Systemic anticancer therapies and the role of primary care

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Cancer therapeutics are complex, constantly evolving, and aim to prolong the life of a patient with cancer by cure, inducing remission, or by slowing disease progression. Cancer treatments can be delivered locally directly against the tumour (i.e. surgery or radiotherapy) or systemically (i.e. chemotherapy, hormone therapy). Systemic therapies have traditionally been administered intravenously in a hospital or day unit setting; however many of the more recently discovered systemic cancer therapies are taken as an oral medication. They also pose significant potential risks to a patient's health through side effects, immunosuppression, and later development of secondary cancers.

This article focusses on systemic cancer therapies from a primary care perspective. Recent developments and classifications of systemic therapies are briefly presented. Key considerations around monitoring, potential treatment harms, and patient support are discussed to inform the delivery of primary care for cancer patients receiving systemic therapies.

Systemic therapies

The breadth of cancer treatments available continues to grow over time, as new treatments move from the bench to the bedside, and into clinical practice. New classes of cancer therapeutics, such as immunotherapy and targeted therapy, have improved cancer outcomes for patients with certain tumours that previously held very poor prognoses (e.g. metastatic malignant melanoma or lung adenocarcinoma). Table 1 shows the broad treatment types available, and some of the more common sub-types.

The classes of systemic cancer therapies include[1–4]

Chemotherapy – medications delivered in a number of ways (orally, intravenous, topical, intramuscular, intracavitary) that inhibit the cell cycle, exploiting the fact that cancer cells generally divide more rapidly than normal cells. The non-specific nature of the treatments

mean cells in tissue other than the cancer are also affected, particularly more rapidly dividing cells such as those found in the skin and gut. The efficacy of chemotherapy is variable, and some cancers can become chemoresistant (where the tumours cells have a reduced response to the therapy).

Targeted therapy – treatments that target specific genes, cell signalling pathways, or proteins that are unique to cancer cells or to the cellular environment that enable tumour growth to occur. Targeted therapies provide benefit by affecting primarily abnormal cancer cells, while minimising the effects or normal cells. These medications are most commonly administered orally, and usually metabolised by the liver.

Immunotherapy – a range of treatments that enable or enhance the ability of the patient's own immune system to identify and eliminate cancer cells within the body. This can be achieved using several techniques, including vaccines, antibodies, and oncolytic viruses.

Hormone therapy – the development and progression of breast cancer in women and prostate cancer in men is often influenced by hormones. There are some other cancer types (e.g. ovarian, endometrial) that have a lesser, but still important, response to the hormonal environment in the body. Hormone therapy can be used for primary treatment of advanced/metastatic cancer, as an adjuvant to reduce the risk of recurrence, or neoadjuvantly to reduce tumour size prior to localised treatments.

Stem cell/Bone marrow transplant – haematological cancers can be treated by eliminating a patient's bone marrow with intensive chemotherapy and other treatments, and then replacing it with their own cells (autologous) or another person's cells (donor).

Chemotherapy		
	IV cytotoxics	Anthracyclines (e.g. Doxorubicin) Antibiotics (e.g. Bleomycin) Platinum drugs (e.g. Cisplatin)
	Oral alkylating agents	e.g. Temozolomide, Chlorambucil, Cyclophosphamide, Lomustine, Melphalan
	Oral antimetabolites	e.g. Capecitabine, Hydroxycarbamide, Mercaptopurine, Tioguanine, Methotrexate
Targeted therapies		
	Growth Inhibitors	Tyrosine kinase inhibitors (e.g. Imatinib) Proteasome inhibitors (e.g. Bortezomib) mTOR inhibitors (e.g. Everolimus)

	Anti-VEGF	e.g. Bevacizumab
	Poly ADP ribose polymerase (PARP) inhibitors	e.g. Olaparib
Immunotherapy (or biologic therapy)		
	Monoclonal antibodies	e.g. Rituximab, Trastuzumab
	Checkpoint inhibitors	Programmed cell death protein 1 (PD-1) (e.g. Nivolumab) Programmed death ligand 1 (PD-L1) (e.g. Atezolizumab)
	CAR T-cell therapy	
Hormone therapy		
	Androgen Deprivation Therapy (ADT)	LHRH agonist (e.g. Goserelin) Non-steroidal anti-androgen (e.g. Bicalutamide) Steroidal anti-androgen (e.g. Cyproterone acetate) Antiandrogen synthesis inhibitor (e.g. Abiraterone acetate)
	Selective Estrogen Receptor Modulators (SERMs)	e.g. Tamoxifen
	Aromatase inhibitors	e.g. Anastrazole, Letrozole, Exemestane
Stem cell or bone marrow transplant		
	Autologous	
	Donor	

Table 1 – Categories of systemic cancer therapies, with some examples

Prescribing in primary care

Systemic cancer therapies are most often prescribed by secondary or tertiary care clinicians, and administered in inpatient and/or outpatient settings. Clear communication between oncology teams and primary care is vital to maintain accurate, contemporary records and to prevent drug-drug

interactions from any new prescriptions initiated in primary care. These interactions may reduce the effectiveness of the cancer treatment or induce unwanted side effects.

Hormone therapies are often prescribed and administered in primary care for breast cancer in women and prostate cancer in men. They are usually commenced by the patient's oncologist or surgeon, and once the patient is stable GPs are asked to continue the prescription and treatment monitoring for these patients for a specified length of time. For women, hormone therapy has been shown to reduce breast cancer mortality and risk of recurrence[5]. Tamoxifen is given as an adjuvant treatment for pre-menopausal women, with chemical or surgical ovarian suppression for high-risk women. Postmenopausal women are often offered an Aromatase Inhibitor. A woman may be recommended to receive hormone therapy for 2-10 years, depending on the indication and other treatments given. For men, androgen deprivation can improve survival in the adjuvant setting, and slow disease progression for advanced stage cancers[6]. Hormone therapy is not a primary treatment for localised prostate cancer. The length of hormone therapy treatment for men can also vary, depending on the indication. It could be delivered intermittently, or by depot injection, if the man will be receiving it long-term.

There are a number of important health impacts and side effects experienced by women receiving hormone therapy that prescribers need to be aware of, and to mitigate where possible[5]. Aromatase Inhibitors (e.g. Letrozole) can have the following effects

Osteoporosis and bone fractures – oestrogen deficiency leads to increased bone resorption, putting these women at increased risk of osteoporotic fractures. Baseline bone density measurement with dual-energy x-ray absorptiometry (DEXA) is advised, and repeat monitoring depends on the woman's menopausal status and treatment regime[7]. All women should aim for at least 800IU of Vitamin D_3 and 1200mg of total calcium in their diet per day. Postmenopausal women and premenopausal women undergoing ovarian suppression should be recommended osteoporosis treatment (e.g. Zolendronic acid).

Sexual dysfunction – oestrogen deficiency can also lead to vaginitis, dyspareunia, recurrent cystitis, and decreased libido. Sexual dysfunction is often a complex issue that is under-reported, requiring a varied approach to help patients maintain their sexual relationships. In addition to recommending lubricants and dietary supplements, patients may benefit from psychosexual counselling.

Musculoskeletal problems – arthralgia, myalgia, tendinitis and carpal tunnel syndrome have all been reported by patients receiving hormone therapy. Following discussion with the

oncologist, switching to an alternative aromatase inhibitor may help alleviate symptoms. Usual primary care management of musculoskeletal problems, such as anti-inflammatories, exercise, or possibly acupuncture may also prove to be of some benefit.

Cardiovascular disease (CVD) risk – women with oestrogen deficiency are at increased risk of hypertension and hyperlipidaemia, potential raising their risk of cardiovascular disease. Close monitoring and management of CVD risk factors in primary care is needed.

The more common adverse effects of Tamoxifen, and other anti-androgens, include the following[5]

Hot flushes – a very common side effect of Tamoxifen. Conservative management includes loose, light clothing and bed covers. Patients can be co-prescribed an SSRI or SNRI, but strong CYP2D6 inhibitors such as paroxetine or fluoxetine should be avoided to prevent reducing the efficacy of Tamoxifen.

Venous thromboembolism (VTE) – patients receiving anti-androgens are at a 2-3 times higher risk of VTE, particularly in prolonged courses of hormone therapy (>5 years). Caution should be taken in patients with non-cancer related risk factors for VTE.

Endometrial cancer – any patients on Tamoxifen with features of possible endometrial cancer, such as abnormal vaginal bleeding, should be promptly investigated due to an increased risk of these cancers.

Ocular pathology – Tamoxifen increases the risk of cataracts and other ocular pathologies that can affect vision. Patients exhibiting any visual symptoms should be assessed in primary care and/or the patient's optometrist.

Androgen Deprivation Therapy (ADT) for men with prostate cancer can have physical and psychological effects on patients, including the following[8]

Osteoporosis – though this is a less recognised health issue for older men relative to women, reduced bone mineral density can occur in men receiving ADT. Baseline bone density monitoring would ideally be performed. Men should also be advised to consume at least 800IU of Vitamin D_3 and 1200mg of total calcium as part of their diet per day. The decision to commence bisphosphonate therapy will depend on a patient's risk of osteoporotic fracture, which can be calculated using the FRAX or QFracture scores.

Sexual dysfunction – men on ADT commonly experience reduced libido and/or erectile dysfunction (ED). A trial of a Phosphodiesterase type 5 (PDE5) inhibitor is recommended. Psychosexual counselling may be beneficial for some men, and referral to urology for

consideration of other ED treatments may be warranted if there is no improvement in symptoms.

Hot flushes – vasomotor symptoms are common for men on ADT, and can persist for years, even after completion of treatment. Medroxyprogesterone (20mg once daily) can be trialled for a minimum of 10 weeks to help manage symptoms. Cyproterone acetate (50mg twice daily for 4 weeks) is an alternative if medroxyprogesterone is not effective or not tolerated.

Anaemia – ADT can result in a normocytic, normochromic anaemia. Routine monitoring is not recommended, but this effect should be considered if men become symptomatic (e.g. exertional dyspnoea) or an incidental anaemia is found.

Systemic cancer drug-related problems

There are a number of potential drug-related problems to consider for patients taking systemic cancer therapies[9]. The side effect profile of each drug will vary, but there are some side effects which are common to many systemic cancer therapies. There are also some severe adverse effects of cancer treatments that primary care professionals need to be aware of and act on urgently (see table 2).

Common, seldom severe	**Common, potentially severe**	**Uncommon, severe**
Fatigue	Vomiting	Venous Thromboembolism
Nausea	Diarrhoea	Febrile neutropaenia
Mucositis	Rash	Tumour lysis syndrome
Constipation	Pain	Hyperuricaemia, renal failure
Hair loss	Neuropathy	Teratogenicity
Skin erythema		Cardiomyopathy

Table 2 – More common adverse effects of systemic cancer therapies

Patients and their partners/carers can be empowered to monitor, manage, and report their symptoms with the provision of good quality treatment information, and symptom reporting tools (see figure 1 for an example).

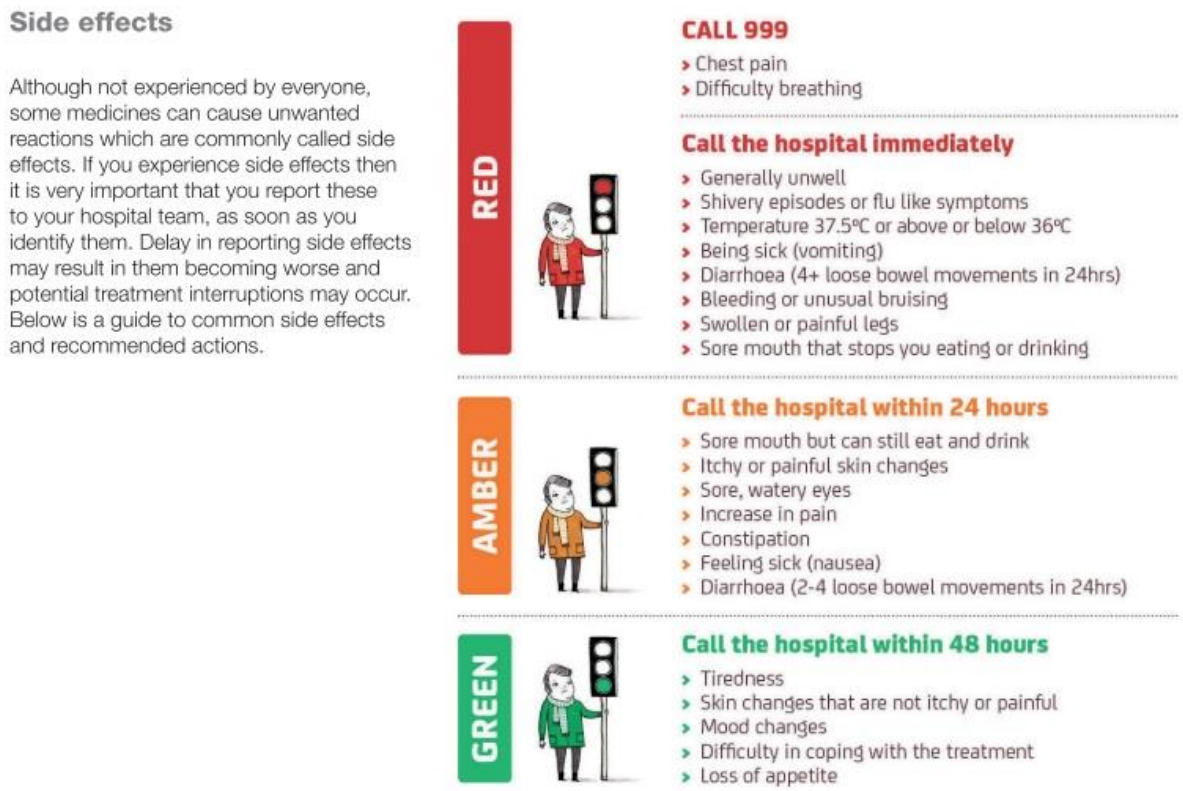

Figure 1 – Traffic light symptom reporting tool (reproduced from the National Chemotherapy Board Good Practice Guidelines [2016][10])

Drug interactions are a significant potential problem for cancer patients. Estimates of the prevalence of potential drug-drug interactions for cancer patients receiving systemic therapy range from 17 – 46%[11,12]. These drug interactions particularly affect older cancer patients, who are more likely to have multiple co-morbidities and take multiple long-term medications. Risk factors for drug interactions are listed in Table 3. These challenges re-emphasise the importance of clear communication between primary care and oncology teams to ensure anyone prescribing a new medication for a cancer patient is clear on what systemic therapies they are receiving and what their regular medications are.

Risk factors for drug interactions
Older age
Polypharmacy
Low body weight
Renal impairment
Haematologic cancer
Multiple medical co-morbidities

Longer hospital stays
History of adverse drug reactions
Intake of highly protein bound drugs

Table 3 – Risk factors for drug interactions from Campen et al[13]

Each type of systemic cancer therapy has their own known drug-drug interactions, as well as potential interactions with over-the-counter (OTC) medications, alternative therapies, and foods. There are some more common potential drug-drug interactions to be aware of when prescribing in primary care[13,14] =

Cytochrome P450 inhibitors/inducers – drugs that competitively inhibit (e.g. Ciprofloxacin) or induce (e.g. Phenytoin) cytochrome P450 binding sites can have an impact on the efficacy and safety of a number of oral and intravenous systemic cancer therapies, including Tyrosine Kinase Inhibitors (TKIs), SERMs and ADT agents.

Gastric acid suppression – H2-antagonists (e.g. Ranitidine) and Proton Pump Inhibitors [(PPIs) e.g. Omeprazole] alter the gastric pH, which can affect the absorption and bioavailability of oral systemic cancer therapies. If a patient is symptomatic and needs acid suppression, taking these medications at least two hours before or after their oral cancer treatment may reduce their impact on drug absorption.

Anticoagulants – Some oral systemic cancer therapies, such as Ibrutinib (a TKI), can increase the INR and cause bleeding. Patients taking oral anticoagulants (e.g. Warfarin) for other indications, such as atrial fibrillation, will need careful assessment of the risks and benefits of both treatments, and close monitoring.

QTc prolongation – A number of targeted therapies are known to cause QTc prolongation (e.g. Sorafenib, Sunitinib), perhaps provoking serious arrhythmias. Prescribers giving long-term (e.g. amitriptyline) or short-term (e.g. clarithromycin) medications that can also affect the QT interval need to be aware of the possibility of drug-drug interaction, prolonging the QT interval.

Optimising primary care for cancer patients

Supporting cancer patients receiving systemic cancer therapies optimally requires a multidisciplinary approach that includes primary care. The treatment journey for these patients can have physical, psychological, social and emotional effects. Some patients will recover from treatment with the cancer in remission or cured, but many will need further treatment with curative intent or for

palliation if there is disease progression in spite of treatment. Primary care plays a key role in identifying and managing physical effects of treatment, providing psychosocial support, and arranging specialist review where needed. Regular and accurate communication is critical to ensure all professionals involved in the patient's care are informed of current and planned treatments, and to avoid preventable adverse drug reactions.

Word count – 1990/2000

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