases, for example, the presence of a therapeutically relevant resistance mutation. However, the term also encompasses other body fluids such as CSF and urine as well as the detection of circulating tumor cells, nucleic acid-containing membrane vesicles (exosomes), or "tumor-educated platelets".

MicroRNAs (miRNAs) have been reported to have a potential to be early markers with both upregulating and downregulating miRNAs in cancer patients compared with normal healthy controls. Another aspect to be mentioned is the role played by the microbiomes, especially in oral cancers [10–15].

1.3 Survivorship

"Survivor" is a word commonly used in the professional field of oncology denoting anyone who has been diagnosed with cancer. This is not the case among cancer survivors as they may not like the idea or the word attached to themselves for varying

reasons. In other words, it denotes someone who is living with a known diagnosis of cancer.

The survivors may belong to two groups, those that have no signs of cancer, clinically or through common markers, or those that are living with cancer through therapy. We may be able to define three phases of cancer survivorship such as the following: (1) acute survivorship starts at diagnosis and goes through to the end of initial treatment, (2) extended survivorship starts at the end of initial treatment and goes through the months after, and (3) permanent survivorship is when years have passed since cancer treatment ended.

1.4 Opportunities for Precision Medicine and Oncology

It is abundantly clear that cancer risk, behaviors, and response to treatment vary dramatically across individuals. Likewise, patients' risk of treatment-related toxicities is not uniform. Why is it that one person can smoke a pack of cigarettes for years and live into her 90s, while another develops oral cancer in his 50s? Why is there such variability in response to standard cytotoxic cancer regimens? While one patient with oropharyngeal cancer lives far beyond his concomitant chemoradiation therapy, another with exactly the same demographic, tumor diagnosis, and comorbidities has a recurrence within 2 years of completing initial therapy. How come some patients develop severe oral mucositis following induction chemotherapy, while others sail through treatment with hardly a bump in their quality of life?

Historically, oncology risk and diagnosis were based on averaging overall patient experiences. Tumor characterization and behavior were associated with histological criteria. Hence, all patients with a particular cancer were assumed to have a similar disease. We now know that this is not the case. Advances in technology have permitted scientists to characterize individual tumors [16]. By far, the most significant and clinically meaningful targets have been somatic mutations. Although still relatively new, these discoveries have already had an impact on individualizing tumor diagnosis and, importantly, guiding treatment to specific patients, rather than the "one-size-fits-all" approaches of the past. The results have been profound. Take, for example, the case of checkpoint inhibitors, a form of immunotherapy. At the broadest level, only 20% of patients treated with these drugs respond. Thirty years ago a clinical trial which evaluated an anti-cancer drug based on general histological diagnosis, lung cancer for example, may have concluded that the experimental agent was ineffective. In contrast, further defining patients' cancers genetically might have revealed that patients with cancers having a specific genetic signature did respond to the drug, whereas others did not. However, by recognizing that tumor susceptibility was genomically determined and by being able to screen patients for markers associated with response, the development of the drug for a targeted population where the likelihood of response was high was permitted [17]. Not only was this a huge win for patients and their providers but also for payers who could feel assured that the drug was most likely to be effective in patients treated.

Furthermore, it has become clear that genomic similarities are more important in assessing tumor response than are histomorphological similarities. This provides the basis for novel clinical trial designs in which inclusion criteria are based on common genomic mutations.

Recognition of the genomic diversity of head and neck cancers has provided a platform for both risk prediction and treatment response. Wang et al. noted somatic mutations and HPV in the saliva and blood of patients with head and neck carcinomas [18]. By extension, it is not difficult to imagine a screening application of technologies to detect any of the mutations associated with head and neck cancer [19–21].

Whereas somatic mutations are most associated with tumor diagnosis, behaviors, and treatment response, not much attention has been given to germline mutations—those mutations that are inherited. Tumors have been largely considered to be autonomous. They may be biologically active, but that activity has been considered to be a one-way affair emitting from the tumor and impacting the host. In fact, it seems more realistic that the host affects the tumor in many ways. Consequently, there exists a significant opportunity to assess both somatic and germline mutations and to better understand how they mutually interact. Putting one's eggs into a single basket seems naïve—there is more going on to determine an individual's response than genomics. Future studies will need to assess patients' unique profiles consisting of proteomics, microbiomics, metabolomics, and epigenomic elements and consider how they simultaneously interact to determine an individual's risk and response to treatment.

Germline genomics is especially an important determinant of patients' risk of developing treatment regime-related toxicities and side effects. While, as noted above, other elements contribute to this risk, it is clear that genomics play an important part in determining how well patients tolerate specific drug and radiation regimens. Predicting a patient's risk profile to a variety of treatment options before starting therapy will provide patients and oncologists actionable information to guide individualized treatment [22].

1.5 Challenges in Cancer Supportive Care

Cancer supportive care has emerged as a critical component in tumor management. While still markedly underreported and underappreciated, regimen-related toxicities (RRTs) impart a dramatic burden of illness in overall cancer management. Not only do patients suffer a range of debilitating symptoms including emesis, pulmonary fibrosis, lymphedema, mucositis, arthralgia, neuropathy, and cognitive dysfunction, but their ability to comply with optimal cancer therapy is compromised which threatens their survival. Furthermore, patients with toxicities require additional care resulting in incremental costs that add to the financial burden of their treatment.

Last year, over $11 billion dollars was spent on drugs associated with regimen-related toxicities.

Anyone who has cared for a cancer patient knows that many of the toxicities listed above often happen simultaneously. This observation speaks to the likelihood of common pathobiologic features and provides opportunities for the development of interventions that target multiple toxicities, rather than just one. Better understanding of the biological underpinnings which are associated with toxicity risk and development is critical. But studies that focused on a single toxicity lose the potential value of broader applications. A simple example is the way the epidemiology of RRTs has been studied in so directed ways that characterization of a toxicity constellation—the course, severity, and incidence of multiple toxicities in the same patient over time—has not been achieved. Further compounding RRT assessment has been a lack of standardized reporting criteria. This has extended to frequency of assessment, aggressiveness of RRT evaluation, and inconsistencies in RRT scales.

Oncology remains the number one indication for pharmaceutical development. The activity in field represents the compelling need for effective treatments and the commercial potential for successful interventions. From a supportive care standpoint, this means that the identification, characterization, and interventions for RRTs are a moving target. Mouth sores associated with a cytotoxic agent might be entirely pathobiologically and clinically from mouth sores associated with a targeted therapy as is the case with mucositis caused by melphalan versus stomatitis caused by mTOR inhibitors. Thus, RRTs represent both a continually changing group of challenges and, importantly, opportunities.

RRTs will likely never disappear. Our challenge is to actively engage in finding ways to effectively mitigate or attenuate them so they did not pose a threat to the delivery of optimum cancer care.

Oral oncologists play a significant role in amelioration of cancer complications from diagnosis through hospital stay and survivorship.

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2 Hematologic Malignancies, Classification, and Update on Modern Interventions

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2.1 Introduction

Hematologic malignancies as a combined group are the fourth largest group of cancers in terms of the incidence rates in both men (after prostate, lung, and colorectal) and women (after breast, lung, and colorectal).

Malignancies of the hematopoietic and lymphoid tissues include the lymphomas, leukemias, myeloproliferative neoplasms (MPNs), plasma cell dyscrasias, histiocytic tumors, and dendritic cell neoplasms.

2.2 Classification

There have been different classification schemes that were used through the years. WHO 2016 classification system is the most commonly used, which encompasses features of morphology, immune phenotype, genetics, and clinical features to classify these diagnoses. The full classification of these tumors is beyond the scope of this chapter. Whenever possible, different tumors are grouped by lineage.

Myeloid Neoplasms: These are the neoplasms which are derived from progenitor cells in the bone marrow which develop into erythrocytes, megakaryocytes, granulocytes (neutrophils, basophils, and eosinophils), or monocytes. These include acute myeloid leukemia (AML), MPNs, and myelodysplastic syndromes (MDS).

Lymphoid Neoplasms: These are the neoplasms which are derived from the progenitors of the B cell (bone marrow derived) or T cell (thymus derived) lineages or from mature B or T lymphocytes. The WHO classification generally classifies

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Table 2.1 Some examples of mature B cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL)
Lymphoplasmacytic lymphoma (LPL)
Mantle cell lymphoma
Follicular lymphoma
Diffuse large B cell lymphoma (DLBCL)
Marginal zone lymphoma

these neoplasms depending on whether they are derived from progenitor lymphoid cells or from mature T or B cells.

(a) Precursor lymphoid neoplasms: Includes precursor B lymphoblastic leukemia/lymphomas (B-ALL) and precursor T lymphoblastic leukemia/lymphomas (T-ALL).
(b) Mature lymphoid neoplasms: Includes mature B cell (Table 2.1) and mature T cell neoplasms. These are generally called the non-Hodgkin lymphomas.
(c) Hodgkin lymphoma: These lymphomas are pathologically and clinically distinct B cell lymphomas and thus are classified separately.

Neoplasms with Myeloid and Lymphoid Lineage: These are the tumors which presumably are derived from multipotent stem cells and show evidence of both myeloid and lymphoid differentiation. They are grouped in a separate category.

Histiocytic/Dendritic Neoplasms: These neoplasms are derived from cells that develop into dendritic cells or histiocytes which are the antigen-presenting cells and connective tissue macrophages, respectively.

NK Cell Neoplasms: These neoplasms are derived from the natural killer cells which are part of the innate immune system which recognizes virus and other pathogens.

2.2.1 Leukemias

There are four major types of leukemia classified by their rapidity of growth (acute vs. chronic) and by the cell of origin (myeloid vs. lymphoid). They are AML, acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphoid leukemia (CLL). There are also other leukemias which are very low in incidence.

Acute leukemia	Chronic leukemia
AML	CML
ALL	CLL

2.2.1.1 Clinical Features

Most of the signs and symptoms of acute leukemia occur due to the infiltration of organs with leukemic blasts which are proliferating in an uncontrolled fashion.

Fatigue, dyspnea, bleeding, and life-threatening infections are some of the common features. In some patients, especially with a myelomonocytic or monocytic leukemia, involvement of the spleen, liver, lymph nodes, skin, or gums where these cells accumulate and cause enlargement can be observed. CNS involvement is noted especially in patients with ALL. Laboratory workup can show anemia and thrombocytopenia with normal, low, or elevated white cell counts. Most leukemia patients present with blasts in the blood, but some will present with low blood counts due to replacement of the marrow with the abnormal blast cells.

Chronic leukemias, on the other hand, present with indolent features. Chronic myelogenous leukemia can manifest symptoms of fatigue, night sweats, weight loss, and abdominal discomfort over many weeks to months. Sometimes these are found on a routine blood work performed for other reasons. In CML, the elevated white count can include a spectrum of myeloid progenitors. CML may transform into accelerated or blastic phase. Chronic lymphocytic leukemia can present with enlarged lymph nodes, splenomegaly, and an increased number of mature lymphocytes on a blood smear.

2.2.1.2 Diagnosis

The diagnosis of leukemia is usually facilitated by examination of the peripheral smear for blasts or other precursor cells, but for the most part in order to make a definitive diagnosis, a bone marrow biopsy and aspirate is required. Morphology, immunohistochemistry, and flow cytometry for immunophenotyping help to further distinguish these leukemias. All patients suspected of leukemia should undergo cytogenetic analysis which aids in diagnosis, treatment, and posttreatment monitoring. Molecular studies for abnormalities in certain genes are important which confer prognostic significance. For example, TP53, ASXL1, and MECOM gene mutations are associated with adverse risk in AML, and NPM1 without FLT3-ITD mutation is associated with favorable risk AML. Karyotype analysis also helps in predicting outcomes, for example, t(8;21), inv(16), and t(15;17) predict good outcome, and monosomy 5 or 7 or a 17p abnormality predicts adverse outcome.

2.2.1.3 Management

Acute Leukemia

Acute leukemias, if untreated, are usually fatal, leading to death in weeks to months. Initial treatment is directed at decreasing the number of leukemic cells. For many years, this was achieved using chemotherapy. In AML, the first or induction therapy is often with continuous infusion cytarabine for 7 days and an anthracycline drug given for 3 days, the so-called "7 + 3" regimen, which has been in use for many decades. Depending on specific mutations, other medications, for example, midostaurin for the fms-like tyrosine kinase 3 (FLT3 mutation), are used. Acute promyelocytic leukemia (APL), a subtype of AML, has a unique feature where it shows high sensitivity to all-trans retinoic acid (ATRA) and arsenic trioxide, which can sometimes be used without chemotherapy. CPX-351, a liposomal formulation of cytarabine and daunorubicin co-encapsulated to maximize the synergy between

these agents, has recently been shown to improve the overall survival in certain subtypes of AML. Post-remission, these patients are usually offered high-dose cytarabine to consolidate the remission, or they undergo allogeneic hematopoietic stem cell transplant (allo-HCT). If medically unfit, low-intensity chemotherapy approaches such as the combination of 5-azacitidine, a hypomethylating agent and venetoclax, an inhibitor of Bcl-2 are used.

In ALL, a standard induction chemotherapy regimen with vincristine, anthracycline, prednisone, and asparaginase is often utilized. About 90% of the patients achieve complete remission with this regimen, but if no further therapy is administered, the duration of remission is very short-lived. Post-remission therapies for consolidation and prevention of central nervous system involvement are used, and allogeneic HCT can be considered for those who are fit and who have high-risk features. TKI inhibitors like imatinib or dasatinib are added to the regimen in patients with Philadelphia chromosome-positive ALL which is present in about one third of adults with ALL, and anti-CD20 antibodies like rituximab can improve responses in CD20-positive ALL.

Chronic Leukemia

The treatments in chronic leukemia have evolved over the last few years. In CML, since the development of oral tyrosine kinase inhibitors (TKIs), they are the treatment of choice for initial treatment, where the overall survival was found to be greater than 85% after 4–6 years. Some of the commonly used BCR/ABL TKIs are imatinib as well as second- and third-generation TKIs such as nilotinib and dasatinib. Failure to respond to multiple TKIs with disease progression is an indication for allogeneic HCT.

In CLL, the standard treatment is moving away from chemoimmunotherapy as a first-line treatment to Bruton's tyrosine kinase (BTK) inhibitors like ibrutinib. In patients with relapsed or refractory disease, monotherapy with ibrutinib, idelalisib with rituximab, and venetoclax with or without rituximab are some of the treatment options. Also, more selective second-generation BTK inhibitors like acalabrutinib are currently being studied. Venetoclax is a BCL-2 inhibitor which showed high response rates especially in patients with 17p deletion with previous failure of ibrutinib. Also, CD19-directed chimeric antigen receptors (CAR)-modified T cell therapies also showed encouraging early results. Rarely, these patients undergo HCT with advanced and high-risk CLL which has not responded to other drugs.

2.2.2 Lymphomas

There are multiple types of lymphomas classified into the broad groups as discussed above and shown in Table 2.1. Clinically, we tend to classify these tumors into indolent lymphomas and aggressive lymphomas.

- Indolent: These lymphomas are characterized by slow growth which sometimes occurs over years. The most common are the follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma (LPL),

and some cases of mantle cell lymphoma. In these lymphomas, there is a lifetime risk of about 30% chance of transformation into an aggressive form of lymphoma. They are associated with prolonged survival, though relapses are common.

- Aggressive: These lymphomas are characterized by rapid growth associated with related symptoms. The most common subtypes are the diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma, and other rare T and B cell lymphomas which represent a small fraction of all lymphomas.

2.2.2.1 Clinical Manifestations

Clinical presentation of lymphoma varies from asymptomatic patients with associated lymphadenopathy, organomegaly, or lymphocytosis detected during a routine examination which is usually seen in indolent lymphomas to constitutional symptoms like weight loss, low-grade fever, and drenching night sweats associated with rapid growth of aggressive lymphomas. Some of the symptoms can be related to compression of different organs leading to neurologic, urinary, or lung problems. LPL produces paraprotein, an abnormal protein detected on blood chemistries, usually a monoclonal IgM. In this subtype of lymphoma, symptoms related to hyperviscosity are common especially when the levels are high. Cytopenias are seen commonly in these patients especially when bone marrow is involved. Marginal zone lymphoma causes symptoms depending on the organ involved. Gastric marginal zone lymphoma, the most common MZL, typically presents with abdominal discomfort, nausea, vomiting, or bleeding. Splenic MZL presents with symptomatic splenomegaly, sometimes associated with associated lymphocytosis and marrow infiltration.

2.2.2.2 Diagnosis

Diagnosis of lymphoma requires adequate tissue for hematopathology review, architectural assessment, immunohistochemistry, and flow cytometry. An excisional biopsy is the gold standard as fine needle biopsies often do not adequately define nodal architecture for accurate diagnosis. Cytogenetic analysis and chromosome rearrangements may be diagnostic and also help support the diagnosis of particular subtype of lymphoma. In about 50% of patients, bone marrow is involved by the lymphoma, which requires a bone marrow biopsy and aspiration to document.

2.2.2.3 Staging

Staging is important as it aids in treatment decisions. Lugano staging is currently used for staging NHL.

Stage	Involvement	Extranodal
I	One node or group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I/II by nodal extent with limited contiguous extranodal involvement
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

2.2.2.4 Treatment

Indolent Lymphomas

Follicular Lymphoma: Most of the indolent lymphomas especially in their early stages with no associated symptoms do not require treatment. Patients who are symptomatic, have high tumor burden, or are in advanced stages can be treated with immunotherapy, chemoimmunotherapy, or radiation. Rituximab and obinutuzumab are anti-CD20 monoclonal antibodies which are used alone or in combination with chemotherapy. R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab) and BR (bendamustine and rituximab) are the common chemoimmunotherapy regimens in use. There is a role of radiation especially in the early stages. In the advanced stages, radiation is used for palliation purposes. In relapsed follicular lymphoma, alternative chemoimmunotherapy modalities are used, sometimes with the addition of stem cell transplantation. Anti-CD19-directed CAR-T therapies are also being explored in follicular lymphomas.

LPL: As with other indolent lymphomas, treatment is usually indicated only in symptomatic and advanced disease. First-line treatment options include rituximab, a BTK inhibitor ibrutinib, chemoimmunotherapy, or bortezomib-based therapy.

Marginal Zone Lymphoma: In the early stages of gastric marginal zone lymphoma, the treatment is focused on *H. pylori* eradication, with triple therapy (proton pump inhibitor (PPI) plus two antimicrobials) or quadruple therapy (PPI, bismuth, tetracycline, metronidazole). Patients who are resistant to this therapy or have negative *H. pylori* should receive second-line options like rituximab monotherapy, rituximab plus chlorambucil, or ibrutinib which are especially used in advanced/relapsed disease. Historically, splenectomy was considered in splenic marginal zone lymphoma, but rituximab or fludarabine can be used in patients to avoid surgery.

SLL: This is the tissue counterpart to CLL, and treatment is similar to CLL as discussed above.

Aggressive Lymphomas

DLBCL: About 20% of patients present with limited stage disease (stage 1 or nonbulky stage II). Chemoimmunotherapy with involved field radiotherapy is commonly used in limited stage disease. Chemoimmunotherapy alone is an acceptable alternative especially when radiation therapy is thought to cause long-term toxicities depending on the disease sites. R-CHOP is the preferred chemoimmunotherapy regimen in DLBCL. Advanced stage disease (bulky stage II, stages III and IV) cannot be contained within one radiation field. These patients account for about 70–80% of DLBCL. R-CHOP has been the standard of care in advanced DLBCL, with an OS of approximately 60% at 5 years. The overall survival was found to be inferior especially in patients with double-hit DLBCL (translocations of the MYC gene together with rearrangement of BCL2 and/or BCL6), in whom a more aggressive regimen called dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) is used. Currently, there are multiple clinical trials evaluating adding lenalidomide, ibrutinib, and bortezomib to the R-CHOP base, especially in the advanced and activated B cell (ABC) type of

DLBCL. Even though there is an improved cure rate in DLBCL, slightly less than half of these patients relapse or have primary refractory disease. These patients are treated with salvage chemotherapy with plan for hematopoietic stem cell transplant, in patients who show response. Recently, CAR-T cell therapy is being considered in patients who do not show significant response to chemotherapy or have a relapse after a previous stem cell transplant.

Mantle Cell Lymphoma: Initial treatment in mantle cell lymphoma depends on whether the patient is eligible for HSCT. Conventional chemoimmunotherapy with autologous HCT and maintenance rituximab showed improved progression-free survival. Patients who are not eligible for HSCT showed complete remission with chemoimmunotherapy and maintenance rituximab. Intensive chemoimmunotherapy with hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alone is another option in younger patients who do not want to undergo HSCT. Relapse is common and seen in almost all patients who enter remission. These therapies are not curative, but an occasional patient may be cured after allogeneic stem cell transplantation. Some of the potential salvage regimens include ibrutinib and acalabrutinib, which are BTK inhibitors, lenalidomide, an immunomodulatory thalidomide derivative, and bortezomib, a proteasome inhibitor. CAR-T therapy has also been approved for use in mantle cell lymphoma.

Burkitt Lymphoma: This is one of the most aggressive lymphomas, and these patients require an intensive, multiagent, short-duration chemotherapy with CNS prophylaxis. Common regimens used are CODOX-M with IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate with ifosfamide, cytarabine, etoposide) with intrathecal methotrexate and dose-adjusted EPOCH (infusional etoposide, vincristine, and doxorubicin with oral prednisone and bolus dose-escalated cyclophosphamide chemotherapy) can also be used. Prognosis in cases not associated with the human immunodeficiency virus (HIV) is favorable.

Hodgkin Lymphoma (HL)

Hodgkin lymphoma has been separated from other B cell lymphomas due to its special clinicopathologic features. It has a unique cellular composition, wherein there are minimal neoplastic cells in an inflammatory background. The selection of treatment for HL is usually based on presenting stage. Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for three to four cycles followed by involved field irradiation are the preferred treatment in early stage (I–II) HL. In advanced stages (III–IV), combination chemotherapy with ABVD for a maximum of six cycles is the main treatment. About 15% of patients have refractory HL, and about 15% relapse after complete remission. These patients are generally treated with salvage chemotherapy (e.g., ifosfamide, carboplatin, etoposide (ICE), dexamethasone, high-dose cytarabine, cisplatin (DHAP), or gemcitabine, cis-platinum, and dexamethasone (GDP)), and patients who show a complete response on restaging proceed to autologous HCT, if eligible. Targeted therapy (e.g., brentuximab, an anti-CD30 conjugated monoclonal antibody) and immunotherapy (e.g., nivolumab or pembrolizumab) are also used especially in patients who relapse after autologous HCT or after two prior multiagent chemotherapy regimens. HL survivors are at risk

of developing late complications related to the therapy like second malignancies, cardiac disease, radiation side effects, and others.

There are many other lymphoma subtypes which are rare in incidence and beyond the scope of this chapter.

2.2.3 Myeloma

Multiple Myeloma: MM is a neoplastic process where there is uncontrolled proliferation of plasma cells producing monoclonal immunoglobulin.

Clinical Features: The clinical signs and symptoms are related to the infiltration of the plasma cells into different organs and deposition of the monoclonal proteins in various organ systems. The most common clinical features noted are anemia, bone pain, kidney dysfunction, fatigue, weight loss, and symptoms of hypercalcemia with a minority of patients having symptoms of paresthesias and organomegaly. It is very important to distinguish multiple myeloma from other plasma cell disorders such as light chain amyloidosis for prognostic purposes and treatment.

2.2.3.1 Diagnosis

When multiple myeloma is suspected, patients should be tested for the presence of monoclonal protein. Serum protein electrophoresis (SPEP), serum immunofixation (SIFE), urine protein electrophoresis (UPEP), urine immunofixation (UIFE), and serum free light chain assay will aid in detecting the monoclonal proteins. A bone marrow biopsy and aspirate with immunohistochemistry and flow cytometry are needed for diagnosis. Examination of all bones using plain radiography or preferably whole-body low-dose CT scan is required to diagnose lytic lesions. MRI is the most sensitive modality of bone involvement, while PET/CT may be more sensitive for extramedullary involvement.

2.2.3.2 Management

The initial treatment in MM depends on whether a patient is eligible for autologous stem cell transplant (ASCT). In patients who are not eligible for ASCT, VRd (bortezomib/lenalidomide/dexamethasone) is the standard of treatment for initial therapy followed by Rd (lenalidomide and dexamethasone) as maintenance. VCd (bortezomib/cyclophosphamide/dexamethasone) and VTd (bortezomib/thalidomide/dexamethasone) are other options to use especially if lenalidomide is not available. The anti-CD38 antibody, daratumumab is also being added to upfront treatment regimens. The same regimens are used in induction in patients eligible for ASCT, but they are given for only a few cycles before transplant commences.

Almost all patients with MM will eventually relapse. There is no clear standard regimen to use in relapsed patients. Generally, an alternative regimen than the regimen used in induction is used. Many newer drugs are currently being evaluated regarding their optimal role in myeloma treatment. Some of the newer drugs include proteasome inhibitors like carfilzomib and ixazomib, monoclonal antibodies like daratumumab and elotuzumab, and histone deacetylase inhibitors like panobinostat.

Venetoclax is also being examined as are CAR-T cells directed to the BCMA (B cell maturaton) antigen. Present studies do not provide us with a clear indication of which of these medications and combinations are optimal for treatment of relapsed myeloma. They are often used in succession. Also, patients with MM may receive bisphosphonates like pamidronate or zoledronic acid once per month to prevent bone disease.

2.2.4 Myeloproliferative Neoplasms

Myeloproliferative Neoplasms (MPNs): MPNs exhibit proliferation of the terminal myeloid cells resulting in erythrocytosis, leukocytosis, thrombocytosis, bone marrow fibrosis, and, in some cases, splenomegaly. The common MPNs seen in practice are polycythemia vera (PV), CML, essential thrombocythemia (ET), and primary myelofibrosis (PMF). Most of these patients have mutations in the JAK2, CALR (calreticulin), or MPL (thrombopoietin receptor) genes. CML has a characteristic reciprocal translocation between chromosomes 9 and 22 called the Philadelphia chromosome which results in a bcr/abl fusion gene. These disorders tend to progress and can transform into an acute leukemia over the years. PV and ET can transform into a secondary myelofibrosis.

2.2.4.1 Clinical Features

Patients are usually symptomatic in the advanced stages with associated fatigue, fever, weight loss, night sweats, and organomegaly. RBC counts are elevated in PV, and thrombocytosis is seen in ET. It is important to rule out secondary causes of elevation of these blood cell types. Symptoms related to elevated RBC counts like headache, fatigue, visual changes, and pruritus can occur. In ET, erythromelalgia, a painful burning in the pads of fingers and toes, can occur. If platelet counts are extremely high (>1,000,000/μL), abnormal bleeding rather than thrombosis can occur. Early satiety due to splenomegaly is also often seen in patients with myelofibrosis. Patients especially with myelofibrosis can develop bone pain due to skeletal changes associated with marrow fibrosis.

2.2.4.2 Treatment

The goal of treatment in MPNs is to alleviate symptoms and prevent complications like thrombosis or bleeding and to decrease the progression to myelofibrosis and transformation into an acute leukemia. For low-risk PV patients, usually antiplatelet therapy like aspirin is recommended as well as phlebotomies to decrease the hematocrit to <45%. In high-risk PV patients, cytoreductive therapy is recommended in addition to the above. Hydroxyurea is usually the first choice of cytoreductive agent. Other second-line agents like interferon-alpha and anagrelide are used in patients resistant or intolerant to hydroxyurea. Ruxolitinib, a JAK-2 inhibitor, has been approved in PV which is superior to standard treatment in those who progress or are intolerant of hydroxyurea. In patients with low-risk ET, low-dose aspirin to decrease the thromboembolic complications is recommended, whereas in high-risk ET,

hydroxyurea is used for cytoreduction. For low-risk PMF, close observation or hydroxyurea may be appropriate, but for high-risk PMF, allogeneic HCT should be considered in patients of appropriate age who have available donors. Ruxolitinib has shown substantial benefit in both primary and secondary myelofibrosis, by decreasing spleen size and systemic symptoms. CML has been discussed above in Sect. 2.1.

2.2.5 Myelodysplastic Syndrome (MDS)

MDS are a group of hematopoietic disorders characterized by ineffective hematopoiesis. This is most commonly seen in older adults >65 years and rarely seen in those <50 years of age.

2.2.5.1 Clinical Features

Most of the patients present with nonspecific symptoms related to low counts like fatigue, bleeding, or infections. Peripheral smear and bone marrow examination shows dysplastic cells with hypercellular marrow.

2.2.5.2 Treatment

Treatment strategies primarily depend on the risk group. Erythropoietin is shown to improve anemia in 20–30% of patients with MDS. Lenalidomide has been used in transfusion-dependent MDS with 5q-deletion, and it showed transfusion independence and cytogenetic response in many patients. Azacytidine and decitabine, both hypomethylating agents, are approved in MDS, and these have shown overall survival benefit and decrease in transformation to AML. Allogeneic HCT is the only curative therapy in MDS. Patients who are old and frail and who cannot undergo the above therapies are given supportive care with RBC and platelet transfusions as needed. Infections are also common, often requiring antibiotic therapy.

Recent Advances in the Field of Hematologic Malignancies

In the last few years, the field of hematologic malignancies has seen significant discoveries and advances. Advances in drug development helped in discovery of multiple drugs, especially immunotherapy and molecular targeting agents. Immunotherapies are being incorporated into multiple disease treatment regimens. These include TKIs, antibody therapies, immune checkpoint inhibitors, and CAR-T cell therapy, among others.

CAR-T Cell Therapy

Genetically modifying the T cells to target the cancer is a new disruptive cancer treatment option that is approved currently in some B cell malignancies. CAR-T cells that target CD-19 were recently approved by the FDA for treatment of the advanced ALL in children and large cell non-Hodgkin lymphoma in adults. Since then, CAR-T cells are being developed to target different receptors in other cancer

cells. Most of this work remains investigational, but clinical trials in several hematologic malignancies are under way.

With new treatments come unique side effects. Cytokine release syndrome (CRS) and neurotoxicity are the common side effects noted with CAR-T cell therapy. CRS occurs in the first few days after the T cell infusion and in its severe form causes very high fever, tachycardia, hypotension, coagulopathy, and respiratory compromise. Neurotoxicity is seen with symptoms of headaches, seizures, focal neurological deficits, and in some cases loss of consciousness, which is often treated with steroids.

Side Effects of Therapies Used in Hematologic Malignancies

Chemotherapy is long known to have significant side effects related to damage of the normal cells along with malignant cells. Some of the common side effects seen with chemotherapeutic agents are cumulative fatigue, nausea, vomiting, decreased blood counts, increased infections, effects on organs like liver and kidney causing elevated liver function tests (LFTs) and elevated creatinine, respectively, neuropathies, and skin rash. Some of the side effects are specific to a particular chemotherapy regimen or agent used.

We now have multiple new drugs being developed and used in these cancers. Immunotherapy and targeted therapy are being used more and more frequently, and thus it is important to know the side effect profile of these medications. Treatment with the immunotherapy is associated with immune-related adverse effects. Some of the common side effects noted are mild fatigue; infusion-related reactions; dermatologic toxicities; inflammation of the organ systems causing colitis, hepatitis, and pneumonitis; and endocrinopathies.

Hematopoietic stem cell transplant patients are subject to toxicity affecting multiple organ systems sometimes even warranting intensive care admission. Anemia, neutropenia, and thrombocytopenia are common. Nausea, vomiting, and diarrhea are the common gastrointestinal system-related side effects. Infections are a major risk in transplant patients. Bacterial infections with gram-positive and gram-negative organisms and fungal infections with candida and viral infections with herpes simplex virus and cytomegalovirus are commonly seen in transplant patients.

Acute graft versus host disease (acute GVHD) is usually restricted to allogeneic transplant patients, seen in the first 3 months after transplant. The typical presentation will be skin involvement with erythematous or maculopapular rash and GI tract involvement with nausea, vomiting, diarrhea, and abnormal liver function tests. Less commonly eyes, kidneys, hematopoietic system, and lungs are involved. Sometimes symptoms of acute GVHD are seen beyond the 3-month period post-transplantation, called late-onset GVHD. Skin involvement manifests as lesions resembling scleroderma, and liver involvement is suggested by elevated alkaline phosphatase and bilirubin levels. GI tract involvement manifests as dry oral mucosa with ulcerations, dysphagia, chronic diarrhea, and malabsorption. This is dealt with in detail in a separate chapter.

Oral Side Effects

Oral side effects are common with these agents, and these include acute and long-term side effects. Mucositis is the most common acute side effect causing dysphagia, odynophagia, and impaired nutrition. Late side effects include mucosal atrophy and xerostomia. Gingival bleeding is seen especially in patients with low platelets. Bacterial, fungal, and viral infections are commonly seen. Osteonecrosis is seen in patients who are treated with bisphosphonates, often in multiple myeloma patients. A referral to a dentist is important before initiation of some of these medications. These are dealt in more detail in the later sections of this textbook.

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