

Chemotherapy for advanced cancers

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Abstract: The decision to treat with chemotherapy in advanced cancers is a complex process that requires oncologists to weigh the indications and benefits. Treatment of patients with advanced cancer is typically multidimensional and should ideally include oncologists in coordination with palliative care specialists. When the intent of chemotherapy for patients with advanced neoplasms is no longer curative, palliative care can and should be delivered simultaneously with antineoplastic agents. Often, chemotherapy for advanced cancers is delivered in an attempt to palliate symptoms, and therefore improve quality of life (QOL). The role of palliative chemotherapy should be continually reevaluated throughout the trajectory of the patient's illness. When chemotherapy is no longer controlling the disease or helping symptoms, the role of chemotherapy should be reconsidered. This review aims to provide a foundation for discussions about treatment of patients with advanced malignancies.

Keywords: Palliative care; neoplasms; antineoplastic agents

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Introduction

The use of palliative chemotherapy in patients with advanced cancers is complex. Palliative chemotherapy has been associated with increased risk of cardiopulmonary resuscitation and death in an intensive care unit (ICU) (1,2). However, the length of survival for patients with advanced cancer depends on the type of malignancy and its sensitivity to chemotherapy, but is generally worse than for patients without advanced cancer (*Figure 1*). The goals of chemotherapy for incurable cancer are prolongation of life, alleviation of symptoms, and maintenance or improvement in quality of life (QOL), despite the toxicity associated with treatment. Important factors for treatment decisions also include the patient's preferences, comorbidities, and performance status (PS), a measure of a patient's activity level and general well-being (*Figure 2*). The indications and benefits for chemotherapy (*Table 1, Figure 3*) need to be continually reassessed to ensure the risk-benefit ratio favors treatment (*Figure 4*).

This review will discuss the decision-making process

involved in the treatment of some common advanced malignancies. Each section begins by defining what constitutes "advanced" disease. The prognosis for each malignancy and the indications for treatment are explained. The chemotherapy and palliative care treatment options are discussed.

Melanoma

In 2014, there will be an estimated 76,100 new cases and 9,710 deaths from melanoma in the United States. Melanoma is the 5th most common cancer among men and the 7th among women (4).

Advanced melanoma

Four percent of patients in the U.S. present with advanced melanoma, meaning it is stage IV, metastatic, and incurable (3).

Prognosis

The probability of surviving 5 years after diagnosis with

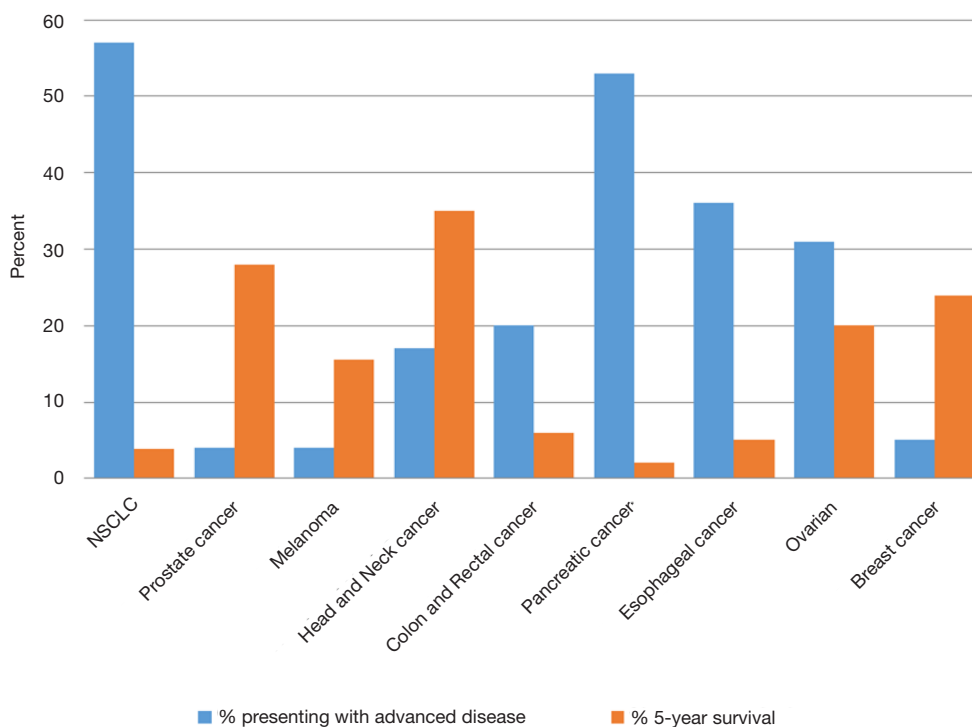


Figure 1 Percent of patients with advanced disease and overall survival by malignancy (3).

metastatic melanoma is approximately 15.5% (3). Median overall survival (OS) of untreated or progressive disease generally ranges from 4 months to 1 year depending on metastatic sites (5).

Treatment

Immunotherapy

Interleukin-2 (IL-2) is a T-cell growth factor that shows efficacy in 15-20% of patients and a complete response (CR) in 4-6% of patients. Most importantly, 80-90% of responders remain alive after 10 to 15 years (6-8). IL-2 can cause hypotension, cardiac arrhythmias, pulmonary edema and fever. It requires significant supportive care (Table 2) (9).

Ipilimumab, a monoclonal antibody that targets the inhibitive CTLA-4 receptor on T cells, has shown a 20% response rate (RR) to therapy with an OS increase of 2 to 4 months (10,11). Twenty to 25 percent of patients survive beyond 3 years. Immunotherapies may cause transient worsening of disease or have long latent periods before response (12).

Targeted therapy

Approximately 40-60% of melanomas have a *BRAF* gene

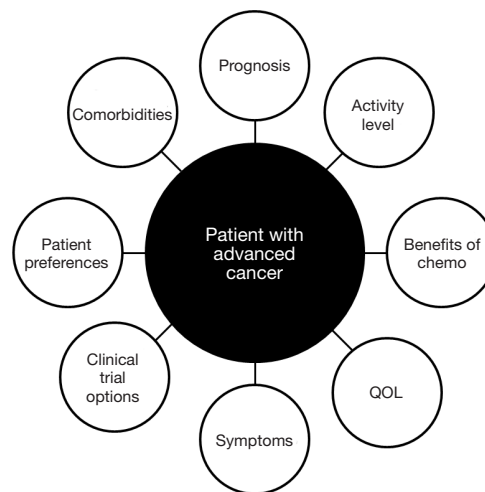


Figure 2 Mapping decision points for initiating palliative chemotherapy. QOL, quality of life.

mutation. The most common *BRAF* mutation in melanoma leads to an amino-acid substitution (V600) that upregulates the MAPK signaling pathway (13). Vemurafenib and dabrafenib are *BRAF* inhibitors. Among patients with a V600 mutation, vemurafenib and dabrafenib each had a 50% RR

Table 1 Indications and benefits for initiating palliative chemotherapy			
Cancer type	Therapy types	Relative indications	Relative contraindications
NSCLC	EGFR TKI's (erlotinib, gefitinib, afatinib)	EGFR mutation	No EGFR mutation; existing toxicities (rash, GI, weakness); fear of recurrence
	ALK inhibitor (crizotinib)	ALK mutation; improve QOL	No ALK mutation or ROS1 translocation; existing long QT; existing toxicities (GI, BM, hepatotoxicity)
	Cytotoxic chemotherapy	Improve QOL	Intolerance to platinum toxicities Poor PS
Breast cancer	HER2 targeted therapy (trastuzumab, pertuzumab, lapatinib)	HER2 overexpression	Normal HER2 expression; existing toxicities (heart failure, pain, respiratory failure, hepatotoxicity); increased bleeding tendency
	Hormonal therapy	ER+, PR+ tumor	ER-, PR- tumor; life-threatening metastatic effect; visceral metastases; large tumor burden; premenopausal (for aromatase inhibitors); concurrent warfarin therapy, history of DVT or PE
	Cytotoxic chemotherapy	Hormone receptor negative cancer; endocrine resistant disease; large tumor burden; significant visceral disease	3 prior lines of cytotoxic chemotherapy with ongoing progression; ECOG performance status ≥ 3 ; intolerance to anthracyclines or taxanes
Prostate cancer	GnRH	Avoidance of orchiectomy	Impending spinal cord compression; urinary tract outflow obstruction; castrate-resistant disease
	Abiraterone, enzalutamide	Castrate-resistant disease	
	Cytotoxic chemotherapy		Intolerance to taxanes
Melanoma	Immunotherapy (IL-2, ipilimumab)	Symptom relief, QOL, survival	Desire to avoid hospitalization given multi-organ toxicity (hypotension cardiac arrhythmias, pulmonary edema, fever); poor PS; history of severe response
	BRAF inhibitors	BRAF mutation	Fear of disease recurrence; poor PS; no BRAF mutation
Head and neck cancer	EGFR monoclonal antibodies (cetuximab)	K-RAS negative	Renal failure; lung disease
	Cytotoxic chemotherapy		Intolerance to platinum toxicities; poor PS; significant comorbidities
Colon and rectal cancer	HER2 targeted therapy		Increased bleeding tendency; use with anthracyclines; existing toxicities (heart failure, pain, respiratory failure, hepatotoxicity)
	EGFR monoclonal antibodies (cetuximab)	No RAS mutation	RAS mutations; renal failure; lung disease
	Cytotoxic chemotherapy	Even if asymptomatic; improve QOL	Intolerance to platinum toxicities ; poor PS
Pancreatic cancer	Erlotinib	EGFR overexpression	No EGFR mutation; existing toxicities (rash, GI, weakness)
	Cytotoxic chemotherapy	Improved QOL	Poor PS; poor biliary drainage; reduced stamina
Esophageal cancer	HER2 targeted therapy	HER2 overexpression	Increased bleeding tendency; existing toxicities (heart failure, pain, respiratory failure, hepatotoxicity)
	Cytotoxic chemotherapy		Poor PS; intolerance to platinum toxicities
Ovarian	HER2 targeted therapy		Increased bleeding tendency; use with anthracyclines; existing toxicities (heart failure, pain, respiratory failure, hepatotoxicity)
	Cytotoxic chemotherapy		Poor PS; degree of progression; intolerance to platinum toxicities; platinum hypersensitivity; progression on 2 consecutive regimens

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; QOL, Epidermal growth factor receptor; ER, estrogen receptor; PR, progesterone receptor; GnRH, gonadotropin-releasing hormone agonists; PS, performance status.

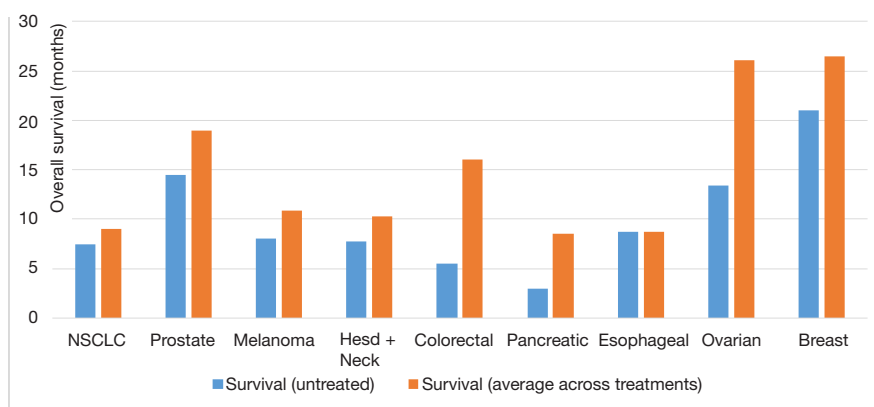


Figure 3 Estimated relative improvement of overall survival for advanced malignancies with palliative chemotherapy.

and demonstrated extended progression-free survival (PFS) and OS by approximately 3 to 6 months (14-16). Patients responsive to BRAF inhibitors almost always have disease recurrence (17).

Trametinib is a MEK1/2 inhibitor that has been shown to have a 22% RR and improve PFS by approximately 3 months (18). Combination with dabrafenib had RRs of 76% and nearly doubled PFS seen with dabrafenib alone (19).

At this time, there is no data on the superiority or order of administration between immunotherapy and BRAF inhibition. Guidelines recommend initial treatment of advanced melanoma based on mutation status and PS (20,21). Patients with good PS (regardless of mutation) can be treated with immunotherapy as first-line, and BRAF+ patients can subsequently be treated with targeted therapy. BRAF+ patients with poor PS or brain metastases should be started on targeted therapy before ipilimumab. Ipilimumab is recommended for BRAF- patients with poor PS.

Cytotoxic chemotherapy

No single or combination chemotherapy agents have been shown to improve OS in clinical trials (22). Dacarbazine, the only FDA-approved chemotherapeutic agent, has an overall RR (mostly partial) of 10-25% and durations of survival from 5.6 to 11 months (23,24).

Role of palliative care

Palliative care for patients with advanced melanoma involves the management of a multitude of symptoms, depending on metastatic site(s). Fatigue, pain, and nausea are common. Localized therapy with surgery or radiation has a role in palliation of advanced melanoma

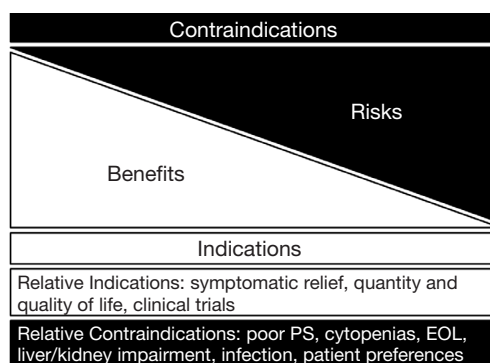


Figure 4 Assessing risks and benefits of chemotherapy for advanced cancers.

for symptomatic relief (21). Palliative resection of gastrointestinal metastases can relieve symptoms (abdominal pain, constipation, bowel obstruction, anorexia, nausea, vomiting, bleeding) for patients with melanoma found in the bowel (25). About 20-50% of patients with advanced melanoma present with brain metastases and associated symptoms, including headaches, mental status changes, seizures and bleeds (26). Surgical resection and radiation are options for patients with metastatic brain lesions (27).

Non-small cell lung cancer (NSCLC)

In 2014, there will be an estimated 224,210 new cases and 159,260 deaths from lung cancer in the United States. Lung cancer represents the second most common cancer diagnosis and the leading cause of death for both men and women. NSCLC represents over 80-85% of this disease (4).

Table 2 Chemotherapy toxicities

Classes	Examples	Side effects
Antimetabolites	5-fluorouracil	GI, BM, mucositis, diarrhea, angina, palmar-plantar dysesthesias
	Capecitabine	
	Gemcitabine	GI, BM, pulmonary, HUS
Antifolates	Methotrexate	BM, mucositis, GI, rash
	Pemetrexed	
Taxanes	Paclitaxel	Interactions (P450), BM, GI, stomatitis, hypersensitivity, bradycardia
	Docetaxel	
Vinca alkaloids	Vincristine	Neurotoxicity, BM
	Vinorelbine	
	Vinblastine	
Topoisomerase inhibitors	Irinotecan	BM, GI (diarrhea)
	Anthracyclines	BM, alopecia, mucositis, cardiotoxic
	Etoposide	BM, hypersensitivity, liver, mucositis
Alkylating agents	Cyclophosphamide	BM, pulmonary, renal/bladder, infertility
Platinum analogs	Cisplatin	GI, renal, ototoxic, BM, neuropathy, rash
	Carboplatin	
	Oxaliplatin	
Thalidomide analogs	Revlimid	BM, constipation, rash, neuropathy, DVT
Molecular targeted drugs	Monoclonal antibodies	BM, GI, skin rash, cardiac (heart failure, hypertension, thromboembolism), fatigue, pulmonary, mucositis, hypersensitivity reactions
	Kinase inhibitors	

Advanced NSCLC

Fifty-seven percent of patients present with stage IV disease (3). Patients with distant, disseminated metastases that cannot be cured through localized radiation or surgical therapy, or patients with relapsed disease, have advanced NSCLC.

Prognosis

The 5-year survival rate with advanced NSCLC is 3.9% (3). Median survival rates of advanced NSCLC depend on location of metastases: extrathoracic metastases have a median survival of 4 to 7 months, pleural disease 7 to 10 months, and contralateral lung 9 to 11 months (28). Treatment at this stage can offer a median increase in survival of 1.5 months without detracting significantly from QOL (29).

Treatment

Targeted therapy

Mutation-targeted therapies have proven efficacious in

NSCLC. Treatment of advanced NSCLC depends on genetic markers and PS of patients. Patients with ECOG PS 3-4 [approximately 35% of patients (30)] have only been shown to benefit from targeted, and not cytotoxic, therapy (31-33).

Epidermal growth factor receptor [(EGFR), HER-1/ErbB1] is a cell-surface receptor which, when overexpressed, results in inappropriate stimulation of oncogene pathways (34). Ten to 15 percent of NSCLC adenocarcinomas in the U.S. have mutations in EGFR, which are found more frequently among nonsmokers, women, and in the Asian population (35). Among patients with EGFR mutations, treatment with erlotinib (36,37), gefitinib (38-40), or afatinib (41) can obtain RRs of approximately 50-80% and has been shown to significantly prolong PFS up to 6 months relative to chemotherapy, but without clear OS benefit (42,43). Almost all patients with EGFR treatment will acquire resistance (44).

The anaplastic lymphoma kinase (*ALK*) gene participates in a chromosome 2 translocation to produce multiple fusion oncogenes (45). Two to 7 percent of

NSCLC adenocarcinomas in the U.S. contain *ALK* gene arrangements, which usually occur among younger patients with minimal smoking history (46). Crizotinib, a small molecule tyrosine kinase inhibitor, strongly inhibits *ALK* among other proteins. Crizotinib has shown RRs of 50-65% and improved PFS of 4 to 10 months, although the effect on OS is unclear (47-49). Notably, patients report increased QOL on crizotinib (47).

ROS1 is an insulin receptor tyrosine kinase with homology and fusion activity similar to *ALK*. One to 2 percent of NSCLC patients have *ROS1* rearrangements. Treatment with crizotinib for patients with the *ROS1* translocation is recommended whenever possible (50,51).

Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). It is FDA-approved to treat advanced non-squamous NSCLC in combination with platinum doublets. Bevacizumab increases the RR of platinum-based regimens to 30-35% and offers a PFS and OS increase of up to 2 months (52-54).

Cytotoxic chemotherapy

Platinum-doublet chemotherapy is the preferred initial cytotoxic regimen (33). These doublets tend to increase the RR of single agents to 25-35%, PFS to 4 to 6 months, 1-year survival to 30-40%, while improving symptoms and QOL (33,55,56). Single-agent treatment may be appropriate for older patients or those with borderline PS (57).

Both carboplatin and cisplatin may be used in advanced NSCLC patients. Multiple meta-analyses suggest both better RR and OS for cisplatin, but carboplatin has less severe toxicity and improved QOL (58-61). Docetaxel alone not only improves OS by approximately 3 months (62), but also improves QOL compared to best supportive care (63,64). Compared to other platinum-based doublets, platinum with pemetrexed improves OS (for non-squamous patients) by approximately 2 months (65,66). Pemetrexed also has less toxicity compared to docetaxel (67). Paclitaxel, gemcitabine, and vinorelbine are also used (68).

Role of palliative care

Palliative care for patients with advanced NSCLC includes focusing on dyspnea, fatigue, pain and depression (69). Opioids help with dyspnea in NSCLC (69). Brain and bone metastases are common in these patients (70,71), warranting palliative relief (72). Early palliative care consultation has been shown not only to improve QOL, but also to extend survival by a median of 3 months (73).

Breast cancer

In 2014, there will be an estimated 235,030 new cases and 40,430 deaths from breast cancer in the United States. Among U.S. women, breast cancer is the most common cancer and the second leading cause of cancer death (4).

Advanced breast cancer

Five percent of patients with breast cancer present with metastatic disease (3). Patients with advanced breast cancer have disease that cannot be removed with surgery or radiation alone.

Prognosis

The 5-year survival for advanced breast cancer is 24% (3). The median OS of the disease is 18 to 24 months (74). Median OS can increase by 3 to 5 months with chemotherapy and 4 to 8 months with endocrine and targeted therapies (75).

Treatment

Hormonal therapy

About 60% of breast cancers are considered hormone-receptor positive through expression of estrogen receptor (ER) and/or progesterone receptor (PR) (76). Tumors expressing both have a 70% likelihood of response to hormone therapy, while tumors expressing only one have a 40% likelihood, and tumors expressing neither have a 10% likelihood (76,77). A Cochrane meta-analysis recommended initial management with endocrine therapy for hormone-positive patients over chemotherapy unless patients had life-threatening, rapid or extensive visceral metastases (78). Selective estrogen receptor modulators (SERMs) such as tamoxifen are estrogen antagonists in the breast and agonists in the bone and uterus. While premenopausal women benefit from tamoxifen (24% RR), it demonstrates the greatest efficacy among postmenopausal women with both ER+ and PR+ disease (86% RR) (79,80). The median OS for SERMs among advanced breast cancer patients is 27.7 months, with median time to progression of 6 months (81). Aromatase inhibitors (AIs) such as letrozole, anastrozole, and exemestane block aromatase from synthesizing peripheral estrogens. They are contraindicated in premenopausal women as they can induce ovarian estrogen upsurge. Among postmenopausal women, AIs show a significant OS benefit over SERMs/ other endocrine therapies by approximately 3 months as well as decreased risk of vaginal bleeding and thromboembolic

events (82-85). Fulvestrant, an ER antagonist, shows similar efficacy to AIs in women with breast cancer progression on other antiestrogens (86-88). Use of the combination of fulvestrant with AIs, or SERMs remains controversial (89-91).

Cytotoxic chemotherapy

Chemotherapy results in higher and more rapid RRs than endocrine therapy, and is often the initial treatment strategy for highly symptomatic metastatic breast cancer patients even if hormone-positive, especially those with visceral metastases. Numerous agents have demonstrated efficacy with median OS 11 to 15 months, PFS 3 to 7 months, RR 85%. Anthracyclines and taxanes are the most commonly used and can be given as infrequently as once every three weeks with preserved efficacy (92-94). Sequential single-agent chemotherapy with agents of different classes shows increased PFS, similar OS and lower toxicity, but slower onset of effect compared to combination chemotherapy (95). NCCN guidelines suggest transition to supportive care only after 3 sequential lines of chemotherapy with progression or ECOG PS ≥ 3 (96).

Targeted therapy

Fifteen to 20 percent of patients with breast cancer demonstrate HER2 overexpression (97). A meta-analysis of eight trials concluded that addition of any HER2-targeted agent to an existing chemotherapeutic regimen for a patient with susceptible disease improves OS, PFS and RR (98). Trastuzumab, a monoclonal antibody to the HER2/Neu extracellular receptor, added to a standard chemotherapeutic regimen demonstrates an increase in OS of 2 to 5 months (25.1 *vs.* 20.3 months), PFS of 3 months (7.4 *vs.* 4.6 months), and RR of 18% (99,100). T-DM1, a conjugate of trastuzumab with an antimicrotubule agent, increases median PFS by 4 to 5 months and OS by 6 months, and RR by 13% among women who progress on trastuzumab (101,102). Pertuzumab is a monoclonal antibody directed against HER2 dimerization. In the CLEOPATRA study, the addition of pertuzumab increased PFS from 12.5 to 18.7 months compared to trastuzumab and a taxane alone (103,104). Lapatinib, a tyrosine kinase inhibitor against EGFR1 and HER2, has demonstrated inferior outcomes to trastuzumab in preliminary studies (105).

Role of palliative care

Palliative care for patients with advanced breast cancer can aid in the management of bone or visceral pain, cognitive impairment, depression and lymphedema (106). Osteoclast inhibitors such as denosumab, a RANK ligand antibody,

and bisphosphonates reduce the risk of skeletal events and reduce bone pain (107,108). Osteonecrosis of the jaw can be reduced through a preventative dentistry exam prior to osteoclast inhibitor treatment (109). Psychological interventions (cognitive behavioral therapy, supportive-expressive therapy, etc.) have shown to be beneficial (110).

Prostate cancer

In 2014, there will be an estimated 233,000 new cases of prostate cancer in the United States (4). There will be 29,480 estimated deaths due to prostate cancer in 2014 (4). Prostate cancer is the most common cancer in men (4).

Advanced prostate cancer

Patients with metastatic or disseminated disease are considered to have advanced prostate cancer. Approximately 4% of patients in the U.S. present with distant disease (3).

Prognosis

The 5-year survival for advanced prostate cancer patients is 28% (3). The sites of metastatic disease influence OS. A phase III trial comparing docetaxel plus prednisone to mitoxantrone plus prednisone showed decreasing OS as the extent of disease increased from limited to lymph nodes only (median 27 months), to bones only (19 months), to lung with or without bone and lymph nodes (14 months), and to liver regardless of other sites of disease (10 months) (111).

Treatment

Androgen deprivation therapy (ADT)

Systemic treatment of metastatic prostate cancer usually involves ADT to help lower serum testosterone levels to castrate levels. The optimal time to initiate systemic therapy is uncertain for patients with metastatic disease, but several trials have found that immediate compared to delayed ADT was associated with a statistically significant decrease in prostate cancer-related death although there was no OS benefit (112). A trial seeking to assess whether intermittent ADT was non-inferior to continuous therapy found a median survival of 5.8 years in the continuous-therapy group and 5.1 years in the intermittent-therapy group (113). Gonadotropin releasing hormone agonists (GnRH) are used as "medical castration". A meta-analysis comparing a GnRH agonist with orchiectomy found no significant difference between the two groups (median survivals of 20 to

40 months) (114). GnRH agonists can cause a transient surge of luteinizing hormone known as the “flare phenomenon” which can initially worsen disease. This proves problematic in cases such as impending epidural spinal cord compression or urinary tract outflow obstruction. Antiandrogens (flutamide, bicalutamide) may be useful in preventing this phenomenon.

Castrate resistant disease

Patients with disease progression (PSA increase, new metastases, progression of metastases) while receiving ADT are considered to have castrate resistant disease. Abiraterone and enzalutamide have both shown significant improvements in OS compared with placebo in phase III trials with castrate resistant prostate cancer. Abiraterone, an oral small molecule that blocks the synthesis of androgens, is approved for patients who have metastatic castrate resistant prostate cancer based on phase III data. Abiraterone prolonged OS compared with prednisone alone (14.8 *vs.* 10.9 months) in men who had previously been treated with docetaxel and in those who were chemotherapy naïve (115,116). The phase III data for enzalutamide in metastatic, castration resistant patients showed a median OS of 18.4 months versus 13.6 months for placebo (117). Alternative endocrine therapies such as glucocorticoids, ketoconazole (118), and antiandrogens (bicalutamide, flutamide) (119) may help stabilize disease but have not shown OS benefits.

Sipuleucel-T, an autologous dendritic cell therapeutic vaccine designed to enhance the immune T cell response to prostatic acid phosphatase, is a treatment option in asymptomatic or minimally symptomatic men (PS 0 or 1) with metastatic, castration resistant prostate cancer. Phase III data for sipuleucel-T showed improvement in OS (25.8 *vs.* 21.7 months in the placebo group) (120).

Another option for advanced prostate cancer and bone metastases is radium-223. A phase III trial randomly assigned patients to receive radium or placebo. This trial was terminated for efficacy, as it showed a survival benefit (14.9 *vs.* 11.3 months) (121).

Cytotoxic chemotherapy

Taxanes are the standard chemotherapy agents for castrate-resistant prostate cancer. Their use is supported by phase III data showing docetaxel in combination with prednisone significantly prolonged OS compared to mitoxantrone plus prednisone (19.2 *vs.* 16.3 months) (122).

Role of palliative care

Palliative care for patients with advanced prostate cancer

includes management of bone metastases, bone pain, urinary tract symptoms, pelvic pain, hematuria, and obstructive rectal symptoms. Bone metastases in prostate cancer are usually osteoblastic lesions to the axial skeleton that cause pain, functional impairment, and debility. Radiotherapy (123), osteoclast inhibition (bisphosphonates, denosumab) (124), radium-223, and adequate analgesia are options for treating painful bone metastases. Radiation can help relieve the following: rectal symptoms (75%), pelvic pain (69%), urinary obstruction (54%) and haematuria (42%) (125).

Head and neck (H&N) cancer

H&N cancer includes the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. In 2014, there will be over 100,000 estimated new cases of H&N cancer in the United States: 42,440 oropharynx, 12,630 larynx, and 62,980 thyroid (4). There will be over 13,000 deaths in the U.S. attributed to H&N cancer: 8,390 oropharynx, 3,610 larynx, and 1,890 thyroid (4).

Advanced H&N cancer

The focus of this discussion will be patients with recurrent or metastatic H&N squamous cell cancer (SCC). Approximately 17-18% of patients in the U.S. present with advanced oropharyngeal or laryngeal cancer (3).

Prognosis

The 5-year survival for advanced oropharyngeal and laryngeal cancer patients is 17-18% (3). The median OS for metastatic H&N carcinoma treated with cisplatin-based combination chemotherapy has been shown to be 7.8 months. Weight loss, poor PS, and prior RT were found to predict worse outcomes (126). The HPV status of H&N cancer plays an important role in prognostication, as HPV positive tumors have a better prognosis than cancers not associated with HPV. HPV positive tumors may have lower incidence of metastases (10% *vs.* 15%), but data suggests that HPV positive cancers develop metastases later and in different patterns than HPV negative cancers (127).

Treatment

Cytotoxic chemotherapy

The backbone of chemotherapy for H&N SCC is usually platinum compounds (cisplatin, carboplatin). Carboplatin

is associated with less neurotoxicity, nephrotoxicity, and nausea and vomiting compared with cisplatin. Data suggests these agents result in similar responses (128). Other common agents include: taxanes (docetaxel, paclitaxel), methotrexate, 5-fluorouracil (5-FU), and cetuximab. Combination chemotherapy is generally preferred, but for patients with poor PS or significant comorbidities, single agent therapy with carboplatin, paclitaxel, or cetuximab can be attempted. For patients with good PS and favorable prognostic features, combination chemotherapy using platinum plus fluorouracil, with or without cetuximab, or platinum plus a taxane, is usually employed. A phase III trial comparing cisplatin plus fluorouracil to cisplatin plus paclitaxel showed no significant difference in median survival (8.7 *vs.* 8.1 months) (129).

Second-line chemotherapy must take into consideration the patient's prior treatments, overall condition, and the toxicity profiles of future chemotherapy. Methotrexate, docetaxel, cetuximab, and gemcitabine have shown activity in previously treated patients (130-132).

Targeted therapy

Cetuximab, a monoclonal antibody to the EGFR, has demonstrated activity in H&N SCC. The EXTREME trial studied cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic H&N SCC (128). The addition of cetuximab prolonged median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (128).

Panitumumab, another monoclonal antibody targeting the EGFR receptor, has activity in advanced H&N SCC. The SPECTRUM phase III trial of cisplatin plus 5-FU, with or without panitumumab, showed a non-significant improvement in OS (11.1 *vs.* 9.0 months in the control group) (133).

Role of palliative care

The radiation, surgery, and chemotherapy that many H&N patients receive can cause multiple side effects, including: xerostomia, thyroid disorders (134), dysphagia and weight loss which may prompt the use of feeding tubes. Feeding tubes may help prevent cachexia and improve QOL (135), but the multitude of adverse effects related to feeding tubes merits the frequent reassessment of their use (136). Speech pathologists and nutrition specialists can play a valuable role

as part of the multidisciplinary treatment team. Patients with H&N may SCC struggle with mood disorders (137), and studies have shown benefits with antidepressant use in H&N cancer (138).

Colorectal cancer (CRC)

In 2014, there will be an estimated 136,830 new cases and 50,310 deaths from CRC in the United States. CRC represents the third most common cancer and the third leading cause of cancer deaths among both men and women (4).

Advanced CRC

Twenty percent of patients with CRC present with metastatic disease (3). Patients with advanced CRC demonstrate metastatic disease that cannot be surgically removed or cured.

Prognosis

Six percent of advanced colon cancer patients live to 5 years (3). The median OS with best supportive care alone is approximately 5 to 6 months (139). Chemotherapy can prolong PFS and OS by approximately 3 to 18 months (139,140).

Treatment

Cytotoxic chemotherapy

Palliative chemotherapy should be initiated at diagnosis even if patients are asymptomatic. Length of OS correlates strongly with exposure to all of the active chemotherapeutic agents (5-FU, irinotecan and oxaliplatin), rather than specific sequences of chemotherapy (141-143). Techniques such as chemotherapy switching, drug holidays, and maintenance therapy are frequently employed (144-146). Patients with poor PS can gain benefit from chemotherapy if toxicities permit (147).

Chemotherapy commonly used in CRC includes: oxaliplatin with fluorouracil/leucovorin (FOLFOX) or capecitabine (CapeOX), irinotecan with fluorouracil/leucovorin (FOLFIRI) and chemotherapy plus targeted therapies (148). FOLFOX and FOLFIRI can be combined with all of the targeted chemotherapies described below, albeit in very specific regimens, as well as with each other. Patients prefer the convenience of oral capecitabine, although outpatient fluorouracil/leucovorin has been associated with better QOL (149). Irinotecan as an independent agent has demonstrated an OS increase

of 3 months (to 9 months) (150). FOLFIRI can improve PFS of 6 to 8 months and OS of 15 to 20 months (151-154). In studies of second-line therapy, FOLFIRI and irinotecan are comparable regarding PFS (3 to 6 months), toxicities, and QOL (155,156).

Oxaliplatin alone shows weak efficacy in advanced CRC, with a PFS of 4 months (157). FOLFOX demonstrates a median PFS of 6 to 9 months and OS of 11 to 20 months (158,159). Capecitabine and oxaliplatin (CapeOX or XELOX) demonstrate a median PFS of 8 months and OS of 20 months; this regimen is considered non-inferior to FOLFOX (160-162). Peripheral neuropathy from oxaliplatin can be alleviated through intermittent dosing or stopping the regimen after 3 months (163,164). FOLFOX and FOLFIRI have similar efficacies (165,166). The combination of oxaliplatin, irinotecan and fluorouracil/leucovorin (FOLFOXIRI) offers a slightly improved median OS of 21.5 to 22.6 months and PFS of 8.4 to 9.8 months. This regimen has greater toxicity than either FOLFOX or FOLFIRI (167,168).

Targeted therapy

Bevacizumab can be used as an adjunct for CRC (148). It adds approximately 2 months to PFS and OS but with increased toxicities (169-174). Aflibercept inhibits VEGF by acting as a “decoy receptor” and binding to circulating VEGF-A, -B or placental growth factor (175). It is FDA-approved as an adjunct with FOLFIRI or irinotecan for patients previously treated with oxaliplatin-based regimens (148).

ASCO recommends testing patients for RAS mutations prior to considering agents targeting EGFR (cetuximab or panitumumab), as mutations in the RAS pathway override the effects of these drugs (176). For wild-type RAS patients, cetuximab improves QOL and doubles the success of supportive care alone with a median PFS of 3.7 months and OS of 9.5 months (177-179). Panitumumab demonstrates similar efficacy to cetuximab (180). Regorafenib, an oral multikinase inhibitor, demonstrates inhibition of VEGF, PDGF, FGFR1, KIT, RET and B-RAF (181). It has been FDA-approved in metastatic CRC patients (148). A phase III trial of patients with progression through multiple standard therapies demonstrated an increase of 1.4 months in OS (182). Multiple toxicities including hand-foot-skin reaction, rash, diarrhea, fatigue, neutropenia, and fatal hepatic toxicity were observed in 1.4% of patients (183).

Role of palliative care

Palliative care for patients with advanced CRC often involves

treating pain, nausea, vomiting, and anorexia (184,185). Fifteen to 20 percent of metastatic colon cancer patients develop bowel obstruction (186). Palliative surgical options include resection and primary anastomosis, colostomy, and bypass (187). Self-expanding metal stents are a common nonsurgical alternative that have been extensively researched. There does not appear to be any significant difference in mortality between these options (188-191). Stents have the benefit of more rapid recovery and reduced likelihood of ICU or stoma requirements (192-194).

Pancreatic cancer

In 2014, there will be an estimated 46,420 new cases and 39,590 deaths from pancreatic cancer in the United States (4). Pancreatic cancer represents the fourth most common cause of cancer death among both men and women.

Advanced pancreatic cancer

Fifty-three percent of pancreatic cancer patients present with advanced disease: stage IV, with metastases to distant lymph nodes or organs, and surgical excision is not possible (3).

Prognosis

Two percent of patients with stage IV disease will survive to 5 years (3). The median survival of untreated patients with metastatic disease is measured in months. Chemotherapy can extend OS by 3 to 8 months and can improve QOL through symptom control (195).

Treatment

Cytotoxic chemotherapy

There is minimal benefit for advanced pancreatic cancer patients with poor PS, thus PS should be considered prior to initiation of chemotherapy (196,197). Chemotherapy is reasonable for patients with good PS, adequate biliary drainage, and for those able to tolerate intensive therapy. FOLFIRINOX, a combination of leucovorin, 5-FU, irinotecan and oxaliplatin, is commonly used for treating metastatic pancreatic cancer. RRs of 31.6% have been seen, along with PFS of 6.4 months, and median OS of 11.1 months (198). FOLFIRINOX has been associated with reduced deterioration in QOL compared to gemcitabine (198,199).

As monotherapy, gemcitabine has superior efficacy for advanced pancreatic cancer compared to weekly 5-FU (200).

Gemcitabine can achieve RRs of 7-12%, PFS of 4 months, and median OS of 6 to 8 months along with symptom improvement (198,200). Some combination therapies with gemcitabine demonstrate improved OS, PFS and RR (201,202). Albumin-bound paclitaxel results in an increase in PFS and OS by 2 months; it has been approved by the FDA for first-line therapy in advanced pancreatic cancer patients (203). Drugs such as capecitabine, 5-FU, oxaliplatin, cisplatin, docetaxel or irinotecan also have activity in pancreatic cancer (204-218).

Second-line treatments in pancreatic cancer can improve median OS by as much as 4 to 6 months; platinum in combination with gemcitabine or 5-FU are commonly used in second-line (219). The phase III CONKO trial provided data for oxaliplatin, folinic acid and 5-FU as second line therapy after progression on gemcitabine (220). This led to the guideline recommendation of using 5-FU based therapy after progression despite gemcitabine and vice versa (221).

Targeted chemotherapy

EGFR is overexpressed in approximately 43% of pancreatic adenocarcinomas and is associated with increased tumor aggressiveness (222). The combination of erlotinib and gemcitabine is FDA approved for first-line treatment of advanced pancreatic cancer on the basis of a phase III trial showing an increase in median OS of 1 week and 5% increased 1-year survival relative to gemcitabine alone (223).

Role of palliative care

Pancreatic cancer patients may require treatment of biliary and gastric outlet obstruction, pain, depression, cachexia and malnutrition (221,224,225). Biliary obstruction occurs in up to 80% of patients with pancreatic head involvement and can cause pruritus, jaundice and anorexia (226). Stents or percutaneous biliary drainage may be necessary to alleviate patients' symptoms (227-231). Malignant gastric outlet obstruction occurs in 15% to 25% of patients and can be managed with either endoscopic stenting or feeding tubes (232-234). Cachexia, anorexia, and weight loss occur in up to 80% of pancreatic cancer patients (235,236). Pancreatic insufficiency can contribute to cachexia, malnutrition and steatorrhea (237,238). Microencapsulated lipase supplements can alleviate these symptoms (239,240). For pain management, celiac plexus neurolysis can help (241,242). Psychological distress can be especially potent in this population (243). One study noted male advanced pancreatic cancer patients had an 11-fold increased risk of

suicide (244). Patients should be monitored for symptoms of anxiety, depression and sleep disturbance throughout the disease process (245). Patients with advanced pancreatic cancer are at a 4- to 7-times increased risk of venous thromboembolism (VTE) compared to other cancers (246). Low-molecular-weight heparin is the preferred agent to prevent VTE compared to warfarin (247-250).

Esophageal cancer

In 2014, there will be an estimated 18,170 new cases and 15,450 deaths from esophageal cancer in the United States (4).

Advanced esophageal cancer

Stage IV adenocarcinoma and squamous cell carcinoma are managed similarly. Fifty to 60 percent of patients present with advanced esophageal cancer; their disease has metastasized or is deemed unresectable (3).

Prognosis

The 5-year survival of patients with advanced disease is 3-5% (3). ECOG PS ≥ 2 , liver or peritoneal metastases are adverse prognostic factors (251). Patients without adverse factors have a median survival of 12 months, while patients with all of them have a median survival of 4 to 7 months (251). Currently, there is no clear evidence of survival benefit with chemotherapy alone (252,253). The goal of chemotherapy is to improve QOL, PS, and symptoms (252,254,255).

Treatment

Cytotoxic chemotherapy

PS should be assessed prior to administration of chemotherapy. Patients with poor PS (Karnofsky < 60 or ECOG ≥ 2) should be managed with supportive care (256-258). No single chemotherapy regimen for esophageal cancer has demonstrated clear superiority (252). Nearly all regimens result in OS of 9 to 11 months, PFS of 6 to 7 months, with RRs of 35-48% (259,260). The most common regimens include oxaliplatin, cisplatin, 5-FU, capecitabine and/or an anthracycline (259,261,262). Irinotecan has also been investigated in this population (263). Capecitabine and oxaliplatin are considered to be as effective as 5-FU and cisplatin based on the REAL-2 trial (259). While no data exists on how many courses of therapy to pursue, NCCN guidelines suggest second-line therapy with irinotecan (264),

paclitaxel (265,266) and docetaxel given their single-agent efficacy (258,267).

Targeted therapy

Approximately 7-22% of esophagogastric cancers overexpress the type II EGFR HER2 (268). The addition of trastuzumab to chemotherapy leads to a 10% increased RR and improves OS for those patients by about 3 months (269).

Role of palliative care

Palliative care for patients with advanced esophageal cancer includes treatment of dysphagia, pain, bleeding, nausea, vomiting and malnutrition (258,270). Treatment of dysphagia usually involves treatment of obstruction; options include a self-expanding metal stent, intraluminal brachytherapy, or external beam radiotherapy (271-273). Dilation or chemotherapy alone, and surgical bypass are not recommended due to their relatively low ratio of benefits to complications (272). Feeding tubes are recommended as necessary to facilitate nutritional support and ease nausea/vomiting (274,275). Esophageal cancers commonly bleed, which can be controlled with electrocoagulation, endoscopic intervention, or radiotherapy (258,276).

Ovarian

In 2014, there will be an estimated 21,980 new cases and 14,270 deaths from ovarian cancer in the United States (4). Ovarian cancer represents the fifth most deadly cancer among U.S. women, and the most common cause of gynecological cancer death.

Advanced ovarian cancer

Thirty-one percent of patients present with stage IV disease (3). Patients with distant metastases that have progressed or recurred after debulking and initial adjuvant chemotherapy with platinum are considered to have advanced disease.

Prognosis

Eighteen to 20 percent of patients with stage IV disease will survive 5 years (4,277). Historically, ovarian cancer showed PFS of 7.1 months and OS of 13.4 months with incomplete treatment (278). This has nearly doubled in the last decade (279). Current median OS depends on

presence of residual tumor after debulking (54.6 months for no residual disease versus 23.9 for greater than 1 cm residual disease), extent of metastases (20.2 months for multi-site disease *vs.* 26.8 months for single-site disease), and PS (19.3 months for ECOG 2 *vs.* 32.8 months for ECOG 0) (279,280). Higher QOL is also associated with improved survival (280). Each course of chemotherapy after recurrence increases survival, albeit with diminishing returns: OS decreases from 11.3 to 6.2 months and PFS from 6.4 to 4.4 months after progression despite three treatment regimens (281).

Treatment

Cytotoxic chemotherapy

Patients who progress or develop recurrent disease after initial chemotherapy should be considered for second-line therapy (282). However, progression despite consecutive chemotherapy regimens without clinical benefit predicts limited gains with the use of further therapy (283). There is no proven single best regimen for recurrence (284). Chemotherapy regimens for recurrent disease depend on sensitivity to platinum agents. Platinum resistant disease is defined as recurrence within 6 months of initial platinum therapy. Platinum sensitive is recurrence 6 months after the initial platinum therapy (285). PS, degree of progression, end-organ status, and pre-existing toxicities from prior chemotherapy must also be taken into account before starting second and third line regimens (283).

Platinum-sensitive disease typically continues to be responsive to platinum agents, with longer "platinum-free intervals" between therapies predictive of better response (285). Combination therapy with two agents has been shown to have better RR, OS, and PFS than monotherapy (286-288). Use of three agents, however, increases toxicity without significant OS or PFS benefit (289). Cisplatin and carboplatin are considered equivalent, although carboplatin regimens are more frequently recommended and are associated with better QOL (282,290,291). Median survival with platinum agents alone is approximately 17 to 24 months (286). Agents used in combination therapy for platinum-sensitive disease include paclitaxel, gemcitabine and pegylated liposomal doxorubicin. The paclitaxel combination has a 25% RR, 21 to 29 months OS, and 13 months PFS (287). Gemcitabine increases RR and PFS, without improving QOL or OS (292). Compared to paclitaxel, pegylated liposomal doxorubicin improves PFS by approximately 2 months without improving OS; while

demonstrating more nausea, vomiting (293,294).

The current standard for platinum-resistant therapy is treatment with sequential single agents given no evidence of improved survival with combinations (286,295,296). Single agents show similar efficacy with RRs of 13-50% and OS of 6 to 16.8 months (294,297).

Targeted therapy

Bevacizumab is an option for relapsed patients in conjunction with a carboplatin/gemcitabine regimen or as monotherapy. Single agent bevacizumab has RRs of 16-21% among platinum-sensitive and platinum-resistant patients with an OS of 10.7 to 17 months (298,299). A meta-analysis in 2013 confirmed improvement upon cytotoxic chemotherapy regimens in RR by approximately 20% and PFS by 4 to 5 months among relapsed patients, albeit not OS (300).

Role of palliative care

Palliative care for patients with advanced ovarian cancer includes a multidisciplinary approach to pain, constipation or diarrhea, nausea and vomiting, anorexia, dyspnea and hypercalcemia (301). Additionally, patients frequently struggle with anxiety and depression throughout the disease process (302). Patients with advanced ovarian cancer frequently develop malignant bowel obstruction (303,304). Octreotide inhibits the secretion of multiple secretory enzymes and is effective for refractory nausea and vomiting associated with malignant bowel obstruction (305). Recurrent ascites is problematic, and may require frequent abdominal paracentesis (306). Case reports suggest that bevacizumab may help control ascites (307).

Conclusions

Optimal care for patients receiving chemotherapy for advanced cancers involves a multifaceted approach which should include oncologists in coordination with palliative care specialists. Comprehensive palliative care consists not only of symptom management and supportive care, but also longitudinal goals of care discussions as well as spiritual and psychosocial support for patients and their families throughout the trajectory of their illness. This review summarized the indications and benefits of the recommended palliative chemotherapies for some of the most common malignancies. The decision to pursue chemotherapy for patients with advanced cancer rests

on prognosis, PS, benefits of therapy, QOL, clinical trial options, comorbidities, patient preferences, and symptom burden throughout the continuum of their care.

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