Cancer Management in Patients With End-Stage Renal Disease

Significant improvements in the management of patients with end-stage renal disease (ESRD) who are on chronic renal replacement therapy (CRRT), has led to an increased prevalence of this population among older Americans. Since cancer is also common in the elderly, oncologists are likely to be faced with patients who suffer from both cancer and ESRD. There is a paucity of information regarding issues surrounding the optimal management of such patients, especially those needing chemotherapy. This review surveys the relevant problems oncologists may encounter in such patients and summarizes the available literature on chemotherapeutic management of common cancers. The reader is strongly urged to consult the original references for details of chemotherapy administration prior to use in an individual patient.

Significant improvement in the management of end-stage renal disease (ESRD) has led to increased survival for patients receiving chronic renal replacement therapy (CRRT)-hemodialysis or continuous ambulatory peritoneal dialysis (CAPD)-over the past 2 decades. In the United States from 1980 to 2001, the overall mortality for patients with ESRD declined by 10% from roughly 275 to 250 deaths per 1,000 patient-years at risk.[1] Since 1985, the mortality rate for patients on dialysis for less than 2 years declined by 23%, from roughly 290 to 220 deaths per 1,000 patient-years at risk.[1] Much of this improvement can be attributed to advances in the dialysis vascular access, improvements in artificial dialyzers, availability of recombinant erythropoietic agents to treat anemia, and improvement in general supportive care.

From 1994 to 2001, however, the mortality of patients who had been on dialysis for more than 5 years increased by 12%, from 259 to 291 deaths per 1,000 patient-years at risk.[1] This suggests an increased need to address medical issues that arise later in the clinical course of patients with ESRD. While the majority of deaths in patients on CRRT are due to cardiovascular disease and infection, cancer is not infrequently observed in this population. Approximately 6% of patients currently initiating hemodialysis in the United States have cancer as a comorbidity.[1] Furthermore, several reports have linked chronic renal insufficiency with an increased incidence of cancer.[2-10] About 300,000 patients were on hemodialysis in the United States in 2001.[1] By the year 2030, an estimated 2,240,000 people in the United States are expected to have ESRD and half these patients will be 65 years of age or older.[1] The life expectancy for patients on CRRT aged 50, 60, and 70 years is approximately 5, 4, and 3 years, respectively.[1] These life expectancies are only one-third to one-sixth that of the general US population, but they represent a significant period of potentially good quality life during which the treatment of cancer with chemotherapy may be appropriate.
Common Chemotherapeutic Agents Requiring Dose Modification and Monitoring for Renal Insufficiency

Although the population of patients requiring CRRT is increasing and ESRD is associated with an increased risk of cancer, there is a paucity of available information on the optimal management of ESRD patients with cancer. Because of uncertainty, general treatment goals may vary widely with clinician and patient preferences. This is even more relevant given that subspecialists such as nephrologists and oncologists increasingly serve as their patient's primary care providers. Challenges facing nephrologists caring for patients with ESRD may include delays in cancer diagnosis, unclear utility of cancer screening, and dilemmas in diagnostic imaging. Furthermore, in patients with advanced or refractory cancer, both nephrologists and oncologists may be called upon to help negotiate ethically complex palliative care issues including the withholding of dialysis treatment.

This article will address the supportive, palliative, diagnostic, and prognostic dilemmas facing clinicians caring for cancer patients with ESRD. We review here the current reports available in the literature and provide an overview of chemotherapy use in ESRD. One recent review focused principally on the pharmacokinetic details for selected single agents. Our review is broader in scope and oriented to guiding the practicing oncologist in clinical decision-making. The use of various chemotherapeutic agents for patients with lesser degrees of renal insufficiency and acute renal dysfunction has been extensively reviewed elsewhere, and the reader is referred to these available sources. Table 1 provides a summary of chemotherapeutic agents requiring dose modification or monitoring in renal insufficiency.

The Comorbidity of Cancer and ESRD

The relationship between chronic renal failure and malignancy is complex. The increased incidence of cancer in ESRD patients may be explained through multiple mechanisms, which are detailed in Table 2 and two pertinent review articles. Several of these pathways are speculative and warrant further study.

Medical Decision-Making

TABLE 2

Interrelationships Between Cancer and End-Stage Renal Disease

As noted previously, elderly ESRD patients on CRRT can have several years of good-quality life. Oncologists should appreciate this when formulating a cancer-directed treatment plan for their patients with ESRD. Performance status can occasionally be difficult to assess in patients on dialysis because of time spent on dialysis and transient complications of CRRT. Given the paucity of information on quality of life in cancer patients with ESRD, decisions to initiate cancer treatment, especially with chemotherapy, are problematic. Oncologists also can expect to face palliative care and ethical dilemmas among cancer patients with ESRD. Dialysis represents a proximate lifesustaining measure, and withdrawal of such support could hasten death far in advance of an incurable malignancy. Formulating a plan for hospice care could additionally include a discussion regarding the option of withdrawal of dialysis support. When considering cessation of dialysis, patients should have a full evaluation (including a psychiatric assessment) and counseling. A discussion of withdrawing CRRT or withholding initiation of CRRT involving patients or their proxies should be documented, and appropriate orders should be
A recent multicenter prospective cohort study of acute hemodialysis in hospitalized patients demonstrated that a diagnosis of cancer was more commonly associated with withholding (ie, not starting) hemodialysis than it was with withdrawing from ongoing hemodialysis. This was particularly true among older patients, and patients viewed as having a poor overall prognosis. This study also demonstrated infrequent recording of decisions in the medical chart, with only 18% of decisions to withhold hemodialysis and 4% of decisions to withdraw hemodialysis documented.

Optimizing palliative care for this complex patient population and their families can prove to be a challenge that greatly benefits from a multidisciplinary approach.

**Diagnostic and Prognostic Issues**

Several confounding factors associated with ESRD can affect the diagnosis and evaluation of a malignancy. These include the following: (1) delayed symptomatic presentation, (2) unclear utility of tumor markers in ESRD, (3) imaging dilemmas, and (4) lack of prognostic information.

- **ESRD and Cancer Presentation**—There are several clinical scenarios in which the common clinical symptoms of malignancy may be missed in the setting of ESRD. For example, hypercalcemia may be associated with malignancy or the secondary hyperparathyroidism of ESRD. An elevated serum phosphate level, however, may favor a renal etiology over malignancy. Oliguria and anuria may mask the symptoms of urinary retention secondary to obstructive uropathy from certain pelvic cancers such as prostate cancer. Other symptoms, such as pruritis related to hyperphosphatemia or anemia from renal disease, may also mask similar initial presentations of malignancy.

- **ESRD and Tumor Markers**—Serum cancer antigen 125 (CA-125) can serve as a useful tumor marker but can be increased by intraperitoneal volume such as ascites, even when nonmalignant. Indeed, CA-125 concentration in the dialysate of peritoneal dialysis patients is a marker of mesothelial mass and can help determine optimal dwell times for continuous ambulatory peritoneal dialysis. Although prostate-specific antigen (PSA) in 63 men on hemodialysis was found to be lower than that of a comparison group of 729 healthy male subjects, the prevalence of abnormally elevated levels of total PSA was similar. In another study of 41 Japanese patients (a population with a low incidence of prostate cancer) on hemodialysis, 4 patients required further diagnostic evaluation based on a cut-off point of 4 ng/mL for PSA, resulting in a biopsy diagnosis of prostate cancer in 2 patients (5%). Although PSA is not dialyzed, fluctuations and increases in PSA levels may still occur secondary to hemoconcentration or alteration in binding proteins following dialysis.

- **ESRD and Imaging**—Imaging studies requiring contrast are frequently ordered for cancer diagnosis, staging, or monitoring. In ESRD patients, controversy surrounds the issue of whether and when to perform dialysis (hemodialysis or CAPD) around the time of intravenous contrast administration. Because of a lack of consensus among radiologists, guidelines were developed by the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). It is important to distinguish the issues of contrast administration in patients with renal insufficiency from those of patients with ESRD and already on CRRT. In the presence of renal insufficiency, water-soluble iodinated contrast agents that are predominantly cleared by the kidney can have a longer half-life and increased toxicity in particular, additional renal toxicity. Recommendations for patients with renal insufficiency who are not receiving dialysis include judicious use of iohexol contrast media with prehydration, use of low or iso-osmolar contrast media, discontinuation of nephrotoxic drugs for at least 24 hours before contrast administration, and possible use of N-acetylcysteine or sodium bicarbonate. Prophylactic hemodialysis prior to contrast administration has not demonstrated any benefit and could be harmful. However, intravenous contrast administration for computed tomography scans is not usually contraindicated in patients already on CRRT, as preservation of residual renal function is of minimal value. While it is recommended that excessive volume load with intravenous contrast be avoided, the subsequent timing of dialysis is unimportant and additional dialysis treatments are not recommended.

The use of gadolinium-based contrast agents has also been studied in renal failure because of their predominant renal clearance, and the frequent performance of magnetic resonance imaging examinations in patients with ESRD. No adverse events were reported in a prospective, randomized, double-blind, placebo-controlled study of patients with chronic renal insufficiency (not requiring CRRT) using gadolinium at a concentration of 0.2 mmol/kg vs saline. However, in patients with renal insufficiency, doses greater than 0.3 mmol/kg should be avoided.
The safety of gadolinium administration in ESRD patients undergoing dialysis has also been established. CAPD is very slow to clear gadolinium, with nearly one-third of administered gadolinium remaining after 20 days.[34] However, no adverse events have been observed with the use of 0.1 to 0.3 mmol/kg of gadolinium-based contrast media. With hemodialysis, gadolinium-based contrast concentrations decline to 97% of initial levels after three dialysis sessions over 6 days.[34] Despite this, no adverse effects were seen in a case series report of 70 hemodialysis patients, even when dialysis was delayed for up to 3 days following contrast administration in 6 of the patients.[35] As with iodinated contrast media, the ESUR does not recommend any specific timing for performance of hemodialysis following gadolinium administration. However, in selected situations, interpretation of gadolinium-enhanced images can be misleading in CRRT patients. For example, in two hemodialysis patients, retention of gadolinium was associated with its excretion into the cerebrospinal fluid, resulting in artifactual subarachnoid enhancement.[36]

**ESRD Impact on Cancer Prognosis**—The validity of conventional prognostic factors and outcome data for specific cancers in ESRD patients on CRRT is uncertain because of the absence of clinical trials in this population. Therefore, treatment recommendations are subject to clinical judgment and extrapolation from cancer clinical trials in patients with adequate renal function. We suggest that the prognosis from ESRD and the specific cancer condition should be judged independent of the other condition, and that known, powerful, and consistent prognostic factors are assumed to be generalizable to ESRD patients.

**Treatment-Related Issues**

Several aspects of chemotherapy administration and CRRT are important to consider in ESRD patients. These include (1) chemotherapeutic agent selection, (2) dosing adjustment, (3) timing of dialysis in relation to chemotherapy treatment, (4) method of dialysis, (5) vascular access for dialysis and chemotherapy, and (6) staff safety considerations.

The renal clearance of a chemotherapeutic agent is important in CRRT-dependent patients. However, clearance of a particular drug by dialysis is not necessarily predicted by its renal clearance in patients with normal renal function. ESRD and dialysis can affect drug clearance in more ways than simple first-order kinetics. The stepwise removal of a chemotherapeutic agent by dialysis is a strong determinant of drug exposure as measured by the effective area under the concentration-time curve (AUC). Alterations in the availability of binding proteins, fluid shifts, and acid-base changes can all influence chemotherapy pharmacokinetics. Furthermore, the pharmacodynamics of these drugs can be influenced by an increased exposure to a drug's active metabolites as well as to the agent itself. For these reasons, studies of the pharmacokinetics and pharmacodynamics of chemotherapeutic agents in dialysis patients should be empirically determined for each drug when possible.

A patient's exposure to a chemotherapeutic agent that is cleared by dialysis can be affected by the dose given as well as the timing and characteristics of the subsequent dialysis. Although dialysis dependence complicates the delivery of cancer therapy, it also offers a way to modulate a patient's chemotherapy drug exposure. The timing (immediate vs delayed) or method of CRRT (hemodialysis vs CAPD) can be adjusted to either generate high peak doses of chemotherapy or maintain low drug concentrations. Additionally, CAPD may facilitate intraperitoneal exposure to chemotherapy that may be of importance for tumors in this location. However, the literature is insufficient to determine the relative advantage of each of these CRRT strategies to optimize chemotherapy delivery.

The preservation of vascular access for dialysis is critical and especially challenging in a patient receiving chemotherapy. The development of the arteriovenous fistula was an important advance in the care of patients with ESRD. The use of such an access for chemotherapy administration must be carefully considered because loss of vascular access due to vascular sclerosis, stenosis, or infection can profoundly impair the ability to provide CRRT. Additionally, while it may be more convenient, the effects of rapidly introducing cytotoxic agents through an arterialized vein have not been adequately studied.

Finally, the administration of chemotherapy in a dialysis unit has implications for the safety of staff and patients. It is therefore recommended that dialysis units institute a policy regarding the safe administration of cytotoxic therapy, including whether or not it may be administered during dialysis. If it is felt that the timing of dialysis in relation to chemotherapy administration is critical, then the appropriate availability of timely CRRT must be ensured.

**Chemotherapy in Patients on CRRT**

| TABLE 3 |
Reports of Chemotherapy Use in Patients on CRRT

We reviewed available reports in which chemotherapy was administered to patients on hemodialysis by performing a Medline search using the key words "cancer chemotherapy" and "hemodialysis." Additional reports were retrieved by cross-referencing the name of a specific chemotherapy or cancer type with "end-stage renal disease," "hemodialysis," or "peritoneal dialysis." Finally, article reference lists and abstracts from the Proceedings of the American Society of Clinical Oncology were also reviewed. Only articles with available English language abstracts or texts were included and are summarized in Table 3 by chemotherapeutic agent and cancer type.

The majority of the literature is limited to case reports and small case series. Some include data regarding the pharmacokinetics and pharmacodynamics of these agents in CRRT and/or information on toxicity and outcome. A variety of dialysis schedules and methods are described. Only a few reports refer to the use of newer chemotherapeutic agents. Although publication bias in favor of cases with a positive outcome is likely, these reports provide a basis for offering chemotherapy to dialysis-dependent patients.

Crooke et al published one of the earliest reports of cancer chemotherapy use in a patient receiving dialysis in 1977. A 24-year-old male with recurrent testicular cancer required hemodialysis for acute tubular necrosis secondary to cisplatin. He was treated successfully with bleomycin and vinblastine on hemodialysis, eventually recovered renal function, and remained in complete remission 7 months later. This report suggested that giving weekly bleomycin to a patient receiving hemodialysis was safe and effective. Since then, a variety of malignancies treated with different chemotherapeutic agents have been reported. However, for some of the common cancers, there have been surprisingly few reports and only limited data presented.

This section provides a brief overview of chemotherapy by tumor type in ESRD patients. Tumor types described include those for which treatment has been addressed in multiple reports (testicular cancer, ovarian cancer, transitional cell cancer, multiple myeloma, leukemia, and lymphoma) as well as those that are common in the United States (breast cancer, prostate cancer, lung cancer, and colorectal cancer).

**Testicular Cancer**

Crooke's original report described above showed that serum bleomycin levels fell to extremely low values within 72 hours even though the drug is renally cleared and nondialyzable. A year later, bleomycin, vinblastine, and cisplatin was used for the treatment of nonseminomatous testicular cancer in a 32-year-old patient on hemodialysis. This patient developed diffuse pulmonary fibrosis suspected to be related to bleomycin (first cycle given at a standard dose of 30 units IV push weekly and "reduced" for the second cycle). Since then, there have been no reports of the complete BEP regimen (bleomycin, etoposide, cisplatin) being used in ESRD patients. There are reports of single-agent etoposide, carboplatin plus etoposide, as well as cisplatin plus cyclophosphamide. Two patients with nonseminomatous germ cell tumors were treated to complete remission with etoposide (100 mg/m², days 1 to 3 or 4) and carboplatin (100 to 300 mg/m², day 1) with hemodialysis performed on day 2. Cisplatin plus etoposide, but without bleomycin, for the treatment of a patient with seminoma, was associated with severe myelosuppression noted at higher doses. This led to the use of lower doses of cisplatin (14 mg/m², days 1, 3, and 5) and etoposide (35 mg/m², days 1 to 5) with hemodialysis on days 1, 3, and 5, which was found to still be effective. The risk-benefit equation for the addition of bleomycin as a third agent in patients with testicular cancer on hemodialysis remains unresolved.

**Ovarian Cancer**

There are at least 10 reports of chemotherapy for ovarian cancer in ESRD patients. The first of these was reported in 1981. Based on a pharmacokinetic profile derived after administration of a
12-mg tracer dose of cisplatin to an anuric patient, cisplatin was then given as a 50-mg infusion. In four subsequent cycles, doxorubicin (30 mg IV on day 1), teniposide (50 mg IV on day 2), and cyclophosphamide (300 mg IM on days 3 and 4) were given in combination with cisplatin, 50 mg IV on day 5. Less than 10% of cisplatin was removed by hemodialysis, which was performed immediately following the cisplatin infusion. A partial objective response was observed in peritoneal metastases with an associated decrease in ascites.

Subsequent reports in ovarian cancer patients have described the use of single-agent carboplatin,[44,45] cisplatin, or carboplatin combined with cyclophosphamide,[46,47] singleagent paclitaxel,[48,49] and cisplatin or carboplatin combined with paclitaxel.[50,51] Of particular interest, six cycles of standard-dose carboplatin (AUC of 5) given every 3 weeks in combination with paclitaxel (175 mg/m\(^2\) over 3 hours) was safely delivered to a patient with surgically debulked advanced ovarian cancer.[51] Hemodialysis was performed 24 hours following the carboplatin dose, although the authors were aware that dialysis has only modest efficacy in clearing carboplatin. The details of their dose calculation, according to the Calvert formula, used a glomerular filtration rate of 0 to arrive at a carboplatin dose of 125 mg. The patient was disease-free 11 months after completion of treatment.

In another report, topotecan was used to treat advanced refractory ovarian cancer in a 58-year-old woman.[52] Infusing topotecan only on days 1 and 3 (rather than standard treatment on days 1 through 5) with hemodialysis on days 2 and 4, grade 3 thrombocytopenia and grade 4 neutropenia without fever, were observed. This toxicity was essentially unchanged by infusing topotecan on day 1 over 30 minutes, beginning at the initiation of hemodialysis, and with a second topotecan infusion on day 2 and subsequent hemodialysis on day 3. Pharmacokinetic sampling showed a fourfold increase in topotecan plasma clearance with hemodialysis, from 5.3 to 20.1 L/h/m\(^2\). The authors recommended consideration of hemodialysis in the event of topotecan overdose or in the presence of severe renal dysfunction while receiving topotecan.

**Transitional Cell Cancer**

MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) was among the earlier regimens administered for transitional cell cancer in patients on hemodialysis.[53-55] In 1993, Yokogi et al gave 20 mg of methotrexate intravenously on day 1 and 30 mg of cisplatin on day 2 followed 2 hours later by hemodialysis.[54] Since the serum methotrexate level of 0.27 μM at 72 hours after low-dose methotrexate administration was in a high-risk range, the authors recommended careful monitoring of methotrexate levels to facilitate leucovorin rescue.

Another patient with advanced recurrent transitional cell cancer previously treated with MVAC, was subsequently treated with a carboplatin- based regimen while on hemodialysis.[54] Hemodialysis was performed 24 hours after IV administration of carboplatin (100mg/m\(^2\)), vinblastine (3 mg/m\(^2\)), and doxorubicin (22.5 mg/m\(^2\)). Three cycles were given at approximately 5-week intervals, complicated by one episode of septicemia but with stable disease observed at 5 months. Recently, a regimen of carboplatin (AUC = 5, calculated according to the Calvert formula) plus paclitaxel (175 mg/m\(^2\) over 3 hours) given to a 69 year-old man with metastatic transitional cell cancer on hemodialysis, resulted in a 20% reduction in tumor size after 3 cycles.[56] Hemodialysis was performed 1 hour after carboplatin administration. Grade 1 thrombocytopenia and grade 3 neutropenia were the principal toxicities observed.

**Multiple Myeloma**

As listed in Table 3, several studies (including eight case series) have described the use of chemotherapy to treat patients with multiple myeloma and renal failure. Overall, these reports demonstrate the utility of most standard therapies for patients with ESRD and encourage aggressive treatment as indicated. Some include a discussion of the form of renal replacement.[57,58] For example, although CAPD may additionally remove myeloma proteins (more so than with hemodialysis), the increased risk of infection and peritonitis outweigh this advantage.

Standard vincristine, doxorubicin, and steroid regimens (VAD [with dexamethasone] and VAMP [with methylprednisolone]) as well as intravenous and oral melphanal plus steroid regimens have been successfully used in patients with renal failure.[59-63] Accumulating evidence supports the use of high-dose chemotherapy with autologous stem cell transplant, occasionally demonstrating a recovery of renal function even after a period of 6 months of dialysis dependence.[64-69] Finally, thalidomide (Thalomid), 100 mg daily, was used in a 64-year-old man on hemodialysis for ESRD associated with IgD lambda myeloma but required dose reduction for neuropathy and constipation.[70]
Leukemia

Several reports of chemotherapy in ESRD patients with leukemia have been published. These are evenly divided among chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), acute myelomonocytic leukemia (AMML), acute promyelocytic leukemia (APML), and acute lymphoblastic leukemia (ALL). Most involve reduced doses of chemotherapeutic agents or alternative schedules.

Consolidation therapy was given to a patient on CAPD for APML with a standard-dose "5 + 3" regimen employing cytarabine (200 mg/m$^2$/d) for 5 days and daunorubicin (50 mg/m$^2$/d) for 3 days.[71] Interestingly, while there were no additional toxicities beyond myelosupression lasting 10 days, plasma cytarabine levels were found to be significantly higher than in leukemia patients with normal renal function. Although the authors could not rule out random interindividual variation in cytarabine metabolism as an explanation, they recommended a dose reduction of the drug for CAPD patients until further studies became available.

Similarly elevated plasma levels of drug without excess toxicity was observed in a child receiving hemodialysis for acute renal failure, when a 5-day course of cladribine, 9 mg/m$^2$/d, was given for AML.[72] The role of plasma drug level measurements in clinical practice remains unclear.

Lymphoma

Doxorubicin pharmacokinetics were studied in five patients on hemodialysis, including two patients with lymphoma who received CHOP (cyclophosphamide, doxorubicin [40-60 mg over 30 minutes], vincristine, and prednisone) chemotherapy, and compared to eight patients not receiving hemodialysis.[73,74] Delayed clearance of doxorubicin and its active metabolite, doxorubicinol, resulted in an AUC 1.5 and 3 times higher, respectively, in hemodialysis patients, but no additional toxicity was reported.

Weekly rituximab (Rituxan) at a standard dose of 375 mg/m$^2$ was given to a 54-year-old man with low-grade lymphoma receiving hemodialysis.[75] Sustained therapeutic rituximab serum levels comparable to patients with normal renal function, were achieved after the infusion as well as after dialysis, without any rituximab clearance into the dialysate.

Standard-dose cytarabine (at a regimen of 100 mg/m$^2$/d) for 7 days was given to an 8-year-old boy with Burkitt's lymphoma on daily concurrent hemodialysis for ESRD secondary to hemolytic-uremic syndrome.[76] Unlike another report of cytarabine use in an AML patient on CAPD,[71] this report found that cytarabine was cleared by hemodialysis, and that standard dosing yielded serum drug levels not likely to cause additional toxicity. This patient's leukemia progressed despite chemotherapy, and given cytarabine clearance by hemodialysis, the authors expressed a cautionary note regarding efficacy of the drug at this dose in hemodialysis patients.

Breast Cancer

Despite the high prevalence of breast cancer, we found only three reports of chemotherapy in patients with breast cancer and ESRD.[77-79] The dose of weekly vinorelbine given after hemodialysis to a patient with metastatic breast cancer had to be reduced by 50% (to 12.5 mg/m$^2$) to eliminate repeated episodes of neutropenic fever.[77] Single-agent doxorubicin, 140 mg, was given intravenously as adjuvant therapy to a woman with breast cancer undergoing CAPD.[78] This was complicated 5 hours later by a clinical syndrome suggestive of chemical peritonitis and loss of peritoneal surface permeability, necessitating transition to hemodialysis. However the relationship of intravenous doxorubicin to peritonitis during CAPD remains conjectural. A male patient with metastatic breast cancer was treated with a combination of epirubicin (Ellence) and fluorouracil (5-FU), leading to an objective tumor response.[79]

We were unable to find reports of standard adjuvant therapy for breast cancer in patients with ESRD. However, doxorubicin and cyclophosphamide have been used successfully in combination with other chemotherapeutic agents (although at variable doses) for other malignancies (see Table 3). Delayed doxorubicin clearance should lead to caution when used in ESRD patients.[73,74] Successful use of endocrine therapy with tamoxifen for bone metastasis and associated hypercalcemia has also been described in a 50-year-old woman.[26] No published reports have described aromatase inhibitor use in ESRD.

Prostate Cancer

In three men with prostate cancer on CRRT, total androgen blockade with leuprolide (7.5 mg IM every 4 weeks) and flutamide (250 mg po tid) effectively lowered serum testosterone but
exacerbated the patient's preceding anemia of chronic renal failure [80]. Goserelin (Zoladex) at 3.6 mg SC every 4 weeks) and flutamide at 250 mg po tid given to a patient on long-term hemodialysis resulted in a complete response in lung metastases from prostate cancer.

There have been no reports of cytotoxic therapy for the treatment of prostate cancer in ESRD patients. Several agents known to have activity in prostate cancer (with the notable exceptions of docetaxel and estramustine [Emcyt]) have been used to treat ESRD patients with other malignancies, including paclitaxel (see Table 3). The dose and schedule of administration of these agents may be judiciously extrapolated to patients with prostate cancer.

**Lung Cancer**

There have been 11 reports of lung cancer treated with chemotherapy in ESRD. Five reports involved patients with small-cell lung cancer, four involved non-small-cell lung cancer, and two did not provide details of histologic subtype. Platinum-containing regimens employed in the treatment of lung cancer in this setting have included single-agent cisplatin,[81] cisplatin with etoposide,[82, 83] carboplatin with etoposide,[84-86] and nedaplatin with etoposide.[87] A dose escalation study of cisplatin and etoposide was conducted in five hemodialysis patients, two with small cell lung cancer and three with non-small cell lung cancer.[83] Full-dose cisplatin (80 mg/m² on day 1) and etoposide (100 mg/m² on days 1, 3, and 5) with hemodialysis performed within 10 minutes of completing chemotherapy administration was found to be safe and effective. Toxicities included grade 3/4 anemia in all five patients (four patients required transfusion support), grade 3 neutropenia in three patients (one patient required a 1-week dose delay), grade 3 thrombocytopenia in two patients, and grade 3 nausea and vomiting in two patients (a single etoposide dose was missed in one patient due to prolonged nausea). All patients recovered completely from these toxicities. A partial response was obtained in four of the five patients.

In another recent report, carboplatin (300 mg/m² on day 1) and etoposide (50 mg/m² IV on days 1 and 3) was given to three patients with small cell lung cancer and followed by hemodialysis within 1 hour of chemotherapy.[86] Two complete and one partial response were achieved. Myelosuppression was prominent in two patients who developed grade 3/4 neutropenia without fever, requiring blood product support for anemia and thrombocytopenia.

Agents with known activity in lung cancer have been used for the treatment of other cancers in ESRD patients such as single-agent gemcitabine (Gemzar) for pancreatic cancer,[88] vinorelbine for breast cancer,[77] and irinotecan (Camptosar) for colorectal cancer.[89] The combination of cisplatin or carboplatin with etoposide, as described above, appear to constitute the most reasonable, tested chemotherapy regimens for lung cancer patients with ESRD.[83,86] There are no reports of docetaxel use in ESRD patients.

**Colorectal Cancer**

Three reports have addressed the use of chemotherapy in patients with both ESRD and colorectal cancer, all of which used 5-FU-based adjuvant therapy.[89-91] Uracil/tegafur (300 mg/d tid) in four patients,[90] as well as 5-FU (425 mg/m² IV daily for 5 days) plus leucovorin (35 mg/m²) in a single patient,[91] were safely administered. The pharmacokinetics of 5-FU were similar to what is seen in patients who have normal renal function.

A 45-year-old woman with stage III colorectal cancer received a single cycle of 5-FU and leucovorin that was complicated by gastrointestinal toxicity.[89] At the time of recurrence with liver metastasis, she went on to receive IV irinotecan, 80 mg/m²/wk, which was well tolerated. Further dose escalation to 100 mg/m²/wk resulted in grade 4 diarrhea. A partial remission lasting 1 year was achieved. These reports are insufficient to make a treatment recommendation for either adjuvant or palliative chemotherapy in colorectal cancer.

**Conclusions**
General Recommendations for Chemotherapy Dose Adjustment in Patients With End-Stage Renal Disease

Cancer chemotherapy will be provided to an increasing number of patients with ESRD. However, data regarding the optimal use of chemotherapeutic agents in this patient population are sparse. For several drugs, case reports indicate that many ESRD patients can tolerate standard treatment. Table 4 summarizes our general chemotherapy dosing recommendations based on a review of available case reports.

The optimal timing of CRRT in relationship to chemotherapy dosing has not been determined for most treatments. A systematic approach to investigating antineoplastic therapy in the growing ESRD population is needed, particularly for the common cancers (such as lung, breast, colorectal, and prostate) for which the data are frequently underrepresented compared to certain rarer cancers (transitional cell, testicular, leukemia). Development of a National Cancer Institute-sponsored registry to capture key data on ESRD patients given chemotherapy in the United States would provide a broader resource for practicing physicians and clinical investigators to draw on, which in turn will advance the care of this group of patients.

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