INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

doi:10.1111/imj.14878

REVIEW

Anti-cancer therapy made easier: a 25-year update

Amy Davies,[1] Caroline Lum,[1] Rachel Raju,[2] Evan Ansell,[1] Kate Webber[1,3] and Eva Segelov[1,3]

[1]Department of Oncology, Monash Health, [2]Department of Oncology, Peter MacCallum Cancer Centre, and [3]School of Clinical Sciences, Monash University Melbourne, Victoria, Australia

Key words
chemotherapy, anti-cancer therapy, side-effect, toxicity, supportive care.

Correspondence
Amy Davies, Department of Oncology, Monash Health, Melbourne, Vic. 3168, Australia.
Email: amygeorginadavies@gmail.com

Received 16 January 2020; accepted 27 March 2020.

Abstract

In 1993, the *Internal Medicine Journal* published 'Chemotherapy made easier', outlining developments in supportive care of patients undergoing chemotherapy. This described the contemporary state of anti-emetics, colony stimulating factors, cardiac toxicity, neurotoxicity, development of drug analogues and venous access devices. Twenty-five years later, we update the measures that improve the tolerability of the plethora of new anti-cancer therapies, which have extended well beyond traditional chemotherapy agents to include immunotherapy and targeted therapies. Optimisation of supportive care is paramount to allow safe delivery with the least possible impact on quality of life of these new treatments, many of which have resulted dramatically improved outcomes across multiple cancer types. This state of the art update summarises advances in supportive care therapies relating to improving the patient experience during and after anti-cancer treatment, including new anti-emetics, hair preservation techniques, bone marrow support and improved venous access devices; the ongoing challenge of neurotoxicity; and the advent of multidisciplinary sub-specialised fields such as cardio-oncology and oncofertility. Supportive care medications for immuno-oncology therapies is a new section; these highly effective (although not universally so) agents were a mere illusion in 1993.

Introduction

Supportive care aims to both reduce symptoms arising as a consequence of cancer itself and from toxicities associated with treatment.[1] In this era of increasingly complex and prolonged anti-cancer treatments, administered to a population living longer with and after cancer, and often much more elderly than previously treated, an update of the advances in supportive care relating to anti-cancer therapy is timely.

Chemotherapy induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared side-effects of cancer treatment, and despite significant progress, it remains problematic for some patients. In a pooled observational study of 1198 patients, almost half experienced nausea, with 42% having two or more episodes of vomiting or reduced oral intake despite modern anti-emetic regimens.[2]

Funding: None.
Conflict of interest: None.

Guidelines for management of CINV recommend a stratified approach predicated on the emetogenic risk of the treatment (Table 1).[3] In Australia, the widely used evidence and quality chemotherapy reference site allocates anti-emetics to treatment regimens using stratification based on Therapeutic Goods Administration and Pharmaceutical Benefits Scheme (PBS) approved indications.[3]

Standard doses of dopamine antagonists such as metoclopramide remain the backbone for low and minimal risk CINV. Since our previous review, new classes of anti-emetic agents have entered clinical practice, including the second generation serotonin receptor antagonists (5HT3-RA), the neurokinin-1 receptor antagonists (NK1-RA) and the atypical anti-psychotic olanzapine. A major advantage of these agents is in reducing the requirement for high dose steroids. A summary is in Table 2.

The mechanism of action of NK1-RAs involves antagonism of substance P neurokinin-1 receptors.[4] A meta-analysis of 23 trials demonstrated that incorporation of NK1-RA significantly improved rates of no emesis for highly emetogenic chemotherapy (HEC) regimens containing cisplatin (odds ratio (OR) 2.62, 95% confidence interval (CI) 2.29–2.99, $P < 0.00001$) and anthracycline/

Table 1 Anti-emetics recommended according to emetogenic risk†[†]

Risk	Examples	Recommended regimen
High (HEC: >90% risk)	Cisplatin Cyclophosphamide plus anthracycline Carboplatin (AUC >4)	3 drug combination 5HT3-RA D1 NK1-RA D1 Dexamethasone D1-4
Moderate (MEC: 30–90% risk)	Carboplatin (except high dose) Cyclophosphamide Doxorubicin Irinotecan Oxaliplatin Temozolamide	2 drug combination 5HT3-RA D1 Dexamethasone D1-3 Note: Add NK1 RA as rescue if prior episode CINV
Low (LEC: 10–30% risk)	Paclitaxel Docetaxel Etoposide Fluorouracil Gemcitabine	Single agent: Dexamethasone D1 or Metoclopramide prn or Prochlorperazine prn

†Adapted from eviQ guidelines.[3] 5HT3-RA, 5-hydroxytryptamine type 3-receptor antagonists; NK1-RA, neurokinin-1-receptor antagonists; D, day; prn, as required.

cyclophosphamide (OR 1.97, 95% CI 1.62–2.41, $P < 0.00001$).[5]

The combination oral preparation of the 5HT3-RA palonosetron and the NK1-RA netupitant (Akynzeo) is commonly used for HEC and some moderate emetogenic chemotherapy (MEC) regimens. Benefit was demonstrated in two randomised phase III studies comparing combination netupitant/palonosetron to 3 days of separately administered aprepitant plus palonosetron or single dose palonosetron, respectively. Each arm also incorporated dexamethasone.[6,7] A complete response (CR; no emesis and no rescue medication) during cycle 1 of HEC or MEC occurred in 81% of patients in the combination palonosetron/netupitant arm compared to 76% in the 3-day aprepitant plus palonosetron arm and was maintained in subsequent cycles.[6] When comparing CR rates in delayed CINV, combination palonosetron/netupitant compared to single dose palonosetron met the primary efficacy endpoint (77% vs 70%, $P < 0.001$).[7]

More recently the atypical anti-psychotic agent olanzapine has entered CINV regimens. Efficacy was demonstrated in a double blind phase III trial of 380 patients receiving HEC who were randomised to receive olanzapine 10 mg on days 1–4 or placebo, in combination with dexamethasone, NK1-RA and 5HT3-RA.[8] Olanzapine resulted in a significantly greater proportion of patients with no acute or delayed nausea (74% vs 45%, $P = 0.002$ and 37% vs 22%, $P = 0.002$, respectively). The proportion of patients with no emesis and no use of rescue anti-emetic medication in the acute and delayed phase was significantly higher compared with placebo (86% vs 65%, $P < 0.001$ and 64% vs 41%, $P < 0.001$, respectively). The main adverse effect was sedation, self-reported as 'severe' in 5%.

Chemotherapy-induced alopecia

Chemotherapy-induced alopecia (CIA) is perhaps the most well recognised side-effect of chemotherapy to the lay public. In a prospective study of 266 women with breast cancer, alopecia ranked second only to the fear of metastases as the consequence of cancer anticipated to have the

Table 2 New CINV agents†

Drug	Half-life (h)	Preparation	Common side-effects	Principal use
5HT3-RA				
Ondansetron	4–11	Oral	Headache, constipation	Acute CINV (HEC and MEC)
Granisetron	9	IV		
Palonosetron	40	Oral or IV		Acute and delayed CINV (HEC and MEC)
NK1-RA				
Aprepitant	9	Oral	Diarrhoea constipation, fatigue, hiccups, elevated hepatic aminotransferases	Acute CINV (HEC, carboplatin (AUC > 4) and oxaliplatin regimens and as rescue for other MEC with prior episode of CINV)
Fosaprepitant (aprepitant prodrug)	14	IV		
5HT3-RA + NK1-RA				
Palonosetron + netupitent	88	Oral	Headache, constipation	Acute CINV (HEC)
Atypical anti-psychotic				
Olanzapine	30	Oral	Sedation	Adjunct use in acute CINV (HEC)

†Adapted from product information and eviQ guidelines.[3,4] 5HT3-RA, 5-hydroxytryptamine type 3-receptor antagonists; CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; IV, intravenous; MEC, moderate emetogenic chemotherapy; NK1-RA, neurokinin-1-receptor antagonists.

greatest effect on their lives. Alopecia was the most distressing factor before, during and after treatment.[9]

CIA is classically caused by anagen effluvium, which is the apoptosis of matrix keratinocytes in the hair follicle, resulting in hair being shed from the bulb.[10] Alternatively, follicle function may be reduced, leading to hair shaft thinning and snappings.[10] CIA affects all areas of body hair, but has a predilection for the scalp and in particular areas prone to lower hair density, such as the crown. Following completion of chemotherapy for solid tumours, hair regrowth is usual but there may be subtle changes in colour and texture.[10]

Mechanisms to prevent CIA fall into two categories: hypothermic and pharmacological. Pharmacological interventions include topical minoxidil and calcipotriol, yet have limited efficacy and are not widely used.[10] The premise of scalp hypothermia is to induce vasoconstriction in the scalp, decreasing blood flow and hence drug delivery to the vulnerable matrix keratinocytes.[10] Both manual and automated cooling caps are commercially available. Manual caps act as ice packs and require regular changing to ensure adequate hypothermia. More modern automated devices use a silicon cap to circulate coolant at a constant rate. Scalp cooling must be used from the first cycle of treatment, otherwise hair follicles are already damaged. Importantly, the outcome of scalp cooling is highly dependent on the 'fit' of the device. Areas of scalp not in direct contact with the device do not derive any benefit.

A recent multi-centre trial of 182 early stage breast cancer patients receiving anthracycline or taxane-based therapy were randomised to automated scalp cooling or standard of care. All patients in the no cooling arm experienced ≥50% hair loss, compared to around 50% of patients in the cooling arm having successful preservation (defined as <50% hair loss and not requiring a wig).[11] Efficacy is supported by a 2015 meta-analysis that included 10 trials (three randomised) using automated scalp cooling, finding a significant reduction in CIA (risk ratio (relative risk) 0.38, 95% CI 0.32–0.45, $P < 0.001$).[12]

Interestingly, studies to date have not demonstrated a significant difference in measured quality of life outcomes, including emotional or social functioning, anxiety and depression and body image scale.[11] This may reflect limitation in the tools used or the populations studied as well as the significant impact of a cancer diagnosis and its treatment.

Adverse effects of scalp cooling include discomfort, cold-induced migraine, dry skin and cold injury.[11] There is a theoretical increased risk of scalp metastases due to reduced delivery of chemotherapy resulting from vasoconstriction; however, this not been borne out in studies of solid tumours, where scalp metastases are rare. A systematic review and meta-analysis of 10 breast cancer trials involving 1959 patients found no significant difference in the incidence of scalp metastasis in those who had scalp cooling compared to those who did not (0.61%, 95% CI 0.32–1.1 vs 0.41%, 95% CI 0.13–0.94, $P = 0.43$).[13] In addition, there are logistical impacts of these devices on cancer day centre resources. Currently, suggested cooling times are 30–60 min pre- chemotherapy infusion and 90–120 min post, greatly increasing chair occupancy time. A dedicated nurse per patient is also required.

In Australia, the cost of outright purchase of a single machine (two automated brands currently available) is upwards of $40 000. This raises discussion regarding resourcing priorities within a limited healthcare system, as hair preservation is viewed somewhat as a 'luxury', despite its psychosocial impact. Anecdotally, uptake is higher in private cancer treatment units, with subsequent concerns around equity.

Bone marrow support

Myelosuppression and its associated clinical presentations, such as neutropenic fever, remain concerning complications of cancer therapy. In the past 25 years, two major changes to bone marrow support have occurred: improved pharmacokinetics of growth factor administration and the development of biosimilars.

Filgrastim is a short-acting granulocyte-colony stimulating factor (G-CSF) formulation which has been registered in Australia since 1995. It is administered subcutaneously and has a half-life of approximately 3–4 h, requiring daily administration for 3–5 days after chemotherapy.[4] Pegfilgrastim is a pegylated formulation with an increased half-life of approximately 42 h.[4] This allows a single injection, administered 24 h after each cycle of chemotherapy. Non-inferiority to filgrastim has been demonstrated, with no significant difference in incidence of neutropenia and neutropenic fever.[14] The agents have equivalent tolerability, with the main side-effects being transient fever and bone pain.

Until recently, access to PBS-funded G-CSF support has been limited to curative intent chemotherapy regimens. The cost-effectiveness of this restriction, compared to toxicity plus any loss of chemotherapy efficacy due to treatment delays or dose reductions (for patient safety), has not been examined. With the end of patent for filgrastim and the concurrent development of biosimilars, a widening of PBS-funded use has been allowed, extending to patients expected to benefit significantly from chemotherapy, whether it be of curative or palliative intent.

US Food and Drug Administration approval for the first G-CSF biosimilar was granted in 2015, and in Australia the Therapeutic Goods Administration has approved biosimilars with the active substance filgrastim. A meta-analysis of eight randomised controlled trials in breast cancer found no statistically significant difference in the duration of severe neutropenia between G-CSF and biosimilar agents (mean difference: 0.06, 95% CI 0.05–0.17).[15] However, because many biosimilar studies are designed as non-inferiority rather than equivalence trials, there is debate about whether there really is true equipoise, particularly in the setting of curative intent cancer treatments. Nevertheless, many hospital pharmacies have switched, with resultant cost savings.

Early data were encouraging that erythropoiesis-stimulating agents (ESAs) such as erythropoietin, would be transfusion-sparing for chemotherapy-induced anaemia. However, increased risk of venous thromboembolic events caused concern, leading to the current American guidelines not endorsing use of ESAs in the adjuvant with curative intent setting.[16] In Australian clinical practice, apart from anaemia secondary to intrinsic renal disease, these agents are rarely used.

Neurotoxicity

Chemotherapy-induced peripheral neuropathy (CIPN) remains a management challenge, particularly with the growing number of cancer survivors. A meta-analysis of 31 studies of neurotoxic chemotherapy reported a prevalence of 68.1% at the first month following treatment cessation, with 30% still present at 6 months.[17] Implicated in CIPN are the older agents cisplatin and vinca alkaloids, and the relatively newer agents, particularly taxanes and the platinum derivative oxaliplatin. For a significant proportion of patients CIPN is irreversible, dependent on drug class, dose and duration.

Although the mechanism varies between agents, CIPN is primarily sensory, with progression through paraesthesia and dysthesia to numbness and loss of proprioception in a glove and stocking distribution. The onset of CIPN can be delayed, particularly for the commonly used platin drugs cisplatin and oxaliplatin, such that the symptoms often worsen after treatment is ceased. This was the major impetus for landmark global studies comparing 6 versus 3 months duration for adjuvant oxaliplatin containing chemotherapy after resection of stage 3 and high-risk stage 2 colorectal cancer. For most trials and in most subgroups (except perhaps very high-risk disease), cancer outcomes were non-inferior and 3 months of adjuvant therapy has been adopted as the new standard.[18] The reduction in oxaliplatin neuropathy with the shorter treatment length was striking. At 3 months, only 2.5% of patients had grade 3 or 4 neuropathy (significant impairment limiting self-care or with life-threatening consequences) and this was mostly fully reversible, compared to 12.5% after 6 months of therapy,[19] with a rate of residual grade 3 neuropathy at 4 years of 8%.[20] A prospective sub-study of Australian patient preferences and trade-offs showed median survival benefit judged sufficient to make longer duration chemotherapy worthwhile was an extra 3 years beyond a life expectancy of either 5 or 15 years.[21]

The mainstay of CIPN management remains early identification and cessation of the offending drug typically once grade 2 CIPN (moderate symptoms; limiting instrumental activities of daily living) develops. Drugs used to treat neuropathy from other causes such as diabetes, are not useful in CIPN. These include anticonvulsants (pregabalin, gabapentin, lamotrigine) and anti-depressants (amitriptyline, venlafaxine, duloxetine). Duloxetine, a selective serotonin and noradrenaline reuptake inhibitor, was studied in a randomised double blind placebo-controlled phase 3 trial of 231 patients who received duloxetine daily or placebo for 5 weeks, followed by treatment cross over for 4 weeks. Although patients in the duloxetine-first arm had a larger reduction in average pain score (mean change: 1.06; 95% CI 0.72–1.40)[22] this does not appear to translate into meaningful benefit in real life practice.

Cardiotoxicity

Cardiac dysfunction induced by chemotherapy occurs through various mechanisms, such as anthracyclines (e.g. doxorubicin), which cause cumulative dose dependent left ventricular failure, and fluoropyrimidines, which cause coronary artery spasm. This has given rise to a new subspecialty, cardio-oncology, defined as the prevention and management of cardiotoxicity resulting from chemotherapy, immunotherapy and targeted therapies. Indeed, centres such as the Moffitt Center in the United States have set up a dedicated cardio-oncology service which combines patient care, research and education.[23] This is particularly relevant for patients on newer targeted agents, immuno-oncology agents and clinical trials. However, evidenced-based clinical pathway is yet to be developed for the Australian setting.

Since our last review, anti-HER2-targeted therapies have entered routine practice. The monoclonal antibodies trastuzumab and pertuzumab and the small molecular tyrosine kinase inhibitors neratinib and lapatinib are now in widespread use for patients with HER2 positive breast and gastric cancers. Initial trials of trastuzumab in breast cancer reported a 3–7% incidence

of cardiotoxicity when used alone and 27% when combined with anthracycline plus cyclophosphamide.[24]

Duration of therapy appears important. In the Herceptin Adjuvant (HERA) trial, 5000 women who had completed adjuvant chemotherapy with HER2 positive breast cancer were assigned to observation or addition of trastuzumab for either 1 or 2 years. The incidence of cardiotoxicity for 1 year of trastuzumab was 4.4%, compared to 7.3% for 2 years of treatment, and 0.9% for observation.[25]

Deterioration in cardiac function is generally reversible after cessation of therapy and use of angiotensin converting enzyme inhibitors and beta receptor blocking drugs. In most cases, treatment with the same or different anti-HER2 drug can be recommenced and more recently, there is a trend not to suspend treatment.

Trials of primary prevention appear to endorse this strategy, although prophylaxis is not yet routine. A randomised trial of lisinopril or carvedilol versus placebo in 468 patients co-administered with adjuvant trastuzumab demonstrated almost 50% less fall in left ventricular ejection fraction (LVEF), and 20% less interruption of trastuzumab dose, but this was restricted to the cohort who had received anthracycline chemotherapy.[26]

Fortunately, use of highly effective combinations of anti-HER2 agents has not shown a compounding of cardiac risk.[27] Furthermore, newer agents such as trastuzumab emtansine (TDM1) appear less cardiotoxic.[27]

Screening for reduction in LVEF while on anti-HER2 therapy is mandated by the PBS, although recently wording has softened from the previous requirement for 3-monthly assessment. Despite image quality of echocardiogram being highly dependent on the skill of the examiner as well as patients' body habitus and anatomy, it remains the most commonly endorsed method of determining LVEF;[28] a second read by an experienced reporter is worthwhile where treatment may be impacted on the result. In contrast, nuclear scans carry high sensitivity,[28] but the dose of radiation delivered with serial scans is considerable and of particular concern in patients receiving adjuvant therapy. The requirement for repeated testing of patients receiving palliative anti-HER2 therapy is also under scrutiny as this is unlikely to be cost-efficient.

Oncofertility

The subspecialty of oncofertility has emerged in an era of improved cancer cure rates, as well as dramatic advances in reproductive technology. Many chemotherapy agents cause dose and age dependent primary gonadal failure; less so the newer targeted and immune therapies. Gonadal failure can be temporary or permanent, resulting in infertility for both sexes, premature menopause in women and primary gonadal failure in men, although the latter is far less common. Spermatozoa are much more resistant to chemotherapy than ova and are relatively easy to store with a high yield even after many years of freezing. Advances in techniques for sperm extraction have resulted in the ability to store adequate samples even for prepubertal boys, men who have severe oligozoospermia, or those unable to ejaculate.

The most significant advance has been the marked improvement in oocyte preservation, due to advances in rapid freeze/thaw technologies that do not disrupt the oocyte membrane, this has moved from an experimental procedure to one that can be offered routinely to female patients without a sperm donor, although the rate of subsequent live births is still significantly lower than *in vitro* fertilisation with embryo storage.[29]

For many years the concept of blocking the gonadotropin-releasing hormone (GnRH)-fertility axis to prevent chemotherapy-induced ovarian failure was tested with variable results. Only recently has there been sufficient evidence to warrant routine use, with availability now for this indication on the PBS. A meta-analysis of 13 trials showed higher rates of spontaneous pregnancy after chemotherapy with use of GnRH agonist prior to and during treatment (RR 1.43, 95% CI 1.01–2.02).[30] For pre-pubertal girls, fertility preservation remains experimental. Ovarian tissue cryopreservation has only case reports of success (17 live births reported from 74 cases of ovarian tissue transplantation).[31]

Side-effects relating to immuno-oncology agents

An entire new anti-cancer strategy, known as immunotherapy or immuno-oncology (IO), has entered routine clinical practice for multiple tumour types due to striking efficacy, which can provide long term durable responses. These agents alter pathways used by the cancer cell to 'hide' from the host immune system. A major class are the 'checkpoint inhibitors', which work by blocking either cytotoxic T-lymphocyte-associated protein 4 (CTLA4; e.g. ipilimumab), programmed cell death protein 1 (PD1; e.g. nivolumab, pembrolizumab) or programmed death-ligand 1 (PDL1; e.g. durvalumab, atezolizumab). There are many other novel and combination IO agents in development.

Longer term data are now available from the first metastatic melanoma IO trials. Five-year follow-up of a phase Ib trial of pembrolizumab in advanced melanoma (Keynote-001, $n = 655$) demonstrated a disease control rate of 65%. Of the 16% who had a complete response, 89% had ongoing response at 5 years.[32] This was

inconceivable at our last review. Similarly, immuno-oncology agents have provided improved survival outcomes for patients with metastatic lung cancer, bladder and renal cancer, squamous cancers of head and neck and many other tumour types.[33]

By reinvigorating the anti-tumour response of T cells, the toxicity profile of IO drugs reflects an 'overshoot' autoinflammatory response, which can affect any organ system, even many months after the last dose. The incidence of immune-related adverse events (irAE) differs between various agents but is higher for combination therapy using CTLA4 and PD1/PDL1, with severe or life-threatening toxicity seen in over half.[34] Recognition of these potential irAE is critical as they can be potentially fatal. This can be challenging for the Emergency Department and physicians not familiar with the irAE profile. A summary of irAE incidence is presented in Table 3.

In general, management of most moderate to severe irAE requires cessation of the IO agent and delivery of high dose corticosteroids to dampen rapidly the autoimmune response, followed by a tapering steroid dose over several weeks. Severe immune-related endocrinopathies often require lifelong hormone replacement of the affected gland. For life-threatening irAE, additional use of immune-modulating drugs is often required, including tumour necrosis factor alpha antagonists (such as infliximab), mycophenolate or tacrolimus. Milder reactions can be managed with oral corticosteroids (or topical for irAE rashes) in the outpatient setting. Given irAE identification and management can involve several specialties there remains a need to establish multidisciplinary teams across different specialty groups to provide optimal management of immune-related toxicity.

Table 3 Immune-related adverse events grouped per incidence†[†]

Most common >15%	Less common 2–15%	Uncommon <1–2%
Mild rash	Rash (combo IO)	Severe skin toxicity
Mild diarrhoea	Colitis	Hypophysitis (single agent nivolumab)
Thyroid dysfunction requiring hormone replacement	Mild–moderate hepatitis	Severe hepatitis
	Pneumonitis	Insulin dependent diabetes
	Hypophysitis (combo IO)	Colonic perforation
	Mild or moderate arthralgias	Severe or life-threatening dyspnoea
	Mild or moderate renal toxicity	Neurological AE
		Other rheumatologic AE (vasculitis, polymyositis, myositis, temporal arteritis)
		Severe or life-threatening renal dysfunction
		Cardiac toxicity
		Occular toxicity
		Haematological toxicity

†Adapted from European Society Medical Oncology Clinical Practice Guidelines.[34] AE, adverse events; combo, combination therapy; IO, immuno-oncology.

Central venous access devices

Since the first totally implantable long-term catheter device was inserted 30 years ago, central venous access devices (CVAD) remain an important aspect of drug delivery and have supported a recent shift to outpatient and in-home therapy. CVAD reduce the need for repeat cannulation as well as venipuncture. They have become more sophisticated, with options for multiple lumens and antibiotic-impregnated catheters (only used for some high-risk patients, such as after bone marrow transplant).

Implanted venous ports offer advantages over peripherally inserted central catheters, with much longer time periods between flushing to maintain patency if unused (6–8 weeks vs 1 week). Being totally subcutaneous reduces the risk of infection and allows unrestricted showering and swimming. Ports are usually inserted using local anaesthetic (with or without sedation) in interventional radiology units, whereas previously most were inserted in a formal vascular operation. Newer ports can be flushed with normal saline thereby reducing the uptake of heparin locking between uses, thus reducing the incidence of heparin-induced thrombotic thrombocytopenia syndrome.[35]

The same CVAD can be implanted subcutaneously in the abdominal wall, with the catheter ending in the peritoneal cavity, to facilitate intra-peritoneal chemotherapy or, more frequently, to allow drainage of recurrent ascites at home by a palliative care team member. In some countries, the patient or family undertake this after training in sterile technique.

Conclusion

In the 25 years since our initial article, there has been enormous progress in the breadth and number of cancer directed therapies. This has driven innovation and refinement of supportive care measures to improve their tolerability. Novel classes of anti-cancer agents have given rise to new challenges in

managing side-effects; the advent of distinct subspecialties such as cardio-oncology and oncofertility now exemplify the multidisciplinary nature of cancer care.

References

1 Lewis CR, Segelov E, Goldstein D, Friedlander ML. Chemotherapy made easier. *Aust N Z J Med* 1993; **23**: 387–92.
2 Dranitsaris G, Molassiotis A, Clemons M, Roeland E, Schwartzberg L, Dielenseger P *et al*. The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. *Ann Oncol* 2017; **28**: 1260–7.
3 Cancer Institute New South Wales. *eviQ Cancer Treatments Online*. Sydney: Cancer Institute of New South Wales; 2019 [updated 2017; cited 2019 Mar 20]. Available from URL: https://www.eviq.org.au
4 MIMS Australia. *MIMS Online*. Sydney: MIMS Australia; 2018 [updated 2018 Oct; cited 2019 Nov 15]. Available from URL: https://www.mimsonline.com.au
5 Jordan K, Warr DG, Hinke A, Sun L, Hesketh PJ. Defining the efficacy of neurokinin-1 receptor antagonists in controlling chemotherapy-induced nausea and vomiting in different emetogenic settings-a meta-analysis. *Support Care Cancer* 2016; **24**: 1941–54.
6 Gralla RJ, Bosnjak SM, Hontsa A, Balser C, Rizzi G, Rossi G *et al*. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol* 2014; **25**: 1333–9.
7 Aapro M, Rugo H, Rossi G, Rizzi G, Borroni ME, Bondarenko I *et al*. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol* 2014; **25**: 1328–33.
8 Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M *et al*. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med* 2016; **375**: 134–42.
9 van den Hurk CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psychooncology* 2010; **19**: 701–9.
10 Paus R, Haslam IS, Sharov AA, Botchkarev VA. Pathobiology of chemotherapy-induced hair loss. *Lancet Oncol* 2013; **14**: e50–9.
11 Nangia J, Wang T, Osborne C, Niravath P, Otte K, Papish S *et al*. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: the SCALP randomized clinical trial. *JAMA* 2017; **317**: 596–605.
12 Shin H, Jo SJ, Kim DH, Kwon O, Myung SK. Efficacy of interventions for prevention of chemotherapy-induced alopecia: a systematic review and meta-analysis. *Int J Cancer* 2015; **136**: E442–54.
13 Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. *Breast Cancer Res Treat* 2017; **163**: 199–205.
14 Kubo K, Miyazaki Y, Murayama T, Shimazaki R, Usui N, Urabe A *et al*. A randomized, double-blind trial of pegfilgrastim versus filgrastim for the management of neutropenia during CHASE(R) chemotherapy for malignant lymphoma. *Br J Haematol* 2016; **174**: 563–70.
15 Botteri E, Krendyukov A, Curigliano G. Comparing granulocyte colony–stimulating factor filgrastim and pegfilgrastim to its biosimilars in terms of efficacy and safety: a meta-analysis of randomised clinical trials in breast cancer patients. *Eur J Cancer* 2018; **89**: 49–55.
16 Bohlius J, Bohlke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M *et al*. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *J Clin Oncol* 2019; **37**: 1336–51.
17 Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR *et al*. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain* 2014; **155**: 2461–70.
18 Yu IS, Pereira AAL, Lee M, Korphaisarn K, Marshall J, Segelov E *et al*. Medical oncologists' perspectives on how the results of the IDEA collaboration impact the adjuvant treatment of stage III colon cancer. *Oncologist* 2020; **25**: 229–234.
19 Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J *et al*. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 2018; **378**: 1177–88.
20 Soveri LM, Lamminmaki A, Hanninen UA, Karhunen M, Bono P, Osterlund P. Long-term neuropathy and quality of life in colorectal cancer patients treated with oxaliplatin containing adjuvant chemotherapy. *Acta Oncol* 2019; **58**: 398–406.
21 Blinman P, Martin A, Jefford M, Goldstein D, Boadle D, Morris M *et al*. Patients' preferences for 3 months versus 6 months adjuvant chemotherapy for colon cancer in the SCOT trial: what survival benefits make longer chemotherapy worthwhile? *J Clin Oncol* 2019; **36** (Suppl): 3602–2.
22 Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T *et al*. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013; **309**: 1359–67.
23 Fradley MG, Brown AC, Shields B, Viganego F, Damrongwatanasuk R, Patel AA *et al*. Developing a comprehensive cardio-oncology program at a cancer institute: the Moffitt Cancer Center experience. *Oncol Rev* 2017; **11**: 340.
24 Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M *et al*. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20**: 1215–21.
25 Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E *et al*. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin adjuvant (HERA) trial. *Lancet* 2017; **389**: 1195–205.
26 Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W *et al*. Randomized trial of lisinopril versus carvedilol to prevent

trastuzumab cardiotoxicity in patients with breast cancer. *J Am Coll Cardiol* 2019; **73**: 2859–68.
27 Jerusalem G, Lancellotti P, Kim SB. HER2+ breast cancer treatment and cardiotoxicity: monitoring and management. *Breast Cancer Res Treat* 2019; **177**: 237–50.
28 Mahabadi AA, Rischpler C. Cardiovascular imaging in cardio-oncology. *J Thorac Dis* 2018; **10**: S4351–s66.
29 Smith KL, Gracia C, Sokalska A, Moore H. Advances in fertility preservation for young women with cancer. *Am Soc Clin Oncol* 2018; **38**: 27–37.
30 Senra JC, Roque M, Talim MCT, Reis FM, Tavares RLC. Gonadotropin-releasing hormone agonists for ovarian protection during cancer chemotherapy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **51**: 77–86.
31 Van der Ven H, Liebenthron J, Beckmann M, Toth B, Korell M, Krussel J *et al*. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. *Hum Reprod* 2016; **31**: 2031–41.
32 Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R *et al*. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol* 2019; **30**: 582–8.
33 Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L. Current challenges in cancer treatment. *Clin Ther* 2016; **38**: 1551–66.
34 Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J *et al*. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28**: iv119–iv42.
35 Lopez-Briz E, Ruiz Garcia V, Cabello JB, Bort-Marti S, Carbonell Sanchis R, Burls A. Heparin versus 0.9% sodium chloride locking for prevention of occlusion in central venous catheters in adults. *Cochrane Database Syst Rev* 2018; Cd008462.