Continuing Professional Development

CPD

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60 Second Summary

Cancer describes a group of illnesses caused by a rapid and uncontrolled growth of abnormal cells. These form a mass, leading to a growth or tumour, which can damage nearby organs or metastasise to invade distant organs.

The most common types of cancer in Ireland are prostate, colorectal and lung cancers for males; and breast, colorectal and lung cancers for females.

Systemic anti-cancer therapy (SACT) involves the systemic treatment of cancer, including, but not limited to, chemotherapy, targeted therapies and immunotherapies. Oral anti-cancer medicines (OAM) can be grouped into three categories: cytotoxic agents, targeted agents and hormonal agents. Targeted therapies are often cytostatic (i.e. they block tumour cell proliferation) whereas standard chemotherapy agents are cytotoxic (i.e. they kill tumour cells).

Systemic anticancer therapy (SACT) involves the administration of medication that often has a narrow therapeutic window and toxic side effects.

Recommendations about communication are also made that highlight the importance of, but current inconsistency in, communication from the hospital about OAM treatment with the patient's GP and community pharmacy. This is required for the safe management of patient care.

When reviewing an OAM prescription as recommended by the Oral Anti-Cancer Medicines Model of Care[7], check the indication and drug dose. If possible, check the calculation for body surface area (BSA) or weight.

In addition to prescription review, it is important to talk to the patient about what information they have already received - the opportunity to talk and ask questions about medications may really be appreciated.

1. REFLECT - Before reading this module, consider the following: Will this clinical area be relevant to my practice?

2. IDENTIFY - If the answer is no, I may still be interested in the area but the article may not contribute towards my continuing professional development (CPD). If the answer is yes, I should identify any knowledge gaps in the clinical area.

3. PLAN - If I have identified a knowledge gap - will this article satisfy those needs - or will more reading be required?

4. EVALUATE - Did this article meet my learning needs - and how has my practise changed as a result?Have I identified further learning needs?

5. WHAT NEXT - At this time you may like to record your learning for future use or assessment. Follow the 4 previous steps, log and record your findings.

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Oral Chemotherapy Medications

Introduction

Cancer describes a group of illnesses caused by a rapid and uncontrolled growth of abnormal cells. These form a mass, leading to a growth or tumour, which can damage nearby organs or metastasise to invade distant organs.[1] The National Cancer Registry Ireland (NCRI) collects, classifies, stores and analyses information about the incidence and prevalence of cancer in Ireland. In 2020, the NCRI estimated that, on average[2], about 36,907 invasive cancers were diagnosed annually during the years 2018-2020 (24,793 cancers excluding the common but rarely fatal non-melanoma skin cancer). Cancer was responsible for nearly 31% of deaths in 2017 and is the most common cause of death in Ireland. The most common types of cancer in Ireland are prostate, colorectal and lung cancers for males; and breast, colorectal and lung cancers for females (Table 1). Lung cancer accounted for the highest proportion of mortality in both sexes: 20% of cancer deaths in women and 22% in men. The risk of dying of cancer was about 33% higher for men than for women. Although the incidence of cancer is increasing, the survival rate is also increasing. Ireland ranked in the top half of countries surveyed for 14 out of 18 common cancers studied in the EU five-year net survival during 2010-2014.

The top risk factors for all cancers are[4]:

- Cigarette smoking and tobacco use
- Infections
- Radiation
- Immunosuppressive medication
- Diet
- Alcohol
- Physical activity
- Obesity
- Diabetes
- Environmental risk factors

The HSE National Cancer Control Programme (NCCP) was established in 2007.[5] It monitors the incidence, mortality and survival patterns of cancer in Ireland using data from bodies

Table 1. The most common types of cancer in Ireland[3]

Type of Cancer	Average Annual Diagnoses
Skin	13,311
Prostate	3,890
Breast	3,704
Bowel	2,819
Lung	2753

like the NCRI, and also aims to monitor and improve the quality of cancer care. National chemotherapy regimens have been developed by healthcare professionals with the NCCP to support safe, evidence-based and cost-effective cancer treatment for all Irish cancer patients.

Treatment

Systemic anti-cancer therapy (SACT) involves the systemic treatment of cancer, including, but not limited to, chemotherapy, targeted therapies and immunotherapies.[6] Oral anti-cancer medicines (OAM) can be grouped into three categories: cytotoxic agents, targeted agents and hormonal agents. Targeted therapies are often cytostatic (i.e. they block tumour cell proliferation) whereas standard chemotherapy agents are cytotoxic (i.e. they kill tumour cells).

- *Cytotoxic chemotherapy* slows the process of cancer cells growing or multiplying. They can be cell cycle phase-specific or cell cycle phase non-specific. These drugs interferes with growth and division of all cells with no discrimination: all rapidly dividing cells in the body are targeted, which gives rise to the side effects commonly associated with chemotherapy.
- *Targeted therapy* (biological therapies) are aimed at specific molecular targets on the cell surface or within the cell that are specifically present in the cancer cells, and not present in healthy cells.
- *Hormonal therapy* works on the hormones that increase cell proliferation in certain types of cancer, i.e. breast, thyroid, prostate and uterine. With these diseases, the action of hormones or hormone antagonists depends on the presence of hormone receptors in the tumours themselves (e.g., oestrogen receptors in breast cancers).

Many treatment regimens use a combination of these categories. Neoadjuvant therapy may be necessary in some cases. This refers to all treatments that are administered before the primary cancer treatment. If the cancer is e.g. too large, in an awkward location, or obstructing an organ, neoadjuvant therapy can be used to shrink the tumour to allow e.g. surgical treatment. Adjuvant therapy refers to regimens administered after the primary treatment. Chemotherapy is often adminsitered to destroy any micrometastases.

Prescribing of OAM in Ireland is usually based on one of the HSE National Cancer Control Programme (NCCP) chemotherapy regimens. A comprehensive list of NCCP OAM regimens is available on the NCCP website.[5]

Dispensing Oral Chemotherapy

Systemic anticancer therapy (SACT) involves the administration of medication that often has a narrow therapeutic window and toxic side effects.[7] OAM have the same potential for risk as parenteral SACT in terms of side effects, toxicities and serious medication errors. Defined quality and safety policies are in place for parenteral SACT in Ireland, but such policies are less well defined for OAM. Treating patients using OAM is a multidisciplinary process that has multiple steps, such as the decision to treat, the prescribing, dispensing and management of a patient. OAM has significant differences to that of parenteral SACT. OAM are dispensed in the community and self-administered at home, while parenteral SACT is dispensed and usually administered in hospitals. The advantages of OAM include the convenience – as it is administered at home, there is no waiting for hospital administration. OAM can also lead to an increased sense of control for the patient.

As new and potentially more complex OAM regimens are developed additional safety challenges are likely to emerge, and it is envisaged that the provision of national guidance through a model of care will help standardise and overcome these. The 2014 NCCP Oncology Medication Safety Review identified the need for a national guideline for the management of the prescribing and dispensing of oral chemotherapy under the following topics:

- Safe prescribing
- Prescription checking
- Prescription format
- Administration
- Service models for dispensing and supply
- Communication system between primary care and secondary care

In response to this, the NCCP published the Oral Anti-Cancer Medicines Model of Care Recommendations in 2018.[7] The main recommendations relevant to community pharmacists in this report that are are the following:

- All OAM prescriptions should be verified prior to dispensing and administration by an oncology pharmacist. Currently there is variation in the practice for the verification of OAM prescriptions. Some prescriptions, but not all, are verified by an oncology pharmacist prior to being given to the patient.
- Community pharmacists should have access to the recommended information (potentially including training and education programmes), where relevant, to allow prescription review prior to dispensing, as OAM are mostly dispensed by community pharmacists.
- Only one cycle of an OAM should be dispensed at a time. The quantity dispensed should not exceed the number of doses required to complete the cycle to reduce the risk of the patient overmedicating.

Recommendations about communication are also made that highlight the importance of, but current inconsistency in, communication from the hospital about OAM treatment with the patient's GP and community pharmacy. This is required for the safe management of patient care. A recommendation was also made that all prescriptions for OAM should include the recommended information either as a standard OAM prescription template, current prescription formats plus a treatment information document, or current prescription formats with the recommended information included as free text. (The NCCP plan to engage with the PCRS with regard to the current format of the High Tech prescription form).

Oral Chemotherapy Medications

Dosing of OAMS can be continuous (the same dose every day) or pulsed dosing. One "pulse" refers to one chemotherapy cycle e.g. "q21d" is every 21 days. Pulsed dosing allows the immune system to recover somewhat between cycles.

Women of childbearing potential or their male partners must use a highly effective method of contraception while taking OAMs.

Drug	Mechanism of Action	Administration	Indication	Dose	Side effects	Interactions
Capecitabine	Prodrug of fluorouracil, antimetabolite inhibiting DNA/RNA synthesis	30 mins after food	Breast, colorectal, gastric	1,250mg/m 2 bd for 14 days, followed by 7 days off treatment	Hand-foot syndrome. (palmar-plantar erythrodysesthesia)	CYP2C9 substrates (warfarin, phenytoin)
Abiraterone	CYP17 inhibitor (reduces androgen synthesis)	Empty stomach (food increases absorption and risk of ADRs)	Metastatic castration resistant prostate cancer (Used in combo with LH agonists, or with orchidectomy)	1000mg od	Should always be disp with prednisolone (This reduces mineralocorticoid side effects)	Strong inducers of CYP3A4 (phenytoin, carbamazepine) Avoid spironolactone: binds to androgen receptor, may cause disease progression
Enzalutamide	Androgen receptor inhibitor	With or without food	Metastatic castration resistant prostate cancer	160mg od	Many patients require treatment for hypertension which occurs in ~7%. Use with caution if previous seizure history	Strong CYP2C8 inhibitors, (gemfibrozil). Induces CYP2B6, CYP3A4, CYP2C9, CYP2C19, UGT1A1 - can lead to increased clearance of drugs.
Palbociclib	Reversible inhibitor cyclin-dependent kinases 4 and 6 inhibitor (involved in cell cycle regulation)	Swallowed whole with food	Hormone receptor (HR) - positive, HER2 - negative breast cancer	125mg od for 21 days followed by 7 days off treatment	Interstitial lung disease (report any respiratory issues)	CYP3A4 inhibitors/ inducers
Lenalidomide	Binds to cereblon (receptor of the cullin 4-RING E3 ligase complex), inhibiting proliferation/enhancing apoptosis	Swallow whole with water	Multiple myeloma	Usual starting dose 25 mg od for 21 days, followed by 7 days off treatment	PE, DVT. The conditions of the Pregnancy Prevention Programme must be fulfilled.	Digoxin, statins, P-gp inhibitors
Tamoxifen	Primarily an oestrogen receptor antagonist	With or without food	Breast cancer	20-40mg daily	VTE, optic neuropathy. Any abnormal gynaecological symptoms should be investigated.	CYP2D6 ihibitors (e.g. paroxetine, fluoxetine)

Table 2. Commonly prescribed OAMs in Ireland[8-13]

Patient Care

When reviewing an OAM prescription as recommended by the Oral Anti-Cancer Medicines Model of Care[7], check the indication and drug dose. If possible, check the calculation for body surface area (BSA) or weight. For BSA, both height and weight are needed. Multiple formulae are available to calculate BSA: the two main ones are Mosteller (which can be performed using your own calculator), and Dubois & Dubois (the most commonly used). Online calculator tools are available to use (e.g. www.halls.md website). There are several limitations to calculating drug dosages based on BSA:

- BSA is estimated, not measured
- BSA formulae take no account of obesity or weight loss
- There is no precise correlation between drug clearance and BSA
- Different BSA formulae give different results
- The most popular nomogram for BSA calculation is DuBois which is based on only 9 subjects

Despite these limitations, drug doses are very frequently based on BSA in cancer care. If the calculated BSA is within 10% of that specified on the prescription, that is generally thought to be acceptable. Rounding usually occurs during calculation of BSA and medication dose to account for the available strengths of tablets. Rounding of OAM doses of 5%[14] is generally accepted. If the prescription is not rounded, contact should be made with the hospital to see if the prescriber prefers to round up or down.

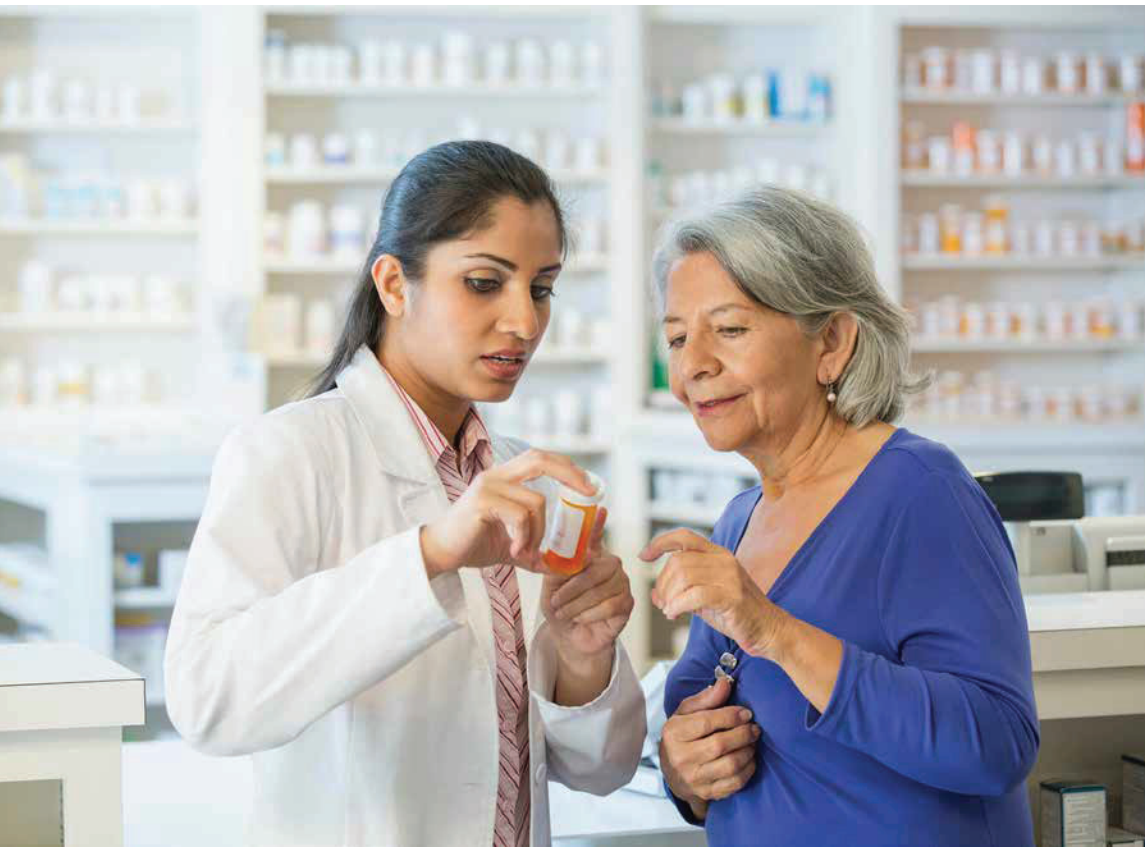
When a query arises from performing an OAM prescription check, useful sources of information include the prescriber, the hospital pharmacy (especially the oncology/haematology pharmacists), liaison nurses, the oncology/haematology day ward/ clinic, hospital treatment protocols, the SPCs for each medication, and the NCCP protocols.

The patient should be made aware that if they have any medication left for disposal they should bring back to the hospital to place in the cytotoxic bins.

The NCCP have multiple leaflets/ booklets also available online that provide important information for cancer patients with one of the most important being about infection prevention. The Irish Cancer Society website is also a great source of information for patients. A UK website called Chemocare is useful for both patients and pharmacists: it provides information about treatments, patient counselling, and managing side effects in a patient-friendly way.

General ADRs

Nausea and vomiting is one of the most frequent side effects experienced by patients undergoing SACT.[15] It is often a distressing side effect, and anxiety about the recurrence of such symptoms from future cycles may become a cause of anticipatory nausea and vomiting. The NCCP has developed a guideline on SACT related nausea and vomiting, setting out the classification of emetogenic risk of SACT drugs, and antiemetics to prevent and treat SACT induced nausea and vomiting. SACT drugs are classified into four levels of emetogenicity (high, moderate, low and minimal). The emetogenic potential of the



SACT must be considered when deciding which antiemetics to prescribe. When antiemetics are prescribed for patients receiving SACT drugs, the goal of antiemetic therapy is prevention of nausea/vomiting. Prophylaxis is better than treatment. If prophylaxis treatment is not fully effective, escalation to a stronger treatment is required immediately. In general, for moderate to high emetogenic drugs, ondansetron should be offered. For low to minimal emetogenic drugs, the recommended options are metoclopramide, prochlorperazine, or ondansetron, with a PPI to also be considered for all.

The type of emesis experienced influences the choice of drug:

- Acute: Nausea and vomiting experienced usually within a few minutes to several hours after drug administration and which commonly resolves within the first 24 hours
- Delayed-onset: Nausea and vomiting developing more than 24 hours after SACT administration and which may last for up to 6 - 7 days
- Breakthrough: Development of nausea and vomiting, despite prophylactic treatment and/or requires rescue with antiemetic agents
- Anticipatory: Nausea and vomiting that occurs prior to the beginning of a new cycle of SACT. It is primarily considered a conditioned response and typically occurs after a negative past experience with SACT
- Refractory: Nausea and/or vomiting that occur during subsequent treatment cycles when antiemetic prophylaxis and/or rescue have not been effective in earlier cycles.

If the patient has poorly controlled nausea, check their compliance and understanding of their regimen: are they taking regular antiemetics, at the right time? Refer the patient to the hospital if the symptoms are poorly controlled despite compliance.

Diarrhoea is generally treated with loperamide. If it is not responding adequately (e.g. 4-6 runny stools a day), the patient should contact the team in hospital.

Immunosuppression is common with the older cytotoxic medications which often cause a reduction in white blood cells and also platelets. Refer the patient to the hospital if their temperature reaches over 38 degrees or if there are any feelings of unwellness, e.g. sore throat, coughing. Any unexplained bleeding should also be reported. Paracetamol may mask a temperature and should never be used to reduce a temperature without reporting the high temperature to the hospital first. Hand hygiene practices are important. The patient should also try and avoid contact with anyone who has an infection such as chickenpox or the flu.

Stomatitis (in the mouth) and mucositis (in the GIT) are also very common side effects. To help reduce irritation in the mouth, patients can be advised to use a soft toothbrush, and a bland mouthwash, such as salty water. Spicy, sharp foods and alcohol should be avoided (16). BMX mouthwash can be prescribed if required. Chlorhexidine mouthwash is not usually recommended as it can sting, and stain teeth.

Neuropathy (numbness and tingling in fingers and toes peripheral nerves) is more common with the cytotoxic agents. If it is not treated, it can become irreversible. Symptoms of neuropathy need to be reported to the hospital by the patient as soon as possible. The hands and feet should be kept warm, and care should be taken with e.g. hot drinks.

Fatigue can be caused by both the cancer itself and the chemotherapy. The patient should be encouraged to rest, but if appropriate, also encouraged to implement a rest/activity cycle that includes some very light exercise. There is also evidence to suggest that american ginseng[17] is beneficial for reduction of fatigue, as long as there are no drug interactions. Anaemia can also contribute to feelings of tiredness.[16]

Capecitabine in particular is associated with hand-foot syndrome (palmar-plantar erythrodysesthesia) where the palms of the hands and the soles of the feet become dry and red, feeling numb or tingling, and the skin becomes flaky. This is common at start of treatment, but also seen later on. To help with this, tight fitting shoes should be avoided. It is also very important to regularly moisturise with an emollient.

The Role of the Pharmacist

In addition to prescription review, it is important to talk to the patient about what information they have already received - the opportunity to talk and ask questions about medications may really be appreciated. Patient education is one of the most important ways to support medication adherence, which is crucial for good treatment outcomes. Check that the patient is aware of their dosing schedule and the need for them to report any high temperature and any feeling unwell (e.g. Sore throat, cough). Pharmacists can support patients in identifying and treating some of the ADRs and toxicities associated with SACTs, and recognise serious symptoms that require referral to the patient's treatment centre. The patient should be advised to follow their management plan in order to prevent, minimise and handle ADRs. If any side effects are getting worse, early referral to hospital is advised. Blood checks need to be performed to the patients commencing a new cycle of treatment.

References available on request