phone calls at the end of February.

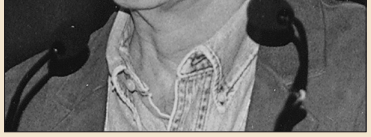
Combinations with cytotoxic chemotherapy agents, steroids, antibiotics, and even a bisphosphonate are all being tested.

'Total Therapy' Includes Thalidomide

Thalidomide is an angiogenesis inhibitor, and its activity as a single agent in refractory multiple myeloma was confirmed in a report by Bart Barlogie, MD, PhD, Director of the Arkansas Cancer Research Center in Little Rock. He described a trial of 169 patients in which 61 responded, including three with complete responses, and 20 others with regressions of greater than 90 percent. The overall survival rate with single-agent thalidomide was 55 percent at 18 months.

Dr. Barlogie said he believes thalidomide is an ideal agent to combine with myelosuppressive cytotoxic drugs, since it is minimally bone-marrow suppressive.

In an interview after the meeting, Dr. Barlogie said a randomized multiple myeloma trial referred to as "Total Therapy II" has already randomized more than 300 newly diagnosed multiple myeloma patients to intensive induction chemotherapy alone or with thalidomide.



Joe Vericker/Photobu

Bart Barlogie, MD, PhD, said he believes thalidomide is an ideal agent to combine with myelosuppressive cytotoxic drugs, since it is minimally bone-marrow suppressive.

The "total therapy" regimen begins with vincristine, doxorubicin, and dexamethasone (VAD); followed by dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP); then cyclophosphamide, doxorubicin, and dexamethasone; stem cell transplant; and then another cycle of DCEP. A second phase consists of two cycles of high-dose melphalan.

Patients are randomized to receive or not receive thalidomide throughout the year-long program, Dr. Barlogie said.

In a trial planned at his center for early indolent (smoldering) myeloma, thalidomide will be combined with the

found declines in prostate-specifc antigen (PSA) levels in 68 percent of 63 androgen-independent patients taking a high-dose regimen, and in 58 percent of men taking low-dose thalidomide, reported William D. Figg, PharmD, Senior Investigator and Head of NCI's Clinical Pharmacokinetic Section.

Low dose was 200 mg/day, and high dose escalated from 200 to 1,200 mg/day. Four patients taking low-dose thalidomide maintained depressed PSA levels for more than 150 days, and two of them were considered partial responders by bone scan criteria.

None of the high-dose patients, however, had more than a 50% PSA response, Dr. Figg noted. "That was probably because few patients tolerated the high doses, and most had to come off trial." But he added that colleagues at the NCI treating Kaposi's sarcoma are using high-dose thalidomide without the same toxicities—probably because the population of patients is younger than in advanced prostate cancer trials.

Dr. Figg pointed out that using changes in PSA as a marker probably underestimated thalidomide's actual effect on reducing prostate tumors, because thalidomide upregulates PSA by about 20 percent. Other drugs also

Hodgkin's Disease

continued from page 25

also to remember that problems can arise with relapse. In the case of a male who receives initial treatment that is nonsterilizing, he may relapse and require high-dose treatment. Spermatogenesis may have lulled, and there may be no further opportunity before sterilization to harvest semen for cryopreservation. Thus, alternative options have to be considered. "Unfortunately, because of the evolving nature of protocols, we are on a moving staircase in terms of fertility treatment and prognosis," Dr. Gosden continued. "It is very difficult, in any particular set of circumstances, to predict exactly what the effects will be upon a young man or woman's future fertility."

Act Before Treatment Starts

mences, Dr. Gosden said. In general, the options for women are more limited than for men. To preserve the possibility of a woman's future genetic parenthood, there is the possibility of embryo, oocyte, or ovary banking. One method of in vivo protection of the ovaries is to perform oophoropexy, in which the ovaries are transposed and then returned to their original site following completion of treatment. There have been successes using this approach when abdominal radiation treatments are required. However, natural fertility may not always return after this procedure.

Several theoretical approaches are now being contemplated. For instance, one strategy may be to use oral contraceptives and gonadotropin-releasing hormone agonists in both males and females to suppress the gonads and thus reduce their radio- or chemo-sensitivity. However, support for this theory is based mostly on animal studies.

ways, specifically in oocytes.

This raises the concern that such agents would also reduce therapeutic benefit. Another concern, said Dr. Gosden, is that this technique might conserve germ cells that should have otherwise undergone apoptosis. They may have acquired germ line damage, leading to effects on later reproduction such as miscarriage or birth defects.

One exciting new technology is the storing of ovarian tissue, either as an ovarian biopsy to be cryobanked for future transplantation or by recovering primordial follicles and maturing them in the laboratory for use in in vitro procedures. Although the latter technology is still a "very long way" from reality, Dr. Gosden has participated in experiments in which autografts of ovarian tissue restored estrus cycles in female sheep.

While cryopreservation of semen is generally accepted as the standard for fertility conservation in men, it is not

NEUMEGA® (Oprelvekin)

BRIEF SUMMARY

Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

Neumega is indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia. Efficacy was demonstrated in patients who had experienced severe thrombocytopenia following the previous chemotherapy cycle. Neumega is not indicated following myeloablative chemotherapy.

CONTRAINDICATIONS

Neumega is contraindicated in patients with a history of hypersensitivity to Neumega or any component of the product.

WARNINGS

Neumega is known to cause fluid retention (see CLINICAL PHARMACOLOGY: Pharmacodynamics), and it should be used with caution in patients with clinically-evident congestive heart failure, patients who may be susceptible to developing congestive heart failure, and patients with a history of heart failure who are well-compensated and receiving appropriate medical therapy (see PRECAUTIONS: Fluid Retention).

Close monitoring of fluid and electrolyte status should be performed in patients receiving chronic diuretic therapy. Sudden deaths have occurred in Oprelvekin-treated patients receiving chronic diuretic therapy and ifosfamide who developed severe hypokalemia (see ADVERSE REACTIONS).

PRECAUTIONS

General

Dosing with Neumega should begin 6 to 24 hours following the completion of chemotherapy dosing. The safety and efficacy of Neumega given immediately prior to or concurrently with cytotoxic chemotherapy have not been established (see DOSAGE AND ADMINISTRATION).

Neumega has not been evaluated in patients receiving chemotherapy regimens of greater than 5 days duration or regimens associated with delayed myelosuppression (e.g., nitrosoureas, mitomycin-C).

The parenteral administration of Neumega should be attended by appropriate precautions in case allergic reactions occur (see CONTRAINDICATIONS).

Fluid Retention

Patients receiving Neumega have commonly experienced mild to moderate fluid retention as indicated by peripheral edema or dyspnea on exertion. Weight gain has been uncommon. The fluid retention is reversible within several days following discontinuation of Neumega. In some patients, preexisting pleural effusions have increased during administration of Neumega. Preexisting fluid collections, including pericardial effusions or ascites, should be monitored. Drainage should be considered if medically indicated. Capillary leak syndrome has not been observed following treatment with Neumega.

Moderate decreases in hemoglobin concentration, hematocrit, and red blood cell count (~10%–15%) without a decrease in red blood cell mass have been observed. These changes are predominantly due to an increase in plasma volume (dilutional anemia) that is primarily related to renal sodium and water retention. The decrease in hemoglobin concentration typically begins within 3-5 days of the initiation of Neumega, and is reversible over approximately a week following discontinuation of Neumega.

During dosing with Neumega, fluid balance should be monitored and appropriate medical management is advised. If a diuretic is used, fluid and electrolyte balance should be carefully monitored. Neumega should be used with caution in patients who may develop fluid retention as a result of associated medical conditions or whose medical condition may be exacerbated by fluid retention.

Cardiovascular Events

Neumega should be used with caution in patients with a history of atrial arrhythmia, and only after consideration of the potential risks in relation to anticipated benefit. Transient atrial arrhythmias (atrial fibrillation or atrial flutter) have occurred in approximately 10% of patients following treatment with Neumega. In some patients this may be due to increased plasma volume associated with fluid retention (See PRECAUTIONS: Fluid Retention); Neumega has been shown not to be directly arrhythmogenic. Arrhythmias have usually been brief in duration and usually without clinical sequelae; however, sequelae including stroke have been observed in patients receiving Neumega who experienced atrial arrhythmias. Conversion to sinus rhythm typically occurred spontaneously or after rate-control drug therapy. Most patients have continued to receive Neumega without recurrence of atrial arrhythmia. A retrospective analysis of data from clinical studies of Neumega suggests that advancing age and other conditions associated with an increased risk of atrial arrhythmias such as use of cardiac medications and a history of doxorubicin exposure are risk factors for the development of atrial fibrillation or atrial flutter in patients receiving Neumega. Ventricular arrhythmias have not been attributed to the use of Neumega.

Ophthalmologic Events

Transient, mild visual blurring has occasionally been reported by patients treated with Neumega. Papilledema has been reported in approximately 1.5% of patients treated with Neumega following repeated cycles of exposure. Nonhuman primates treated with Neumega at a dose of 1,000 µg/kg SC once daily for 4 to 13 weeks developed papilledema which was not associated with inflammation or any other histologic abnormality and was reversible after dosing was discontinued. Neumega should be used with caution in patients with preexisting papilledema, or with tumors involving the central nervous system since it is possible that papilledema could worsen or develop during treatment.

Antibody Formation/Allergic Reactions

A small proportion (1%) of patients receiving Neumega in clinical studies developed antibodies to Oprelvekin and transient rashes were occasionally observed at the injection site following Neumega administration. The presence of these antibodies or injection site reactions have not been correlated with clinical symptoms such as anaphylactoid reactions or a loss of clinical response to Neumega. No anaphylactoid or other severe adverse allergic reactions were reported in clinical studies following single or repeated doses of Neumega.

Chronic Administration

Neumega has been administered safely using the recommended dosing schedule (see DOSAGE AND ADMINISTRATION) for up to 6 cycles following chemotherapy. The safety and efficacy of chronic administration of Neumega have not been established. Continuous dosing (2-13 weeks) in nonhuman primates produced joint capsule and tendon fibrosis and periosteal hyperostosis (see PRECAUTIONS: Pediatric Use). The relevance of these findings to humans is unclear.

Information for Patients

In situations when the physician determines that Neumega may be used outside of the hospital or office setting, persons who will be administering Neumega should be instructed as to the proper dose, and the method for reconstituting and administering Neumega. If home use is prescribed, patients should be instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, drug product, and diluent. A puncture resistant container should be used by the patient for the disposal of used needles.

Patients should be informed of the most common adverse reactions associated with Neumega administration, including those symptoms related to fluid retention (see ADVERSE REACTIONS and PRECAUTIONS). Mild to moderate peripheral edema and shortness of breath on exertion can occur within the first week of treatment and may continue for the duration of administration of Neumega. Patients who have preexisting pleural or other effusions or a history of congestive heart failure should be advised to contact their physician for worsening of dyspnea. Most patients who receive Neumega develop some anemia. Patients who are older or who have other risk factors for the development of atrial arrhythmias should be cautioned to contact their physician if symptoms attributable to atrial arrhythmia develop and are not transient. Female patients of childbearing potential should be advised of the possible risks to the fetus of Neumega (see PRECAUTIONS: Pregnancy).

Laboratory Monitoring

A complete blood count should be obtained prior to chemotherapy and at regular intervals during Neumega therapy (see DOSAGE AND ADMINISTRATION). Platelet counts should be monitored during the time of the expected nadir and until adequate recovery has occurred (post-nadir counts ≥50,000).

Drug Interactions

Most patients in trials evaluating Neumega were treated concomitantly with filgrastim (granulocyte colony-stimulating factor [G-CSF]) with no adverse effect of Neumega on the activity of G-CSF. No information is available on the clinical use of Sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) with Neumega. However, in a study in nonhuman primates in which Neumega and GM-CSF were coadministered, there were no adverse interactions between Neumega and GM-CSF and no apparent difference in the pharmacokinetic profile of Neumega.

Drug interactions between Neumega and other drugs have not been fully evaluated. Based on *in vitro* and need-ful *in vivo* evaluations of Neumega, drug-drug interactions with known substrates of P450 enzymes would not be predicted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the carcinogenic potential of Neumega. *In vitro*, Neumega did not stimulate the growth of tumor colony-forming cells harvested from patients with a variety of human malignancies. Neumega has been shown to be non-genotoxic in *in vitro* studies. These data suggest that Neumega is not mutagenic. Although prolonged estrus cycles have been noted at 2 to 20 times the human dose, no effects on fertility have been observed in rats treated with Neumega at doses up to 1000 µg/kg/day.

Pregnancy Category C

Neumega has been shown to have embryocidal effects in pregnant rats and rabbits when given in doses of 0.2 to 20 times the human dose. There are no adequate and well-controlled studies of Neumega in pregnant women. Neumega should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neumega has been tested in studies of fertility and early embryonic development in rats and in studies of organogenesis (teratogenicity) in rats and rabbits. Parental toxicity has been observed when Neumega is given at doses of 2 to 20 times the human dose (≥100 µg/kg/day) in the rat and when given in doses of 0.02 to 2.0 times the human dose (≥1 µg/kg/day) in the rabbit. Findings in the rat consisted of transient hypoactivity and dyspnea after administration, as well as prolonged estrus cycle, increased early embryonic deaths and decreased numbers of live fetuses. In addition, low fetal body weights and a reduced number of ossified sacral and caudal vertebrae (i.e., retarded fetal development) occurred in rats at 20 times the human dose, but no long-term behavioral or developmental abnormalities were evident. Findings in the rabbits consisted of decreased (fecal/urine) eliminations (the only toxicity noted at 1 µg/kg/day) as well as decreased food consumption, body weight loss, abortion, increased embryonic and fetal deaths, and decreased numbers of live fetuses. There have been no teratogenic effects of Neumega observed in rabbits.

Nursing Mothers

It is not known if Neumega is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Neumega, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Efficacy trials have not been conducted in a pediatric population. Preliminary data are available from an ongoing pharmacokinetic study in twenty-eight patients ages 8 months to 17 years who have been treated with Neumega at doses of 25 to 100 µg/kg following ICE (ifosfamide, etoposide, carboplatin) chemotherapy. Neumega treatment was given once daily for a maximum of 28 days in up to eight cycles. Based upon this study, a dose of 75 to 100 µg/kg in the pediatric population will produce plasma levels consistent with those obtained in adults given 50 µg/kg (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Adverse events in this pediatric open-label, non-comparative study were generally similar to those observed using Neumega at a dose of 50 µg/kg in the randomized chemotherapy studies in adults. Most adverse events that were associated with Neumega in adults occurred either with similar or lower frequency in the pediatric study compared with adults. The incidences of tachycardia (46% [13/28]) and conjunctival injection (50% [14/28]) in the pediatric study were higher than in adults (see ADVERSE REACTIONS). There was no evidence of a dose-response relationship for any of the Neumega-associated adverse events among the pediatric patients.

No studies have been performed to assess the long-term effects of Neumega on growth and development. In growing rodents treated with 100, 300, or 1000 µg/kg/day for a minimum of 28 days, thickening of femoral and tibial growth plates was noted, which did not completely resolve after a 28-day non-treatment period. In a nonhuman primate toxicology study of Neumega, animals treated for 2 to 13 weeks at doses of 10 to 1000 µg/kg showed partially reversible joint capsule and tendon fibrosis and periosteal hyperostosis. The clinical significance of these findings is not known. An asymptomatic, laminated periosteal reaction in the diaphyses of the femur, tibia and fibula has been observed in one patient during pediatric trials involving multiple courses of Neumega treatment. The relationship of these findings to treatment with Neumega is unclear.

Use in Patients with Renal Impairment

Neumega is eliminated primarily by the kidneys. The pharmacokinetics of Neumega have not been studied in patients with mild or moderate renal impairment (creatinine clearance ≥ 15 mL/min). Fluid retention associated with Neumega treatment has not been studied in patients with renal impairment, but fluid balance should be carefully monitored in these patients (See PRECAUTIONS: Fluid Retention).

ADVERSE REACTIONS

Three hundred eight subjects, with ages ranging from 8 months to 75 years, have been exposed to Neumega treatment. Subjects have received up to six (eight in pediatric patients) sequential courses of Neumega treatment, with each course lasting from 1 to 28 days. Apart from the sequelae of the underlying malignancy or cytotoxic chemotherapy, most adverse events were mild or moderate in severity and reversible after discontinuation of Neumega dosing.

In general, the incidence and type of adverse events were similar between Neumega 50 µg/kg and placebo groups. The following adverse events, occurring in ≥10% of patients, were observed at equal or greater frequency in placebo-treated patients: asthenia, pain, chills, abdominal pain, infection, anorexia, constipation, dyspepsia, ecchymosis, myalgia, bone pain, nervousness, and alopecia. Selected adverse events that occurred in Neumega-treated patients are listed in Table 1.

TABLE 1
SELECTED ADVERSE EVENTS

Body System Adverse Event	Placebo n=87 (%)	50 µg/kg n=93 (%)	Body System Adverse Event	Placebo n=87 (%)	50 µg/kg n=93 (%)
Body as a Whole			Nervous System		
Edema*	10 (15)	41 (59)	Dizziness	19 (28)	26 (38)
Neutropenic fever	28 (42)	33 (48)	Insomnia	18 (27)	23 (33)
Headache	24 (36)	28 (41)	Respiratory System		
Fever	19 (28)	25 (36)	Dyspnea*	15 (22)	33 (48)
Cardiovascular System			Rhinitis	21 (31)	29 (42)
Tachycardia*	2 (3)	14 (28)	Cough increased	15 (22)	20 (29)
Vasodilatation	6 (9)	13 (19)	Pharyngitis	11 (16)	17 (25)
Palpitations*	2 (3)	10 (14)	Pleural effusions*	0 (0)	7 (10)
Syncope	4 (6)	9 (13)	Skin and Appendages		
Atrial fibrillation/flutter*	1 (1)	8 (12)	Rash	11 (16)	17 (25)
Digestive System			Special Senses		
Nausea/vomiting	47 (70)	53 (77)	Conjunctival injection*	2 (3)	13 (19)
Mucositis	25 (37)	30 (43)			
Diarrhea	22 (33)	30 (43)			
Oral moniliasis*	1 (1)	10 (14)			

*Occurred in significantly more Neumega-treated patients than in placebo-treated patients.

The following adverse events also occurred more frequently in cancer patients receiving Neumega than in those receiving placebo: amblyopia, paresthesia, dehydration, skin discoloration, exfoliative dermatitis, and eye hemorrhage; a statistically significant association of Neumega to these events has not been established. Other than a higher incidence of severe asthenia in Neumega-treated patients (10 [14%] in Neumega patients versus 2 [3%] in placebo patients), the incidence of severe or life-threatening adverse events was comparable in the Neumega and placebo treatment groups.

The incidence of fever, neutropenic fever, flu-like symptoms, thrombocytosis, thrombotic events, the average number of units of red blood cells transfused per patient, and the duration of neutropenia <500 cells/µL were similar in the Neumega 50 µg/kg and placebo groups.

Two patients with cancer treated with Neumega experienced sudden death which the investigator considered possibly or probably related to Neumega. Both deaths occurred in patients with severe hypokalemia (<3.0 mEq/L) who had received high doses of ifosfamide and were receiving daily doses of a diuretic. The relationship of these deaths to Neumega remains unclear.

Abnormal Laboratory Values

The most common laboratory abnormality reported in patients in clinical trials was a decrease in hemoglobin concentration predominantly as a result of expansion of the plasma volume (see PRECAUTIONS: Fluid Retention). The increase in plasma volume is also associated with a decrease in the serum concentration of albumin and several other proteins (e.g., transferrin and gamma globulins). A parallel decrease in calcium without clinical effects has been documented.

After daily SC injections, treatment with Neumega resulted in a two-fold increase in plasma fibrinogen. Other acute-phase proteins also increased. These protein levels returned to normal after dosing with Neumega was discontinued. Von Willebrand factor (vWF) concentrations increased with a normal multimer pattern in healthy subjects receiving Neumega.

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responded rather dramatically to thalidomide or thalidomide and steroids. These were patients who had extensive disease, especially kidney-based but also GI-based disease, as well as macroglossia."

Macroglossia Responds to Thalidomide & Steroids

At Cedars-Sinai Medical Center in Los Angeles, five of six patients with primary amyloidosis and renal organ involvement responded to thalidomide and a thalidomide-glucocorticosteroid combination, reported James Berenson, MD, Director of the Multiple Myeloma and Bone Metastases Program.

"We treated patients with amyloid who failed other treatments, and most responded rather dramatically to the thalidomide or thalidomide and steroids," he said. "These were patients who had extensive disease, especially kidney-based but also GI-based disease, as well as macroglossia." Four patients had improved renal involvement, and four had what Dr. Berenson termed dramatic improvements in quality of life. "It was also quite impressive to see improvement in albumin levels, which almost returned to normal with the addition of low-dose thalidomide," he said. "That is pretty much

Joe Vericker/Photobureau

Jorge Cortes, MD: "In view of the significance of VEGF in the prognosis of these patients, further studies are warranted using more potent VEGF or angiogenesis inhibitors."