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Abstract

Ramucirumab (Cyramza®), approved April 21, 2014, is a vascular endothelial growth factor receptor 2 (VEGFR2) antagonist with a U.S. Food and Drug Administration (FDA) indication for the treatment of advanced or metastatic gastric/gastroesophageal junction adenocarcinoma. Gastric cancer is a prevalent cancer in the United States with a poor prognosis. The phase 3 trial, REGARD, shows that ramucirumab, when used within four months after the last dose of first-line chemotherapy or six months after the last dose of adjuvant chemotherapy, increases overall survival. Also, ramucirumab has been included in combination therapy, such as in the RAINBOW trial, which demonstrated its effectiveness in combination with paclitaxel as a second-line treatment option. Notable adverse reactions to ramucirumab are severe hypertension and injection site reactions. Because it is a newer anticancer agent, ramucirumab's full potential may not yet be recognized. Possible future uses of ramucirumab may include the treatment of other forms of cancer or utilization as a first-line agent.

Key Terms

Adenocarcinoma; Antibodies, Monoclonal; Antineoplastic Agents; Chemotherapy, Adjuvant; Combined Modality Therapy; Food and Drug Administration (U.S.); Hypertension; Paclitaxel; Prognosis; Review Literature; Stomach Neoplasms; Vascular Endothelial Growth Factor A; Vascular Endothelial Growth Factor Receptor-2

Introduction/Epidemiology

Gastric cancer is one of the most prevalent cancers worldwide, and is currently the 14th most common form of cancer in the United States.^{1,2} Adenocarcinoma-type gastric cancers account for 90 to 95 percent of all gastric malignancies. While gastric cancer is most commonly diagnosed in elderly patients, excluding those cancers affecting the gastric cardia, recent decades have revealed a nearly doubled incidence in gastric cancer among U.S. patients between the ages of 25 and 36 years (0.27 up to 0.45 per 100,000 between 1977-1981 to 2002-2006, respectively). Recent incidence rates for gastric adenocarcinomas involving the gastric cardia and/or gastroesophageal junction are around two and 1.94 per 100,000, respectively.² The American Cancer Society projects that in the United States there will be 22,220 new cases and 10,990 deaths due to gastric cancers for the year 2014.³

Gastric cancer is often difficult to detect until later stages of development, and only 10 to 20 percent of cases are diagnosed in an early stage. Therefore, most patients do not present until the cancer has already metastasized.^{2,4} At best,

five-year survival is typically around 50 percent for cases localized in distal regions of the stomach. Five-year survival drops to almost 0 percent for nonlocalized distal cases and is 10 to 15 percent for cases involving proximal regions of the stomach. Thus, it is recommended that high risk individuals undergo routine screening to monitor for development of gastric cancer.⁴

Known risk factors that contribute to the development of gastric cancer include: age (most common between 60 and 80 years), male gender and a family history of gastric cancer.^{1,2} Lifestyle factors contributing to gastric cancer include a diet low in fruits and vegetables and/or high in salted and preserved foods, smoking and certain industrial occupations.^{1,4} Gastric cancers also tend to be more prevalent among individuals of African, Asian and Native American descent.

Current treatments of gastric cancer include surgery, radiotherapy, chemotherapy and, most recently, targeted therapy.^{1,4} With utilization of first-line agents including fluoropyrimidine, platinum and surgery, there will still be over 10,000 deaths in the United States in 2014 directly caused by gastric cancer. Consequently, new treatment options with improved efficacy toward gastric cancer are needed. Trials of drugs such as bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A) to inhibit angiogenesis) have been conducted to evaluate alternative mechanisms to successfully treat gastric cancer and thus reduce mortality. Ramucirumab, a monoclonal antibody targeting the vascular endothelial growth factor receptor (VEGFR), is the latest angiogenesis inhibitor that helps to increase the survival rate of gastric cancer patients. This novel mechanism categorizes ramucirumab as targeted therapy, which provides a new and unique treatment option for gastric cancer to prolong survival.

Pathophysiology

There is a well-documented correlation between *Helicobacter pylori* (*H. pylori*) infections and development of gastric cancer.^{1,2} These gram-negative bacteria are associated with cases of severe and chronic gastritis as they secrete a number of substances such as proteases, phospholipases, ammonia, acetaldehyde and reactive oxygen species that are capable of inducing histological and genetic changes. These alterations lead to malignant cell growth in infected areas of the stomach. This can initiate a cascade of histopathological changes in gastric mucosa leading to the development of a gastric malignancy, particularly in patients with genetic susceptibility and poor diet.

Gastric adenocarcinoma presents in two histologically distinct forms: intestinal and diffuse.¹ Intestinal gastric adenocarcinomas form differentiated clusters of cohesive neoplastic cells that easily ulcerate. This type tends to have a better prognosis and is more common in the elderly, males and African Americans. It is also heavily influenced by environmental factors, including diet, *H. pylori* infections and obesity. Diffuse gastric adenocarcinomas are not as differentiated and, instead, manifest as a generalized thickening of the stomach wall. Diffuse-type is more common in females, younger patients and may have a genetic predisposing factor linked with type A blood. Advanced or invasive gastric adenocarcinomas develop along a cascade of histological changes.⁵ Initially, atrophy of the stomach lining leads to changes in the parietal cells, which is followed by intestinal metaplasia where the normal gastric cells begin to display an intestinal cell phenotype. Lastly, neoplastic intestinal dysplasia develops and may lead to carcinoma in the affected area. This cascade is more relevant to intestinal-type carcinomas versus diffuse-type.

The link to family history and the actions of *H. pylori* indicate that a number of inherited and pathologically induced genetic changes can lead to the onset of gastric adenocarcinoma.¹ Investigators have determined that, on average, 4.18 gene changes are needed. Mutations in p27, p53, the K-ras oncogene and various cell signaling pathways are commonly seen. More aggressive gastric adenocarcinomas also develop the ability to express VEGF leading to an increased incidence of metastasis.

Clinical Presentation

As previously mentioned, gastric adenocarcinomas are often difficult to detect in early stages as patients are often asymptomatic.⁴ In approximately 50 percent of cases, patients present with minor symptoms, such as dyspepsia, which are associated with a wide variety of gastrointestinal ailments. Due to the lack of symptom manifestation, 80 percent to 90 percent of patients present with locally advanced or metastatic tumors and complain of anorexia and weight loss as well as abdominal pain. Nausea and vomiting can occur with obstructive tumors while ulcerated tumors may cause bleeding that leads to hematemesis, melena and gastrointestinal hemorrhaging. Palpable masses, cachexia, bowel obstruction, ascites, hepatomegaly and lower extremity edema can also indicate advanced gastric adenocarcinoma. In these instances, the tumor has often already metastasized to neighboring structures and/or lymph nodes.

Treatment

Surgical intervention is the primary means of treating gastric adenocarcinomas.² Given the high incidence of presentation in advanced stages of the disease, surgery is often complemented with adjuvant radio- and/or chemotherapy. Surgery can be performed for cases with a localized tumor in the stomach and for cases limited to local node involvement. Cases with distal node involvement or metastasis to other structures outside the stomach often necessitate adjuvant or neoadjuvant chemotherapy. Stage III patients require radical surgery followed by chemoradiation therapy, while patients

presenting at stage IV typically receive intensive palliative chemotherapy and radiotherapy.

Chemotherapeutic agents commonly used in the treatment and palliation of gastric cancers include 5-fluorouracil (5-FU), methotrexate, docetaxel and cisplatin.² Methotrexate and 5-FU are antimetabolites that disrupt normal deoxyribonucleic acid (DNA) synthesis while cisplatin is a platinum-containing alkylating agent that acts to directly damage DNA. Docetaxel is a taxane compound that interferes with mitosis.⁶ There are multiple standard combination protocols as well as numerous clinical trials underway evaluating new combination protocols.^{2,7} Recent progress in the development of targeted therapies has led to an increase in studies for potential future treatments of a wide variety of cancers including gastric. Several drugs showing significant promise in the treatment of advanced gastric cancer include the monoclonal antibodies trastuzumab (for HER-2 positive cancers) and ramucirumab (anti-VEGFR2).^{8,9}

Indications and Mechanism of Action

Ramucirumab is approved for the treatment of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma as a single agent.¹⁰ This treatment regimen should be used if disease progression occurs with or after fluoropyrimidine- or platinum-containing chemotherapy.¹¹ Ramucirumab is an antineoplastic agent and a recombinant monoclonal antibody in the IgG1 class.^{10,11} The drug binds to the vascular endothelial growth factor receptor 2 (VEGFR2) with a high affinity.¹¹ By binding to the VEGFR2 receptor, ramucirumab blocks the binding of VEGFR ligands, including VEGF-A, VEGF-C, and VEGF-D, which inhibits the activation of the receptor. Ligand-induced proliferation and migration of endothelial cells are inhibited. Therefore, tumor vascularity and growth are reduced. Ramucirumab does not affect initial levels of VEGF ligands, unlike bevacizumab, another VEGF inhibitor (which binds to the ligand VEGF itself).¹² By antagonizing the receptor rather than binding the ligand, ramucirumab may have less resistance.

Pharmacokinetics

Ramucirumab is given intravenously (IV) at a dose of 8mg/kg every two weeks.¹² The half-life of ramucirumab at steady-state is 200 to 300 hours and accumulates with increasing doses.^{12,13} A phase 1 clinical trial conducted by Spratlin and colleagues studied the pharmacokinetics and pharmacodynamics of ramucirumab.¹³ Patients with advanced solid malignancies received escalating doses of ramucirumab as a one hour intravenous infusion. The clearance rate of ramucirumab decreased disproportionately as the dose was increased. This nonlinear effect suggests that the drug is eliminated by saturable receptor-mediated clearance.^{12,13} There have not yet been studies evaluating the effects of hepatic or renal impairment on the pharmacokinetics of ramucirumab.¹² The trial by Spratlin and colleagues also showed that circulating VEGF-A concentrations increased almost immediately after treatment to 1.5- to 3.5-fold higher than pretreatment concentrations and remained elevated until the next treatment.¹³ As long as ramucirumab was present, VEGF-A levels remained elevated. The soluble vascular

endothelial growth factor receptors one and two (sVEGFR-1 and sVEGFR-2) concentrations tended to decrease immediately after ramucirumab was administered, but they recovered to near-pretreatment levels. Neither the VEGF-A, sVEGFR-1 or sVEGFR-2 levels were related to the dose of ramucirumab. The pharmacokinetic profile of ramucirumab suggests that weekly dose administrations of the drug are biologically relevant. The minimum target trough level was selected to be greater than or equal to 20 µg/mL based on the pharmacodynamic and efficacy data gathered from human tumor xenografts implanted in mice. This trough level was achieved in all the treated patients from this trial.

Adverse Events/Toxicity

The most prevalent adverse events observed in patients were hypertension, diarrhea, anemia and infusion-related reactions.¹¹ Hypertension occurred in 16 percent of patients with 8 percent of patients experiencing grade 3 or 4, which is classified as severe with a blood pressure reading of greater than or equal to 180/110mm Hg (versus a grade 1 or 2, which is considered mild to moderate with a blood pressure reading of 140 to 179/90 to 109mm Hg).^{11,14} The current recommendation is to temporarily stop the infusion until the hypertension is controlled with antihypertensive medication or to permanently discontinue ramucirumab infusion if the hypertension is severe and uncontrolled.¹¹ The infusion reactions associated with ramucirumab, which usually occur with the first or second infusion, include chills, flushing, hypotension, bronchospasm, dyspnea, hypoxia, wheezing, chest pain or tightness, supraventricular tachycardia, back pain or spasms, rigors or tremors, and paresthesia. Patients should be continuously monitored for infusion reaction symptoms and the treatment should be immediately and permanently discontinued for grade 3 or 4 reactions. Ramucirumab was shown to increase the risk of hemorrhage, including cases of severe and fatal bleeding. Consequently, in the United States, a black box warning for ramucirumab exists, which states that it should be permanently discontinued in patients who experience serious hemorrhagic events. Other serious adverse events that have occurred in patients receiving ramucirumab include arterial thrombotic events, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome, which causes lesions in the parieto-occipital regions of the cerebral hemispheres and is characterized by altered mental status, headache, seizure and visual disturbances.^{11,15} If any of these events occur, it is recommended to discontinue treatment.¹¹ Wound healing impairment is commonly seen in patients who are receiving antiangiogenic therapy; however, ramucirumab has not yet been studied in patients with serious or nonhealing wounds. It is recommended to stop treatment prior to, during and after treatment of such wounds and to continue ramucirumab infusions only when the wound is fully healed.

Drug interaction studies have not yet been conducted with ramucirumab. However, based on its therapeutic category, there are several drugs that should be avoided while on ramucirumab.¹² Monoclonal antibodies have been shown to enhance adverse and toxic effects of belimumab, an IgG1-lambda monoclonal antibody that blocks binding of soluble

human B lymphocyte stimulator protein to receptors on B lymphocytes (and therefore preventing the survival of B lymphocytes), so it has a risk factor of X (avoid combination with ramucirumab).^{11,16} The adverse and toxic effects of bisphosphonate derivatives such as alendronate and ibandronate may be enhanced by systemic angiogenesis inhibitors, which gives them a risk factor of C (monitor therapy when used with ramucirumab).

REGARD Trial: Patient survival rate

Ramucirumab monotherapy for previously treated advanced gastric or gastroesophageal junction adenocarcinoma was evaluated in an international randomized, multicenter, placebo-controlled, phase 3 trial.¹⁷ Also known as REGARD, this is the trial that led to the FDA approval of ramucirumab. The purpose of the trial was to quantify the advantage in survival rate in patients who received ramucirumab versus those who did not. With a sample size of 355 patients and a 2:1 ratio of those who received ramucirumab versus placebo, there was an increased median overall survival rate in those receiving ramucirumab of 5.2 months versus 3.8 months for the placebo group. The study was conducted as a double-blind, randomized placebo-controlled trial in 29 countries all across the world. Inclusion criteria for the study gathered patients ages 24 to 87 with gastric adenocarcinoma, disease progression within the past four months of prior treatment, and an eastern cooperative oncology group (ECOG; see Table 1) performance score of 0 or 1.^{17,18} Exclusion criteria included grade 3 or higher gastrointestinal (GI) bleeding within three months of randomization, arterial thromboembolic events within six months of randomization and uncontrolled hypertension.¹⁷ All parties involved were masked except for in emergencies only. Every patient received recommended supportive care, excluding any additional investigational drugs, and received ramucirumab or placebo until confirmed disease progression, intolerable toxicity or death. The primary measure within the study was overall survival rate. Secondary measures included rates of adverse effects and progression-free intervals. Tumor and quality of life assessments were also obtained. Results of the study concluded that ramucirumab therapy was superior to placebo therapy. Not only did the study conclude that the drug increased the overall survival rate, but also that the risk of death and disease progression were reduced between the two groups. These results, along with ramucirumab's unique mechanism of action compared to other drugs used to treat gastric cancer, prompted the indication for second-line treatment of gastric or gastroesophageal adenocarcinoma. When overall survival rates with ramucirumab therapy were compared to those of bevacizumab (a monoclonal antibody targeting VEGF-A), bevacizumab had slightly better rates, which was deemed to be statistically insignificant.

RAINBOW Trial: Combination Therapy

A double-blind, randomized phase 3 trial, ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma, was conducted by Wilke and colleagues.¹⁹ Also known as the RAINBOW trial, this study evaluated the effects of ramucirumab in combination with

Table 1. Eastern Cooperative Oncology Group (ECOG) Performance Scale.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

As published in *Am. J. Clin. Oncol.*: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: *Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group*. *Am J Clin Oncol* 5:649-655, 1982.

The ECOG Performance Status is in the public domain and therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

paclitaxel in patients with previously treated advanced gastric cancer. The objective of the study was to determine if overall survival rate increased in patients treated with ramucirumab plus paclitaxel versus placebo plus paclitaxel. In this placebo-controlled, multicentered phase 3 trial, patients who had disease progression within four months after platinum plus fluoropyrimidine with or without an anthracycline as a first-line chemotherapy treatment were eligible for the trial. Patients were randomized to receive either 8mg/kg of ramucirumab or a placebo intravenously on days 1 and 15, and both groups received paclitaxel 80mg/m² intravenously on days 1, 8 and 15 of a 28-day cycle. The primary endpoint was overall survival of the patients. The overall survival rate among the patients in the ramucirumab plus paclitaxel group was significantly higher than in the control group, with median survival periods of 9.6 and 7.4 months, respectively. Further, the 12-month overall survival rate was 40 percent in the ramucirumab group and 30 percent in the control group. Taken together, the findings suggest that this combination therapy could become a new standard second-line treatment for patients with advanced gastric cancer. In addition, although this particular study is complete, 13 patients in the ramucirumab plus paclitaxel group and seven in the control group are continuing to receive their respective treatments in order to evaluate an extension phase of the study to determine the long-term results of the treatments.

Handling of Ramucirumab

Vials of ramucirumab are supplied in a concentration of 10mg/ml, and the calculated dose should be diluted with normal saline.²⁰ Ramucirumab is not stable in solutions containing dextrose. The mixture should be inverted to ensure even displacement in a final volume of 250mL. Ramucirumab should be stored under refrigeration at a temperature

between 2 degrees and 8 degrees Celsius (36 degrees to 46 degrees Fahrenheit). The diluted mixture should be stored no longer than 24 hours. When preparing ramucirumab, it is important to ensure quality by inspecting vials for any discoloration or loose particles.²¹ If present, discard the vial immediately. Any unused ramucirumab, as well as supplies used for preparation and administration, and any patient or equipment waste, should be discarded in indicated yellow chemotherapy bins for incineration or according to company policy.

Standard dosing of ramucirumab is 8mg/kg every two weeks.²⁰ This should continue unless the disease progresses or there is evidence of unacceptable toxicity. Before administering ramucirumab, pre-medicate the patient with an H1 antagonist such as diphenhydramine. If the patient has experienced a grade 1 or 2 reaction previously, also medicate with dexamethasone and acetaminophen before ramucirumab is initiated. The patient should be pre-medicated at an appropriate interval prior to administering ramucirumab in order to ensure optimal patient comfort and tolerance level. Diphenhydramine may only take five minutes to take effect if given IV, but up to two hours if taken orally. Similarly, dexamethasone should be administered anywhere from 15 to 30 minutes before treatment initiation, and acetaminophen can be administered five to 10 minutes before.¹¹

The infusion itself takes place over 60 minutes through a single infusion line. Ramucirumab should not be infused in the same IV line as electrolytes or other medications, and should not be given as an IV push.²⁰ During administration, it is important to monitor for any infusion reactions: signs of tremors, back pain, chest pain and tightness, chills, flushing, dyspnea, hypoxia and paresthesia. More serious cases of in-

fusion reactions include bronchospasms, hypotension and supraventricular tachycardia. Close monitoring is required at every administration of ramucirumab as the incidence of infusion-related reactions is slightly more prevalent in the first or second administration but presents a risk throughout treatment. If a grade 1 or 2 infusion reaction occurs, reduce the infusion rate by 50 percent and continue treatment. If a grade 3 or 4 reaction presents itself, permanently discontinue ramucirumab.¹¹

Safety for Health Care Professionals

While the effects of ramucirumab on patients are documented, the effects on those who prepare, administer and dispose of the drug are not. Occupational exposure to hazardous drugs, namely chemotherapy, are highest in pharmacists during its preparation and nurses during its administration.²¹ Lack of chemotherapy precautions at any stage of drug handling can result in hair loss, contact dermatitis and skin injury in the short term, as well as a higher rate of genotoxicity, cancer, fetal loss and infertility in the long term. Appropriate precautions include the use of specific safety cabinets for preparation and appropriate personal protective equipment (PPE). For preparation, this includes a ventilated cabinet that takes both employee safety and product sterility into account, which includes proper disposal of vapors and air circulation. Further precautions include wearing two pairs of chemotherapy-tested gloves to safeguard the preparer against any potential contact with the drug or waste contents, a chemotherapy-tested gown and a face shield or respirator if there is any risk of inhalation or splattering of chemotherapy agents. These same necessities carry to the bedside when nurses administer antineoplastic agents including further precautions such as using needleless systems and ensuring that IV tubing is primed with normal saline or a nonhazardous drug by a pharmacist prior to patient administration. Identical precautions are needed in order to dispose of bodily fluids from a patient receiving chemotherapy, in addition to placing an absorbent pad over the toilet when flushing in order to prevent splashing and contact.²² Disposal of any equipment used in the administration of ramucirumab or care of a patient receiving treatment should be placed in a biohazard bag and be placed in a yellow chemotherapy bin for incineration. This includes absorbent pads, IV tubing and any PPE. Any sharps or needles used in administration or maintenance of ramucirumab should be placed in a specified chemotherapy sharps container for proper disposal and incineration.²¹ These precautions should persist after the initial treatment, as chemotherapy and other hazardous drugs remain in the patient's body for up to 48 hours and are subsequently excreted through waste such as urine, stool and emesis. Education on similar precautions, as well as disposal methods, should be provided to the family and caregivers of those on chemotherapy in order to prevent any accidental exposure.²²

Management of Adverse Effects

As stated earlier, hypertension is one of the most clinically significant adverse effects of ramucirumab.¹¹ Any existing hypertension should be well-controlled before treatment is initiated, and blood pressure should be monitored starting

two weeks prior to infusion initiation and continued every two weeks throughout the course of therapy. More frequent monitoring may be indicated if the patient has a history of hypertension or if the patient develops hypertension over the course of ramucirumab administration.²⁰ If a hypertensive crisis occurs, immediate medical intervention, such as nitroprusside administration, may be indicated, although side effects must also be monitored.²³ Educating patients on measuring their blood pressure at home may help prevent a hypertensive crisis from occurring. It is also important to ensure that patients are aware of side effects, such as flushing, headaches and heart palpitations, which may indicate a hypertensive crisis. This knowledge, as well as health care provider contact information, may help patients avoid a crisis and follow a medication regimen that effectively controls their blood pressure. Education on medication compliance, as well as lifestyle modifications, may provide additional benefit over the course of treatment.

The incidence of bleeding and hemorrhage risk in those taking ramucirumab is slightly increased over those who received a placebo.²⁰ A proactive approach to this adverse effect is prevention and, consequently, the use of bleeding precaution procedures should be followed in both the health care setting and as the patient is discharged. This involves avoiding unnecessary invasive procedures, such as rectal temperatures. In addition, the use of small gauge needles and direct pressure on bleeding sites for up to five minutes may help with clotting.²³ Monitoring blood counts for abnormal values in platelets or prothrombin time, as well as hemoglobin and hematocrit values that may indicate an internal bleed, is crucial. Observing trends in vital signs while the patient is in the hospital to monitor for signs of tachycardia and hypotension may alert health care providers to any potential hypovolemia indicating the presence of an internal bleed. Related to personal hygiene, soft toothbrushes and safety razors should be used. Any sharp corners that may cause bleeding should be covered in padding. Patients should receive education on providing these safety measures at home, as well as observing for abnormal bruising or feelings of dizziness and heart palpitations. Patients should be instructed to immediately report to their health care provider if they notice any of these symptoms.

Cancer-related fatigue (CRF), while comparable among the treatment modalities, still affects 36 percent of patients on ramucirumab.²³ Cancer-related fatigue is defined by Horneber et al. as "the syndrome of fatigue and exhaustion in cancer patients."²⁴ This syndrome affects all aspects of health and manifests itself not only by a lack of energy, but also by a loss of drive and social withdrawal in addition to impaired concentration and memory loss. Many of these symptoms are subjective and can be identified by thorough communication between the patient and the health care provider. Symptoms may not be directly observed due to a focus on the treatment modality of the cancer itself, or they may not be reported if the patient withholds information due to fear of judgment or delay in treatment. A degree of patient trust, as well as constant follow-up, may help providers to diagnose CRF more readily and, consequently, facilitate initiation of appropriate

treatment. Of all the side effects that accompany cancer patients undergoing treatment, CRF is considered the worst due to its severe debilitation on the patient's quality of life. It can occur at any stage of the disease process including after admission. Proper education on CRF as a condition is imperative for treatment as patients who recognize the symptoms are more open to treatment options.

While pharmacological components such as hematopoietic growth factors and corticosteroids may improve CRF, they are only effective for a minority of patients and are often a short-term solution with added risks. However, nonpharmacologic activities such as physical exercise may provide the same benefits without as many of the risks. In a meta-analysis completed by McMillan and Newhouse, it was shown that all modes of physical activity, especially aerobic exercise, and to a lesser degree resistance exercise, may help not only decrease the manifestations of CRF, but also the symptom clusters that accompany it such as depression and anxiety.²⁵ Improvement in cardiac reserve, lung ventilation and perfusion may explain such changes, especially since such characteristics are diminished in cancer patients both during and after treatment.

Conclusion

Gastric cancer is a prevalent disease that has a very low survival rate once it becomes advanced or metastatic. Once disease progression has led to metastasis, survival rates significantly drop despite the utilization of first-line therapies. Ramucirumab is a monoclonal antibody that targets VEGF receptors and is used for the treatment of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma as a single agent. Through studies such as REGARD and RAINBOW, ramucirumab has been shown to be an effective second-line therapy as monotherapy or combination therapy with paclitaxel in prolonging survival over placebo. Ramucirumab is a novel anticancer agent, as treatment with this agent is categorized as "targeted therapy." However, its application in other types of cancer should also be considered. Because of the efficacy demonstrated by ramucirumab, it is crucial for health care professionals to properly manage adverse effects, such as hypertension and hemorrhage, to allow continuation and success of ramucirumab therapy in the treatment of gastric or gastroesophageal junction adenocarcinoma.

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