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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

HEAD AND NECK CANCER — PART III

NOVEL THERAPEUTIC AND CHEMOPREVENTIVE APPROACHES IN DEVELOPMENT

MEETING COVERAGE

OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

HEAD AND NECK CANCER — PART III NOVEL THERAPEUTIC AND CHEMOPREVENTIVE APPROACHES IN DEVELOPMENT

Head and neck squamous cell carcinoma (HNSCC) is a difficult cancer to treat. Surgery may be effective in early HNSCC but may result in permanent disfigurement. Radiation therapy, used alone or as an adjunct to surgery or chemotherapy, may preserve organ function but it also carries its own complications and may not prove effective over the long term. Second primary tumors also cloud the outlook of those "cured" the first time around while the prognosis of those presenting with advanced disease is uniformly grim.

RADIATION THERAPY

Radiotherapy is the mainstay adjunct treatment for most cases of HNSCC. Various approaches such as continuous hyperfractionated accelerated radiotherapy (CHART), intra-operative radiation therapy (IORT), and interstitial radiotherapy (brachytherapy) have been applied with success as adjunctive treatments for HNSCC. Limitations in using these treatments arises from the radiotolerance of the carotid artery, pharynx, and mandible to therapeutic doses.

CHART, tested in an 11-center randomized controlled clinical trial involving 918 patients with HNSCC (with the general exception of early T1 N0 tumors) over a 5-year period beginning in March 1990, produced similar locoregional control, primary tumor control, nodal control, disease-free interval, freedom from metastasis and survival, as did conventional radiotherapy, despite a reduction in total dose from 66 to 54 Gy with CHART, supporting the importance of repopulation as a cause of radiation failure (Dische S, etal, Radiotherapy and Oncology, 1997 Aug, 44(2):123-36).

Brachytherapy, in which radioactive isotopes such as iridium 192 (^{192}Ir) or palladium 103 (^{103}Pd) are implanted into a body cavity, is part of the standard radiation oncology practice in head and neck cancer management. TheraSeeds, an implantable radiation device based on ^{103}Pd developed by Theragenics (Norcross, GA) has been commercially available in the USA since 1986 for the treatment of prostate cancer. TheraSeeds, which is being marketed by Indigo Medical (Palo Alto, CA), a Johnson & Johnson company, is also being investigated in other types of tumors, including HNSCC.

RADIOSENSITIZATION/ENHANCEMENT

Because of the key role radiation therapy plays in the management of HNSCC, special efforts are being made to find ways to enhance its effectiveness. Various approaches are being evaluated to sensitize tumor cells to radiation and prevent/overcome resistance. These include modification of the molecular markers in tumor cells, killing of radiation-modified cells by adjunctive means, improving tumor oxygenation, or selectively targeting hypoxic cells unaffected by radiation, among others.

Introduction of wild-type p53 (wtp53) DNA into a radioresistant HNSCC cell line using a transferrin-liposome system resulted in reversal of the radioresistant phenotype of the cells in a DNA dose-dependent manner (see FO, p 630).

A serious limitation of radiation therapy is the presence of severely hypoxic cells that may constitute 1-15% of malignant tumor cells. Because radiation therapy requires tissue oxygenation to be effective, hypoxic cells are less susceptible to radiation forming a therapeutically resistant group within solid tumors. Even if a small fraction of tumors is hypoxic, tumor cells survive and proliferate after most of the non-hypoxic malignant tumor cells have been eradicated by radiation. Hypoxic cells also

exhibit resistance to most standard chemotherapeutic agents. One agent, tirapazamine (Tirazone; Sanofi), that preferentially targets hypoxic tumor cells, is in clinical development (see FO, p 642) in a variety of solid tumors.

Improving tumor oxygenation and perfusion by inhalation of carbogen (95% oxygen and 5% carbon dioxide), a hypoxia-modifying agent, and administration of nicotinamide (pyrimidine-3 carboxamide), a biologically active amide of nicotinic acid, or treatment with such vasoactive agents as the calcium channel blockers flunarizine or verapamil, enhances the effects of radiotherapy and improves delivery of chemotherapeutic agents to tumors. Research is currently in progress into the efficacy of accelerated radiotherapy, in combination with carbogen and nicotinamide, in tumors of the head and neck, bladder, bronchi and brain (Bernsen HJ, etal, Nederlands Tijdschrift voor Geneeskunde, 1997 Feb 22, 141(8):364-8).

Pharmacyclics

Pharmacyclics (Sunnyvale, CA) is developing texaphyrins that are proprietary expanded porphyrin molecules which localize in cancer cells and atherosclerotic plaque, where they can be exposed to various forms of energy that activates the molecules to eliminate diseased tissue. One such texaphyrin, gadolinium texaphyrin (Gd-Tex), is being developed as an adjunct to radiotherapy in a variety of solid tumors including head and neck cancer.

Preclinical studies indicate that texaphyrins increase the effect of radiation therapy by absorbing free electrons which are generated during irradiation of tissues with X-rays or gamma rays. Free electron absorption results in formation of relatively long lived texaphyrin and other free radicals that are both reactive and capable of destroying intracellular molecules, such as DNA. In addition to these physiochemical properties, Gd-Tex tends to localize selectively in cancer cells which confers it additional advantages as a radiation sensitizer. Preclinical studies indicate that Gd-Tex uptake in tumors occurs within minutes after administration and lasts for hours. Similar studies also indicate that Gd-Tex enhances radiation-induced killing of various human and animal cancer cells in a dose-dependent manner. When tested in animals, Gd-Tex and radiation resulted in enhanced tumor response and survival rates as compared to controls treated with equivalent dosages of radiation therapy alone. Enhancement of radiation effectiveness with Gd-Tex also is apparent using multifractionated radiation treatment regimens similar to those used in treating human cancers.

In January 1995, Pharmacyclics initiated a phase I clinical trial to evaluate the safety of Gd-Tex in cancer patients treated with radiation therapy. In this study, MRI was used to study the biolocalization of Gd-Tex in malignant and other tissues as well as to collect data on its potential as an MRI contrast agent. In this single dose escalation study, no serious toxicity has been observed to date while localization of the drug was demonstrated in primary and metastatic tumors. Gd-Tex is currently in multi-center phase Ib/II clinical trials in patients treated with radiation therapy for brain metastases arising from various cancers.

In September 1996, Pharmacyclics and Hoechst Celanese's Fine Chemicals (Charlotte, NC) unit signed a definitive manufacturing and supply agreement covering the texaphyrin products, lutetium texaphyrin (Lu-Tex) for photodynamic therapy of cancer and atherosclerosis, and Gd-Tex for radiation sensitization in cancer treatment. According to the agreement, Hoechst Celanese gains exclusive worldwide rights to supply the bulk-drug substance contained in the products using proprietary process technology developed by both parties. Pharmacyclics gains a guaranteed source of supply during the clinical and commercial stages for both products, and substantial process development and validation, as well as analytical and regulatory assistance. Hoechst plans to manufacture the products at its new state-of-the-art facility in Corpus Christi, Texas. Pharmacyclics entered into an initial collaboration with Hoechst Celanese in October 1995 to optimize the process, scale-up, and production of clinical supplies of Gd-Tex and Lu-Tex, based on a memorandum of understanding that has been since replaced by the definitive agreement.

In March 1997, Pharmacyclics announced that the Decision Network Committee of the National Cancer Institute (NCI), Division of Cancer Treatment, Diagnosis and Centers, voted unanimously in favor of supporting additional clinical trials for Gd-Tex and Lu-Tex. The company and the NCI are also structuring a CRADA through which the NCI intends to sponsor multiple clinical trials evaluating Gd-Tex and Lu-Tex in several types of cancer. The company will collaborate with the NCI on the design of such clinical studies and the selection of tumor indications. Both Gd-Tex and Lu-Tex received "DN 3 (Decision Network level 3)" approval, awarded to drugs demonstrating novel mechanisms of action and evidence of efficacy in either preclinical or clinical studies. After negotiation of a research and development plan with the company, the NCI will fund certain clinical and preclinical studies at various NCI-funded institutions, and through cooperative groups.

Enzon

Enzon (Piscataway, NJ) has applied its polyethylene glycol (PEG) modification approach to deliver hemoglobin effectively to hypoxic tumor cells and, thus, sensitize them to radiation therapy. In a currently ongoing phase Ib clinical trial, PEG hemoglobin (PEG-Hb) is administered once-a-week, for each of 5 days of radiation treatment during a three-week regimen. A phase I clinical trial in healthy volunteers that was completed in late 1995, demonstrated that PEG-Hb, in its active form, circulated in the blood for about 11 days. PEG-Hb has been shown to enhance both radiation therapy and chemotherapy.

Vion Pharmaceuticals

Vion Pharmaceuticals (was OncoRx; New Haven, CT) is developing porfiromycin (Promycin), currently in phase III clinical trials, in conjunction with radiation therapy, in the treatment of HNSCC. Promycin, a bioreductive alkylating agent related to mitomycin-C, takes advantage of the oxygen deficit that results in a major exploitable difference between normal and neoplastic tissues, to selectively attack hypoxic tumor cells. The demonstration that mitomycin-C and porfiromycin may be used to kill the hypoxic fraction while irradiation eradicates the oxygenated portion of the tumor, thus producing enhanced cytodestructive effects on solid tumors in animals, led to the clinical evaluation of the mitomycins in combination with radiation therapy in patients with head and neck cancer (Sartorelli AC, etal, Advances in Enzyme Regulation, 1995, 35:117-30). Laboratory studies indicated that porfiromycin destroyed a greater percentage of hypoxic cells relative to oxygenated cells than other agents being tested. In August 1994, Vion entered into a licensing agreement with Yale University (New Haven, CT) to acquire an exclusive license for any data relating to research and clinical studies of porfiromycin conducted by Yale. Because composition of matter patent protection is unavailable for porfiromycin, Vion applied for and obtained orphan drug status.

In a phase I/II trial conducted at Yale, of 21 patients treated with radiation (and, in some cases, surgery) in conjunction with porfiromycin, for certain types of cancer of the head and neck, 7 remained alive with no evidence of disease after a median follow-up of >60 months. Based on these findings, Vion initiated a phase III clinical trial comparing porfiromycin with radiation therapy to radiation therapy alone in patients with head and neck cancer to determine its efficacy as an adjunct to radiation therapy. As of November 1996, this phase III clinical trial, expected to enroll 80-200 patients, was ongoing at Yale and 8 other sites in the USA. Promycin is administered intravenously during the six-week course of radiation therapy. The study is managed by Ilex Oncology (San Antonio, TX).

PHOTODYNAMIC THERAPY

Because HNSCC tumors are often accessible through natural orifices, photodynamic therapy (PDT) may prove a viable palliative and even therapeutic approach in the management of head and neck cancer. Many developers are actively pursuing PDT in the treatment of cancer (see FO, pp 29, 56-64, 101, 296, 369, 494-495, and 589).

QLT PhotoTherapeutics

QLT PhotoTherapeutics (QLT; Vancouver, BC, Canada) is the only company with FDA approval to use PDT in the management of malignancy in the USA. QLT's PDT product, porfimer sodium (Photofrin), was launched in the USA in October 1996 by its strategic partner, Sanofi Pharmaceuticals, for the palliative treatment of esophageal cancer patients with totally obstructing tumors and certain partially obstructing tumors. QLT also filed an supplemental NDA to the FDA for approval of Photofrin for injection as a treatment for specific types of lung cancer. Photofrin has been approved for the treatment of early and advanced recurrent cancers of the lung and esophagus in France and the Netherlands (in 1994), where it is being marketed by Speywood Pharmaceutical (London, UK), part of Beaufour Ipsen (Paris, France), in Japan where it has also been approved for stomach, cervix, and pre-cancerous conditions of the cervix and is marketed by Lederle Japan, and in Canada for the treatment of certain types of bladder and esophageal cancers where it is marketed by Ligand Pharmaceuticals (San Diego, CA).

Photofrin has been evaluated with promising results in cancer of the head and neck in over 450 patients with primary, recurrent or metastatic disease. Early-stage cancers of the oral cavity and larynx are particularly responsive to PDT; of 171 patients with carcinoma *in situ*, or T1 or T2 HNSCC, 145 (85%) achieved CR after only one treatment. Photofrin is also effective in later stage or recurrent cancers of the head and neck, but responses are often short-lived (Biel, MA, J Clinical Laser Medicine and Surgery, 1996;14(5):239-243). QLT is contemplating phase III clinical trials in HNSCC in anticipation of filing an sNDA for this indication.

Scotia

Scotia (Guildford, Surrey, UK), in collaboration with Boehringer Ingelheim, is evaluating meso-tetra(hydroxyphenyl)chlorin (m-THPC), a second-generation photosensitizer that may have several significant advantages over the first-generation porphyrin mixtures, hematoporphyrin derivative and porfimer sodium. A pure compound, m-THPC is 100 times more phototoxic at 652 nm and 10 times more phototoxic at 514 nm, has better selectivity for early carcinomas, and a shorter duration of skin photosensitivity. The therapeutic results indicate a recurrence rate that is similar to that obtained with porphyrin sodium, i.e., about 15%.

After a phase I clinical trial demonstrated the safety of PDT using m-THPC (Foscan), a phase II clinical trial of 25 previously treated head and neck cancer patients with a synchronous or metachronous early second primary cancer was undertaken to establish optimal treatment conditions (injected dose, drug-light interval, light dose, wavelength, etc.) on 33 early squamous cell carcinomas of the mouth, esophagus, and bronchi. Best results in the bronchi and mouth were obtained with an injected m-THPC dose of 0.15 mg/kg, administered 4 days before irradiation. Of 33 lesions treated at the time of this report, 28 (85%) did not recur within a mean follow-up duration of 14 months. Photosensitivity to sunlight did not exceed 6 weeks (Savary JF, etal, Archives of Otolaryngology - Head and Neck Surgery, 1997 Feb, 123(2):162-8).

Exhibit 1
Chemotherapy Regimens in Current Clinical Trials in HNSCC

Drug/Combination Therapy Regimen	Trial Phase	# of Patients Enrolled; Indication	Results	Reference
Cisplatin (20 mg/m^2/day)+ cytarabine (Ara-C; 100 mg/day) IV x 4-5 days *q* 3-4 weeks	I/II	n=16; advanced/ recurrent disease	RR=52.5%; CR=10.5%; PR=42.1%	Icli F, etal, ASCO97, Abs. 1434:402a
Paclitaxel (Taxol) (250 mg/m^2/24 hours)	II	n=30	RR=40%	Ann Oncol 1994;5(S6): 51-54
Methotrexate (MTX) versus 2 schedules of Taxol; arm A: MTX (40 mg/m^2/ week); arm B: Taxol (3-hour 175 mg/m^2 q 3 wks); arm C: Taxol (24-hour infusion of 175 mg/m^2 *q* 3 wks)	II	n=120; recurrent disease not treated yet with chemotherapy; WHO PS ≤ 2	Arm C is most toxic; results pending	Vermorken JB, etal, ASCO97, Abs. 1463:410a
Cisplatin (25 mg/m^2/day) + 5-FU (1000 mg/m^2/day) as a 64-hour continuous infusion without (arm A) or with (arm B) folinic acid (250 mg/m^2/day)	III	n=42 (21 without 21 with folinic acid); Stage III-IV disease	Arm A: (29% did not complete treatment) RR=95%, CR=52%, PR=43%; arm B: (56% did not complete treatment because of toxicity) RR= 94%, CR=39%, PR=55%	Fonseca E, etal, ASCO97, Abs. 1428:400a
Docetaxel (60 mg/m^2) as a 1-hour infusion, *q* 3-4 weeks	II	n=26 observed for CR; WHO PS 0-2	OR=30.4% (13.2-53.0%)	Ebinhara S, etal, ASCO97, Abs. 1425:399a
Docetaxel (80 mg/m^2) on day 1 + cisplatin (40 mg/m^2) on days 1-2 + 5-FU (1000 mg/m^2) on days 1-3, IV, repeated *q* 28 days	I/II	n=21; WHO PS = 0-61	CR=25%; PR=50%; SD=19%	Janinis J, etal, ASCO97, Abs. 1436:402a
Docetaxel (25, 45, or 60 mg/m^2/day, as a 1-hour infusion) +cisplatin (25 mg/m^2/day) +5-FU (5-FU 700 mg/m^2/day, on days 2-5) + folinic acid (500 mg/m^2/day, on days 1-5), *q* 4 weeks x3	II	n=5, 3, 12 at each respective dose (17 evaluable); locally advanced, untreated, curable disease	OR=100% at primary site; CR=67%	Posner M, etal, ASCO97, Abs. 1380:387a
Ifosfamide (1.5 g/m^2/day) as a 4-hour infusion for 5 days, *q* 3 weeks	II	n=25; chemotherapy naive metastatic disease	OR=9.5%; median survival = 4 months	Bandealy MT, etal, ASCO97, Abs. 1412:396a
Vinorelbine (25 mg/m^2/day on days1-8) + cisplatin (100 mg/m^2/day on day 1) + UFT (6 mg/kg/day on days 1-21), *q* 21 days x3		n=47; Stage III (n=18), Stage IV (n=29)	CR=26%; PR=38%; SD=6%; at median 40 weeks, 40 (85%) were disease-free	Rivera F, etal, ASCO97, Abs. 1376:386a
Paclitaxel (175 mg/m^2) as a 3-hour infusion, *q* 3 weeks	II	n=26; chemotherapy naive recurrent/metastatic (n=12) and locally advanced (n=14)	RR=33.3% (41.7% in recurrent/metastatic group, 21.4% in locally advanced group)	Chi KH, etal, ASCO97, Abs. 1421:398a
Paclitaxel (high dose of 200 mg/m^2/day) + carboplatin (AUC 67 IV/day), *q* 28 days	II	n=48 (n=35 with head and neck; n=13 with nasopharyngeal) recurrent/ metastatic disease (n=19 were treated with previous chemotherapy)	Head and neck: CR=2/35 (6%); PR=6/35 (17%) nasopharyngeal: CR=2/13 (15%); PR=6/13 (46%)	Samantas E, etal, ASCO97, Abs. 1453:407a

— *continued on next page*

Paclitaxel (200 mg/m^2 as a 1-hour infusion on days 1, 22) + carboplatin (AUC 6.0 IV on days 1, 22) + 5-FU (225 mg/m^2 on days 1-25)	II	n=26; metastatic squamous carcinoma from any primary site except lung (head and neck=13); WHO PS 0-2	CR (head and neck)= 69.2%	Hainsworth JD, etal, ASCO97, Abs. 1432:399a
Paclitaxel (100-180 mg/m^2/day as a 3-hour infusion) + cisplatin (20 mg/m^2/day on days 1-3) + 5-FU (200 mg/m^2/day bolus, on days 1-3)	I/II	n=22; chemotherapy naive relapsed and/or metastatic	OR=33%; median duration of response, 26 weeks; median overall survival, 26 weeks	Benasso M, etal, ASCO97, Abs. 1415:397a
Paclitaxel (205 mg/m^2/day as a 3-hour infusion) + paraplatin (AUC 4.5), *q* 4 weeks x 3-4	II	n= 15; chemotherapy naïve, median WHO PS=1, stage II (1), III (5), IV (8)	PR=53%; CR=20%	Schwartz G, etal, ASCO97, Abs. 1455:408a
Vinorelbine (30 mg/m^2/week)	II	n=40; recurrent or metastatic disease	Well tolerated with minimal single-agent activity	Canfield VA, etal, ASCO97, Abs. 1382:387a

Key:
CR = Critical response PR = Partial response SD = Stable disease RR = Relative response WHO PS = World Health Organization performance status

COMMERCIALLY AVAILABLE AGENTS IN CLINICAL TRIALS IN HNSCC

Various commercially available chemotherapeutics addressing other cancer indications are also being evaluated in HNSCC. Results of recently reported trials are presented in Exhibit 1.

Gemcitabine

Gemcitabine (Gemzar; Eli Lilly) is a novel nucleoside analog that has been shown to have activity in numerous solid tumors. In a phase II clinical trial of previously treated HNSCC, the response rate was 18% (Catimel G, etal, Ann Oncol 1994;5:543). Gemcitabine may also act in a synergistic fashion with cisplatin as indicated from data obtained from patients with lung cancer (Crinò L, etal, ASCO95, Abs. 1066:352).

Vinorelbine

Vinorelbine (Navelbine; Glaxo Wellcome), a vinca alkaloid approved for treatment of non-small cell lung cancer (nsclc), exhibits single agent activity in head and neck cancer in 22% of cases (Invest New Drugs 1994;12:231). A much higher response rate of 55% in patients with recurrent disease, and 87% in previously untreated patients was observed when the drug was combined with cisplatin (Gebbia V, etal, Am J Clin Oncol 1995;18:293) and UFT (see FO, p 642).

Taxanes

Taxanes are also being investigated in HNSCC, and both paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Rhône-Poulenc Rorer) have shown promising results (see FO, p 641). The former was associated with a 40% response rate as a single agent (Semin Oncol 1993;20(suppl):56-60). Trials are currently ongoing to establish optimal dose schedule as well as use of taxanes in multi-agent regimens. For example, a combination of docetaxel with cisplatin, recently reported in a multi-center phase II clinical trial, achieved an overall response rate of almost 80%, although CR was only 11% (Schöffski P, etal, ASCO96, Abs. 871:310).

NOVEL CHEMOTHERAPEUTICS

Thymidylate Synthase Inhibitors

Direct thymidylate synthase (TS) inhibitors have not proven particularly superior to such indirect TS inhibitors as 5-FU, in the treatment of solid tumors. The latest casualty in this area is nolatrexed dihydrochloride (Thymitaq; Agouron Pharmaceuticals) whose development was discontinued in December 1997 while in phase II/III clinical trials being carried out in the USA, Europe and Asia (see FO pp 641-642). In addition, an agreement with Hoffmann-La Roche, entered in June 1996, providing for the collaborative development and commercialization of Thymitaq and another Agouron anti-cancer agent, AG3340, was dissolved. Roche paid an initial license fee of $15 million and was to make subsequent milestone payments of up to $40 million. Agouron said that although Thymitaq was active it did not prove more effective than competitive approaches.

Retinoids

Retinoids are being investigated both as therapeutic and chemoprevention agents (also see below).

ALRT1550, a retinoic acid receptor (RAR)-selective retinoid under development by Ligand Pharmaceuticals, exhibited potent anti-tumor activity against human oral squamous carcinoma xenografts in nude mice. ALRT1550 inhibited *in vitro* proliferation of UMSCC-22B cells in a concentration-dependent manner with an IC50 value of 0.22 +/- 0.1 (SE) nM. In comparison ALRT1057 (9-cis-retinoic acid), a pan agonist retinoid that activates

RAR and retinoid X receptors (RXR), inhibited proliferation with an IC50 value of 81+/- 29 nM. Oral administration (daily, 5 days/week) of ALRT1550, that began 3 days after tumor implantation, inhibited tumor growth by up to 89% in a dose-dependent manner over the range of 3-75 μg/kg. ALRT1550 (30 μg/kg) also inhibited growth of established tumors by 72% +/- 3% when tumors were allowed to grow to 100 mm^3 prior to treatment. In comparison, 9-cis retinoic acid (30 mg/kg) inhibited growth of established tumors by 73% +/- 5%. Interestingly, retinoids did not appear to alter tumor morphologies in these tumors (Shalinsky DR, etal, Cancer Research, 1997 Jan 1, 57(1):162-8).

GENE THERAPY

HNSCC is a suitable candidate for gene therapy for many reasons. To start with, despite improved response rates with new chemotherapy agents and combinations thereof, significant strides have not been made in improving survival. Thus, novel therapies are particularly welcome in this area. Secondly, some head and neck cancers such as those of the oral cavity, are readily accessible and, thus, easily and locally manipulated. In addition, there are theoretical advantages to working with tumors of epithelial origin, in terms of gene delivery systems using viruses. Finally, because the molecular biology of these tumors is being rapidly elucidated, many potential targets for gene therapy are being identified.

p53

Evidence suggests that p53 is involved with apoptosis induction in head and neck cancers. The first paper in the literature involving gene transfer therapy in head and neck cancer involved the *ex vivo* introduction of the p53 gene using an adenovirus vector into cells derived from a tumor cell line (Liu TJ, etal, Cancer Res 1994 Jul 15;54(14):3662-7). The observation that overexpression of wild-type (wt) p53 gene was associated with tumor growth suppression, led to the first reported human trial using gene therapy performed *in vivo* in patients with microscopic residual head and neck cancer (Clayman GL, etal, Cancer Res, 1995 Jan 1;55(1): 1-6).

Investigators at M. D. Anderson Cancer Center (Houston, TX) compared the efficacy of wtp53 with that of cell-cycle regulator p21 (WAF1/CIP1) as single-agent gene therapy for HNSCC. Wtp53 or p21 genes were transiently introduced into HNSCC cell lines using a recombinant cytomegalovirus-promoted adenovirus as the vector. Also, a nude mouse xenograft model of HNSCC was used to investigate the *in vivo* efficacy of the repeated gene therapy interventions. Western blot analysis revealed significant induction of the WAF1/CIP1 tumor suppressor gene product by both the p21 and wtp53 adenovirus (as a secondarily transcribed product). Wtp53 adenovirus significantly inhibited cell growth *in vitro*, whereas direct induction of the p21 gene product did not. Repeated infection with wtp53 adenovirus significantly reduced the size of established subcutaneous tumors, whereas infection with a replication-defective viral control did not. Wtp53 adenovirus exhibits substantial *in vitro* and *in vivo* tumor suppressor activity in HNSCC. This tumor suppression is not a function of the induced WAF1/CIP1 (p21) transcriptional product (Clayman GL, etal, Archives of Otolaryngology-Head and Neck Surgery, 1996 May, 122(5):489-93).

Introgen Therapeutics (Austin, TX), in collaboration with RPR Gencell (Santa Clara, CA), initiated a phase I/II clinical trial in 1995, involving 30 patients with recurrent head and neck cancer who were treated with Adp53 injected directly into the tumor sites (see FO, pp 642-643). In July 1997, RPR Gencell began a phase I clinical trial in head and neck cancer in Europe and may also conduct a phase II clinical trial in North America. In May 1997, RPR Gencell made a $5 million milestone payment to Introgen Therapeutics. A similar phase I/II p53 gene transfer clinical trial in solid tumors was carried out in 1995 using a retroviral vector (Rv-p53).

Schering-Plough Research Institute (Kenilworth, NJ) is investigating a gene therapy approach using a recombinant adenovirus encoding human p53 (rAd/p53) to treat solid tumors that carry p53 mutations. This technology was originally developed by Canji (San Diego, CA) that was acquired by Schering-Plough in February 1996. Clinical trials with rAd/p53 are ongoing in various indications, including phase I trials investigating intratumoral administration in head and neck cancer. In addition, animal studies were carried out with rAd/p53, in combination with paclitaxel, in various solid tumors, including head and neck cancer.

p16

Another gene therapy target is the p16 gene which is involved in the inhibition of the CDK4 system and may act as a check on cell growth (see FO pp 594 and 600). Studies at M. D. Anderson Cancer Center in this system have shown *in vitro* suppression of growth in cell lines with *in vivo* studies currently underway (Breau RL and Clayman GL, Current Opinion in Oncol;1996:8:227).

Suicide Genes

Suicide genes, when expressed, convert innocuous agents into potent cytotoxics, thus mediating selective killing of transduced tumor cells. This novel approach, although elegant in principle, has many detractors who believe it will not evolve into a practical clinical cancer management modality. Among limiting factors to date include inability to transfect sufficient tumor cells to eradicate tumors, difficulty in delivering vectors to cells of dense tumors, and preventing expression of suicide genes in normal tissues. Researchers at the University of Cincinnati (Wilson KM, etal, Arch Otolaryngology, 1996 Jul, 122(7):746-9) are testing the *in vivo* transfer of the herpes simplex thymidine kinase (hstk) gene in an attempt

Exhibit 2
Drugs in Development for the Treatment of Head and Neck Cancer

Developer ❑ Affiliates	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status ❑ Indications
Agouron Pharmaceuticals ❑ Hoffmann-La Roche (discontinued alliance (12/97)	Nolatrexed dihydrochloride ❑ AG-337 ❑ Thymitaq	Thymidylate synthase (TS) inhibitor that kills tumor cells by inducing apoptosis ❑ IV, PO, intraperitoneal, intramuscular	Phase II/III (IV)➢USA, Europe (discontinued 12/97)
Bernardo Houssay Hospital, School of Medicine, Buenos Aires University	VRCTC-310	Purified snake venom intramuscular	Phase I (5/97)➢Argentina
Canji ❑ Schering-Plough	rAd/p53	Recombinant adenovirus-mediated replacement of defective p53 with wild-type version ❑ intratumoral, bolus, intraperitoneal, intrahepatic	Phase I➢USA ❑ solid tumors
Cel-Sci ❑ Sittona Company BV, American Red Cross	Multikine	Natural mixture of cytokines such as IL-2 and certain lymphokines and other cytokines	Phase I/II (b3/95)➢Canada ❑ metastatic or newly diagnosed head and neck cancer; phase I➢USA (b5/96), Canada (b6/97) ❑ refractory head and neck cancer
Enzon	PEG-hemoglobin	Pegylated hemoglobin-based oxygen carrier ❑ infusion	Phase Ib (10/97)➢USA
GeneMedicine ❑ Boehringer Mannheim (was Corange International, now merged with Hoffmann-La Roche)	IL-2 Cancer GeneMedicine	IL-2 Cancer GeneMedicine consists of a plasmid encoding the IL-2 gene and a proprietary cationic lipid vector gene delivery system and is designed to provide sustained, localized expression of IL-2 to promote a local and systemic immune response ❑ intratumoral	Phase I (b9/97)➢USA
Genetronics (a wholly-owned subsidiary of Genetronics Biomedical)	MedPulser	MedPulser is an electroporation therapy (EPT) device that delivers a series of six pulses each lasting less than a millisecond to a tumor site; the electric field causes pores to appear on cell membranes, increasing their drug permeability; to be used in conjunction with low doses of a chemotherapeutic agent and Genetronics' proprietary needle array applicators ❑ topical injection	Phase II(b12/97)➢USA, (b11/97)➢France
Hyal Pharmaceutical	Diclofenac ❑ Oralease	Oral delivery of diclofenac using hyaluronan-induced targeting (HIT) technology ❑ PO	Phase III (96)➢Canada ❑ pain from oral ulcers; phase II (9/97)➢Canada ❑ pain from oral ulcers in head and neck cancer patients treated with radiotherapy
ImClone Systems ❑ University of California at San Diego (licensor), Rhône-Poulenc Rorer (licensor)	Anti-EGFr chimeric MAb ❑ C225	Chimeric MAbs against epidermal growth factor receptors (EGFr) overexpressed in certain solid tumors, to inhibit uncontrolled cancer cell growth	Phase Ib/IIa➢USA
Institute of Cancer Research	MAb ICR62	Rat MAb to the EGFr	Phase I/II➢UK
Introgen Therapeutics ❑ RPR Gencell, NCI, M.D. Anderson Cancer Center, Sidney Kimmel Cancer Center	Ad-p53 ❑ INGN-004	Adenoviral p53 gene therapy ❑ intraperitoneal, intralesional, intratumoral	Phase I/II (b95)➢USA; phase II (b7/97)➢Europe

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Introgen Therapeutics ❑ RPR Gencell, NCI, M.D. Anderson Cancer Center, Sidney Kimmel Cancer Center	RV-p53	Retroviral p53 gene therapy	Phase I/II (b2/95)➢USA
Lescarden	Catrix	Bovine tracheal cartilage ❑ PO	Phase II (4/97)➢USA, Canada ❑ solid tumors
Ligand Pharmaceuticals	LGD 1069 ❑ Targretin	Retinoid PO ❑ topical	Phase IIb (11/97)➢USA
Ligand Pharmaceuticals	ALRT1550	Retinoic acid receptor (RAR)-selective retinoid that potently and selectively activates RARs	
Ludwig-Maximilians-Universität (Munich, Germany)		Bispecific antibody that binds the EP-CAM on head and neck squamous cell cancer and CD3 on T lymphocytes	
Matrix Pharmaceutical	IntraDose-CDDP ❑ cisplatin/epinephrine	Biodegradable injectable gel-like matrix of cisplatin epinephrine ❑ intratumoral	Phase III (b6/95; c96)➢USA, Europe ❑ accessible solid tumors
Medarex ❑ Dartmouth Medical (licensor), Merck KGaA (licensee)	MDX-447 ❑ EMD 82633	Bispecific MAb consisting of a Trigger antibody fragment and a targeting EGFr component	Phase I/II (b9/95)➢USA ❑ cancers that overexpress EGFr
Onyx Pharmaceuticals	ONYX-015	Genetically engineered E1B-deleted adenovirus that replicates in and kills cells containing mutant p53	Phase I (b4/96)➢USA, Scotland
Pharmacyclics ❑ University of Texas (licensor), Hoechst Celanese (licensee), NCI	Gadolinium texaphyrin (Gd-Tex)	Selectively accumulates in cancer cells sensitizing them to radiation	Phase I (7/96)➢USA ❑ solid tumors
QLT PhotoTherapeutics	Porfimer sodium ❑ Photofrin	Photosensitizer ❑ injection	Phase II (c96)➢USA, Europe, (c97) Japan
Sanofi Pharmaceuticals ❑ SRI	Tirazone ❑ tirapazamine	Benzotriazine-di-N-oxide bio-reductive agent that is selectively activated to a reactive DNA-damaging species in hypoxic tumors	Phase II (6/97)➢USA
Scotia ❑ Boehringer Ingelheim	m-THPC-PDT ❑ F-9 ❑ Temoporfin/Foscan	Meso-tetra(hydroxyphenyl)chlorine-based photodynamic therapy	Phase III (12/96)➢Europe, phase I (12/96)➢USA
Sequus Pharmaceuticals	Cisplatin ❑ SPI-077	Liposomal formulation of cisplatin in long-acting Stealth liposomes ❑ intravenous (IV)	Phase I (b12/96)➢USA ❑ solid tumors
Sparta Pharmaceuticals ❑ Yale University	5-fluoro pyrimidinone (5-FP)	Pyrimidinone-based prodrug that converts into 5-FU, orally-delivered using Sparta's L.A.D.D. Technology ❑ PO	Phase I (b7/97)➢USA ❑ solid tumors
Sugen ❑ Asta Medica (Degussa)	Pan-Her Antagonist (formerly Her2 Antagonist)	Small molecule inhibitors of pan-Her	
University of Pittsburgh		Fibroblasts genetically engineered to produce IL-12 and to express two co-stimulatory molecules CD27L and B7.1	Phase I/II (6/97)➢USA , South Korea ❑ solid tumors
Vical ❑ University of Michigan	Allovectin-7	Allovectin-7 consists of a gene encoding for allogenic histocompatibility antigen, HLA-B7, in a cationic lipid vector ❑ intratumoral	Phase II (b9/95) (c12/96)➢USA ❑ solid tumors; phase I/II (o3/97)➢USA
Vion Pharmaceuticals ❑ Yale University	Porfiromycin ❑ Promycin	Bioreductive agent; destroys hypoxic tumor cells	Phase III (8/97)➢USA and Europe
Zeneca	Quinazolines	Novel class of EGF-receptor tyrosine kinase (RTK) inhibitors which are also potent and selective inhibitors of EGF-stimulated human tumor cell growth *in vitro*	Research (96)➢UK

to confer susceptibility to infected tumor cells to treatment with ganciclovir. In this approach, the mechanism of cytotoxicity involves phosphorylation of ganciclovir by the hstk gene to a compound that terminates DNA synthesis in actively dividing cells. Suicide gene approaches appear best suited for intratumoral administration in localized neoplasms such as those associated with HNSCC and brain cancer.

Onyx-015

Onyx Pharmaceuticals (Richmond, VA) is developing ONYX-015, a genetically engineered E1B-deleted adenovirus that replicates in and kills cells containing mutant p53. The specific modification of the virus prevents it from-replicating efficiently in normal cells. To take control of the cell, the adenovirus must inactivate p53 which acts to prevent abnormal DNA replication. To inactivate p53, the virus makes a protein, E1B 55k, which binds directly to p53 and blocks its function. ONYX-015 has been modified so that it cannot make E1B 55k. As a result, it cannot disarm the p53 system when it infects normal cells, and should not complete its growth cycle. However, in the majority of cancer cells, p53 is already disarmed through mutation of the p53 gene or other mechanisms. When ONYX-015 infects these cells, the virus growth cycle proceeds unchecked, eventually killing the cancer cells. It is also expected that new virus particles will be produced, and neighboring cancer cells will be infected and killed. Unlike the Introgen adenovirus, that replaces p53 and appears to have a bystander effect in which cancer cells surrounding those that are treated directly are also killed, ONYX-015 causes tumor necrosis only at the site of injection.

A phase I/II study of ONYX-015 is ongoing in patients with cancer of the oral cavity, pharynx, and larynx. Escalating doses of the agent are injected directly into the tumor in order to determine drug safety and maximum tolerated dose and to measure its biologic and therapeutic effects. Patients enrolled in the study must be at least 18 years old and have p53-deficient, recurrent, or advanced local disease which is not amenable to standard surgery and/or radiotherapy and a performance status >60% on the Karnofsky Scale.

Human Papillomavirus (HPV)

Because many human oral carcinomas express HPV RNA, the RNA transcript provides a potential target for gene therapy. Three hammerhead ribozymes targeting HPV-18 RNA, were cloned into a plasmid expression vector. Each plasmid was then transfected into the HPV-18-expressing cell line, HeLa, or the non-HPV-expressing oral cancer cell line, Tu167. None of the ribozymes had any effect on the phenotype of Tu167 cells. In contrast, each ribozyme affected the phenotype of HeLa cells, causing reduced growth rates, increased serum dependency, and reduced focus formation in soft agar. A molecule that had the same antisense sequences as a ribozyme, but lacked the catalytic sequences, affected the HeLa cell phenotype to a much lesser extent. The effects of two of the ribozymes could be attributed in part to an increased intracellular concentration of p53 protein. The most effective ribozyme was targeted to nucleotide 309 in the HPV-18 transcript, but each of the three ribozymes appears to have potential for gene therapy of cancers that express HPV-18 (Chen Z, etal, Cancer Gene Therapy, 1996 Jan-Feb, 3(1):18-23).

GROWTH FACTORS/CYTOKINES

Epidermal Growth Factor (EGF) Receptor Inhibitors

It has been demonstrated that fresh tissues and cell lines from patients with HNSCC overexpress transforming growth factor-α (TGF-α) and its receptor, the epidermal growth factor receptor (EGFr), at both the mRNA and protein levels. TGF-α and EGFr are produced by the same epithelial cells in tissues from HNSCC patients further supporting an autocrine growth pathway.

Treatment of several HNSCC cell lines with a pair of antisense oligodeoxynucleotides directed against the translation start site and first intron-exon splice junction of the human EGFr gene, resulted in decreased EGFr protein production and growth inhibition of 86% compared to a 13% reduction in cells treated with sense oligonucleotides. Growth inhibition was specific for carcinoma cells because the same EGFr antisense oligonucleotides had no effect on the proliferation of normal mucosa cells harvested from non-cancer patients.

Two monoclonal antibodies (MAbs 425 and 528) which block ligand binding to EGFr, inhibited the growth of several HNSCC cell lines by up to 97% which suggests that EGFr is participating in an autocrine pathway in HNSCC that is, at least in part, external. PD 153035, an EGFr-specific tyrosine kinase inhibitor under development by Warner-Lambert, also inhibited EGFr phosphorylation in HNSCC cell lines and reduced growth by 68%, although it had no effect on the growth rate of normal mucosal epithelial cells. These experiments indicate that EGFr gene expression and function is critical for HNSCC cell growth but not for growth of normal mucosa cells and, therefore, may serve as a tumor-specific target for preventive and therapeutic strategies in head and neck cancer (Rubin Grandis J, etal, Oncogene, 1997 Jul 24, 15(4):409-16). One EGFr antagonist, C225, under development by ImClone Systems (New York, NY), has completed phase IIa clinical trials in solid tumors (see FO, p 643).

Quinazolines, a novel class of EGF-receptor tyrosine kinase (RTK) inhibitors that are also potent and selective inhibitors of EGF-stimulated human tumor cell growth *in vitro*, have been identified by researchers at Zeneca Pharmaceuticals (Macclesfield, Cheshire, UK). Because the mitogenic action of EGF is mediated by ligand-induced autophosphorylation of the EGFr, inhibitors of receptor tyrosine kinase (RTK) activity may prove effective antitumor agents. A selected compound, 4-(3-chloroanilino)-

quinazoline (CAQ), inhibited EGF-stimulated growth in a concentration dependent manner; complete blockade was observed at concentrations (1-10 microM) which had no effect on basal growth (Wakeling AE, etal, Breast Cancer Research and Treatment, 1996, 38(1):67-73).

MDX-447, under development by Medarex (Annandale, NJ) in collaboration with Merck KGaA (Darmstadt, Germany), completed a phase I clinical trial in June 1997, involving successive groups of 36 patients with solid tumors including kidney, head and neck and bladder cancer. Patients were treated with MDX447 IV weekly (days 1, 8, 15, 22, 29, etc.) alone or with subcutaneous G-CSF (3 µg/kg/day). MDX-447 was immunologically active at all doses. There was no response in 22 evaluable patients but 15 experienced stable disease lasting approximately three to six months (Curnow, RT, etal, ASCO97, Abs. 1571:438a). Optimal dose and dose limiting toxicities have yet to be defined.

MAb ICR62, the first rat monoclonal antibody to the EGFr, was clinically evaluated in a phase I trial in patients with unresectable squamous cell carcinomas by investigators at the Institute of Cancer Research (Sutton, UK). This antibody effectively blocks binding of EGF, TGF-α and HB-EGF to the EGFr, inhibits growth *in vitro* of tumor cell lines which overexpress EGFr, and eradicates such tumors when grown as xenografts in athymic mice. Among 11 patients with HNSCC and 9 patients with squamous cell carcinoma of the lung, whose tumors expressed EGFr, 12 were separated into groups of 3 patients and treated with 2.5 mg, 10 mg, 20 mg, or 40 mg of MAb ICR62, and the remaining 8 patients were treated with 100 mg. No serious Grade III-IV toxicities were observed in patients treated with up to 100 mg of MAb ICR62 which was detected at 4 hours and 24 hours in the sera of patients treated with 40 mg or 100 mg, respectively. Human anti-rat antibody (HARA) responses occurred in 4 of 20 patients (one at 20 mg, one at 40 mg, and two at 100 mg doses) and, of these, only the former two were anti-idiotypic responses. In 4 patients treated with 40 mg or greater doses of MAb ICR62, biopsies confirmed localization of MAb ICR62 to the membranes of tumor cells; this phenomenon appeared to be more prominent at the higher dose of 100 mg (Modjtahedi H, British Journal of Cancer, 1996 Jan, 73(2):228-35).

Interferon as Adjuvant Therapy

Newer approaches to adjuvant therapy are also being reported. For example, 13-cis-retinoic acid combined with interferon α-2b (Intron A; Schering-Plough) is currently being investigated in a phase II pilot clinical trial. Eight patients in complete remission with Stage III/IV head and neck cancer were treated and compared to 23 eligible patients who declined participation in the trial. The disease-free survival at 28 months was 74% versus 52%, in favor of the treated group (Sanders D, etal ASCO96, Abs.874:311). Because of promising results, plans are under way for a larger trial. Intron A was also effective as an induction agent followed by chemotherapy and radiation (see FO, p 643).

Tumor Necrosis Factor α (TNF-α)

Tumor necrosis factor alpha (TNF-α) induces apoptotsis in HNSCC cell lines. TNF-α, at a concentration of 10,000 U/ml induced cytotoxic effects of varying sensitivities in all 4 cell lines (UMSCC-1, UMSCC-8, UMSCC-19, and CAL-27) investigated. Significant cytotoxic effects required 3 to 4 days of exposure. TNF-α induced double-stranded DNA fragmentation consistent with apoptosis. Further studies are needed to elucidate the role of TNF-α in HNSCC *in vivo* (Briskin KB, etal, Archives of Otolaryngology, Head and Neck Surgery, 1996 May, 122(5):559-63).

IMMUNOTHERAPY/VACCINES

Cel-Sci

Cel-Sci (Alexandria, VA) is developing Multikine (see FO, p 314, 321, 455) for treatment of various solid tumors. Approved by the FDA in February 1996, a phase I clinical trial is being conducted at Wayne State University (Detroit, MI), involving up to 30 patients who failed conventional therapies. In September 1996, Cel-Sci announced that the Sir Mortimer B. Davis Jewish General Hospital, Lady Davis Institute for Medical Research (Montreal, Quebec, Canada) and Hamilton Regional Cancer Centre (Hamilton, Ontario, Canada) were also added sites for the trial.

In March 1997, Israeli health authorities approved a clinical trial of Multikine in newly diagnosed head and neck cancer; a trial of 10 patients was initiated in April 1997, being conducted by Dr. Raphael Feinmesser at the Rabin Medical Center (Petach-Tikva, Israel) at Tel Aviv University which is expected to conclude by the end of 1997. The protocol calls for Multikine treatment of newly diagnosed patients divided into two dosage groups, before they are treated with surgery or radiation. Multikine therapy is administered during the first two weeks, with surgery or radiation to follow during the third week. In September 1997, Cel-Sci also started a clinical trial of Multikine, designed to enroll 14 patients with newly diagnosed squamous cell carcinoma of the oral cavity, in conjunction with surgery or radiation, at Hospital Notre Dame (Montreal, Canada) under principal investigator Dr. Louis Guertin. Approval to initiate this study was obtained from the Canadian HPB in June 1997.

In October 1997, Dr. Raphael Feinmesser presented initial results in head and neck cancer at the First Annual Congress on Multikine, held in Alexandria, VA. All of the first 4 patients treated experienced substantial tumor reductions in a period of only 3 weeks, at which point the clinical protocol required that surgery or radiation be performed. Tumor reductions were achieved with no side effects. Also, in head and neck cancer trials Multikine reduced

or eliminated pain from the tumors and in addition, some patients noted improvement in their ability to talk, chew, and swallow, which had been compromised by the tumor.

GeneMedicine

GeneMedicine (The Woodlands, TX) is developing IL-2 Cancer GeneMedicine, which comprises a plasmid encoding the IL-2 gene and a proprietary cationic lipid vector gene delivery system and is designed to provide sustained, localized expression of IL-2 to promote a local and systemic immune response. The company obtained clearance from the FDA in January 1997 and began a phase I clinical trial in September 1997 in approximately 12 head and neck cancer patients which is expected to last 6 months. A second trial is also planned in Germany.

In July 1995, GeneMedicine entered into a collaboration with Boehringer Mannheim (was part of Corange International which has since merged with Hoffmann-La Roche) to research and develop gene-based medicines for the treatment of head and neck cancer and melanoma. Within the initial three years of the collaboration, Boehringer Mannheim has an option to expand the agreement to include additional cancer indications. Pursuant to the agreement, GeneMedicine could receive over $47 million in research, development, and equity funding by the year 2000. When products enter phase II trials, GeneMedicine may elect either to receive up to 50% of profits by agreeing to share development and commercialization expenses, or receive royalty payments based on worldwide product sales. In February 1997, Corange purchased $4 million of GeneMedicine's Common Stock at $7.50 per share. As of July 1997, Corange made payments of $25 million ($13 million in R&D payments and $12 million in equity).

University of Pittsburgh

Michael Lotze, MD, and colleagues at the University of Pittsburgh are using autologous fibroblasts genetically engineered to produce IL-12 that when injected into various solid tumors, including head and neck cancer, cause established tumors to regress and appear to induce tumor-specific immunity. In a phase I/II clinical trial, 18 patients were treated with four peritumoral injections of *ex vivo* transduced fibroblasts at escalating doses, on a weekly basis. To date, reductions in tumor size of 50% or more at the site of the injection and at distant sites were observed in one patient with recurrent melanoma, 3 with head and neck cancer, and one with breast cancer. A similar trial is underway in South Korea that is evaluating production of larger amounts of IL-12 levels by administration of higher doses of the transduced fibroblasts.

MANAGEMENT OF TREATMENT-RELATED COMPLICATIONS

Various agents are in development to prevent/ameliorate various oral complications of radiation therapy, including dry eye and xerostomia (dry mouth), oral inflammation, ulceration and pain. Salagen, developed by MGI Pharma (Minneapolis, MN), has been available in the USA since 1994, after obtaining FDA approval in March 1994, for treatment of dry mouth and eyes attributable to radiotherapy in head and neck cancer. Salagen was also launched in Canada in 1997 by Pharmacia & Upjohn, MGI's marketing partner, for radiotherapy-induced dry mouth in cancer patients. Salagen will be marketed in Europe, by Chiron and in Japan by Kissei that is still conducting clinical trials with the agent.

Amifostene

Amifostene (Ethyol; U. S. Bioscience), a cytoprotective, is being evaluated in a multi-center randomized clinical trial in patients with head and neck cancer. It is suggested that pretreatment with amifostine may reduce some of the side effects of radiation therapy, such as inflammation and dryness of the mouth. Enrolled patients are being randomly assigned to either radiation treatment plus amifostine or radiation treatment alone.

Lisofylline

Lisofylline, a synthetic small molecule drug, under development by Cell Therapeutics (CTI; Seattle, WA), is targeting mucositis resulting from chemotherapy and radiation therapy. In November 1996, CTI entered into a collaboration and license agreement with Ortho Biotech (Raritan, NJ) and the R. W. Johnson Pharmaceutical Research Institute (Raritan, NJ) for the joint development and commercialization of lisofylline to prevent or reduce toxic side effects in cancer patients treated with high dose radiation and/or chemotherapy followed by bone marrow transplantation (BMT) and in patients with acute myelogenous leukemia (AML) undergoing high dose chemotherapy. Johnson & Johnson (J&J) paid a $5.0 million license fee and purchased 14,925 shares of CTI's newly issued Series B Convertible Preferred Stock at $335 per share for an aggregate purchase price of $5 million. J&J has agreed to fund 60% of CTI's development expenses relating to obtaining regulatory approval for lisofylline in the USA and has agreed to fund CTI development expenses of up to $12 million annually for 1997 and 1998. CTI is responsible for the development of lisofylline in the USA and will manufacture lisofylline for development and commercialization purposes until November 1999, with J&J assuming responsibility thereafter. CTI and J&J will co-promote lisofylline in the USA. J&J has the exclusive right to develop and market lisofylline, at its own expense, for markets outside North America, subject to royalty and milestone payments.

Oralease

Hyal Pharmaceutical (Mississauga, Ontario, Canada) is developing Oralease, a proprietary oral gel formulation of the NSAID diclofenac, using its hyaluronan-induced targeting (HIT) delivery system for the relief of pain in head and neck cancer caused by oral ulcers attributable to radiotherapy. As of May 1997, Oralease has been available

to patients in Canada under the Canadian Emergency Drug Release (EDR) program. Under EDR, a physician may request Oralease for cases refractory to alternative drugs or patients may request Oralease from their physician. In 1996, Hyal announced that in a single center phase III clinical trial, Oralease was superior to both placebo and lidocaine in providing sustained pain relief from oral ulcers. Also, pain relief experienced with Oralease was not accompanied by the usual anesthetic side effects associated with lidocaine.

DRUG DELIVERY

Genetronics

Genetronics (San Diego, CA) is developing an electroporation drug delivery system that was shown effective in solid tumors such as head and neck, pancreatic, liver and prostate cancer and melanoma and may be applicable in other accessible solid tumors such as breast and brain cancer. Electroporation involves the application of instantaneous, controlled electrical pulses to cells to open cell membrane pores which promotes tissue entrance of a previously injected anti-cancer drug. A study conducted at Genetronics demonstrated that *in vitro* killing power of some chemotherapeutic agents can be substantially enhanced by pulsed electric fields. In the breast cancer cell line, MCF-7, cytotoxic enhancement was found to be the highest with bleomycin, and with some concentrations of mitomycin-C (Nanda GS, etal, AACR97, Abs. 1745:260). In another Genetronics-sponsored preclinical study, conducted at the University of South Florida, a total of 151 rats with liver cancer were treated with EPT and either of five chemotherapeutic agents; bleomycin demonstrated a 69% CR rate and cisplatin a 50% CR rate (Jaroszeski M, etal, AACR97, Abs. 1744:259).

In a phase I/II study, conducted by Dr. William Panje at Rush Presbyterian St. Luke's Medical Center (Chicago, IL) between the end of 1996 and the beginning of 1997, 5 of 10 patients with HNSCC, treated regionally with bleomycin, experienced CR and 3 PR. In late 1997, Genetronics commenced a 25-patient phase II clinical trial in the USA and a 30-patient trial in France in late-stage HNSCC and it is seeking orphan drug status for the product. Abbott Laboratories (Abbott Park, IL) agreed to supply the bleomycin.

CHEMOPREVENTION

Chemoprevention and differentiation therapy is particularly relevant in HNSCC because premalignant lesions are easily detectable in accessible regions of the head and neck; both leukoplakia and erythroplakia are considered to be premalignant, with histologic features of hyperplasia and dysplasia. Also, such factors as tobacco or alcohol abuse or certain viral infections, that have been linked to the development of HNSCC, may be used as a means of selecting candidate populations for chemoprevention.

Various agents have been studied as chemopreventatives in HNSCC. Studies have shown that vitamin E supplementation is associated with a reduced risk of oral cancer. Also, a diet high in fresh fruits and vegetables, vitamin A and C, and carotenoids may have protective effects against oral cancer. However, the carotenoids may enhance tumor growth under the appropriate carcinogenic environment (Schwartz JL and Shklar G, Nutrition and Cancer, 1997, 27(2):192-9). Retinoids have been shown to reverse histologic changes in 55-100% of cases (Devita, Principles of Oncology, 5th edition, 1997). Although it was demonstrated that treatment with isotretinoin at high doses is associated with a 67% response rate, regression occurs in 50% of the patients after withdrawal of therapy (NEJM 1986;315:1501). In a more recent study lower maintenance doses of isotretinoin avoided toxicities of prolonged high dose therapy and resulted in a progression rate of only 8%, compared to 55% seen with β-carotene (NEJM 1993;328:15). Also, it has been shown in clinical trials that although daily treatment with isotretinoin (13-cis-retinoic acid) for one year significantly reduced incidence of second tumors, it had no demonstrated beneficial effect on survival (Hong WK, etal, NEJM 1990; 323(12):795-801; Fitzpatrick PJ, etal, Journal of Radiation Oncology, Biology, Physics 1984; 10(12):2273-2279; Black RJ, Clinical Otolaryngology and Allied Sciences 1983; 8(4): 77-281).

MEETING COVERAGE

OPPORTUNISTIC INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

FROM THE 37TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC), TORONTO, ONTARIO, CANADA, SEPTEMBER 28-OCTOBER 1, 1997

Infections whether bacterial, viral, or fungal in general, and drug-resistant infections, in particular, continue to be a major cause of morbidity and mortality in immunocompromised patients. This article highlights developments relating to treatment strategies in cancer patients with febrile neutropenia or who are otherwise immunocompromised, For more information regarding infectious diseases in cancer patients and their treatment, please see FO, pp 127-129, 159-164 and 402-407.

Bacterial Infections

Gram-positive bacteria such as staphylococci and enterococci, account for 47% to 52% of nosocomial blood stream infections and approximately 30% of all nosocomial infections in the USA. In Europe almost 50% of all infections in intensive care units are attributed to staphylococci. Streptococci infections are also becoming increas-

ingly problematic because of modified virulence of *Streptococcus pyogenes* strains and of *Streptococcus viridans* infections that cause potentially fatal bacteremia in neutropenic hosts. All these organisms are developing resistance to available antimicrobials. Enterococci are becoming resistant to glycopeptides (vancomycin and teicoplanin), staphylococci to penicillinase-resistant penicillins (oxacillin and methicillin) and fluoroquinolones (ciprofloxacin and ofloxacin), and *Streptococcus viridans* to penicillin and some other β-lactams (Cormican MG and Jones RN, Drugs, 1996, 51 Suppl 1:6-12).

Although gram-positive bacteria are the predominant organisms causing bacteremia in febrile neutropenic cancer patients, an increase in gram-negative bacteremia was observed in children and adolescents with cancer at the University of Texas Southwestern Medical Center (Dallas, TX). A study that reviewed 153 episodes of bacteremia in the pediatric oncology unit during a 6-year period, found that over the January, 1988 to December, 1990 period, gram-positive organisms comprised 73 (74%) of the 99 isolates, with *Staphylococcus epidermidis* being the most common isolate. However, in the January, 1991 to December, 1993 period, gram-negative organisms were seen with greater frequency and represented 50% of isolates with *Pseudomonas aeruginosa* being most common (22% of all isolates). It is hypothesized that use of more intensive chemotherapy, in the later period, resulted in an alteration in the epidemiology of bacteremia, influencing antibiotic regimens and the outcome of such infections (Aquino VM, etal, Pediatric Infectious Disease Journal, 1995 Feb, 14(2):140-3).

In 1996, researchers at the Arkansas Cancer Research Center (Little Rock, AR) observed a 24% increase, from 17% to 41%, in gram-negative bacteremias. The most frequently isolated organisms were waterborne pathogens such as *Stenotrophomonas maltophilia, Acinetobacter spp.,* and *Klebsiella pneumoniae.* Patients who cared for their own central venous catheters were more prone to develop bacteremia attributable to these pathogens (Penzak SR, etal, ICAAC97, Abs. J-213:328).

Risk Factors For Gram-Positive Infections

In profoundly neutropenic patients, several risk factors have been identified for gram-positive infections, depending on the organism. Incidence rate and risk factors were evaluated in 513 consecutive neutropenic patients (PMN<500/mm^3), who were followed for one month. Prevalence of risk factors were compared between gram-positive and non-gram-positive, non-gram-negative bacterial infections. The major underlying diseases were leukemia (57%) and lymphoma or myeloma (31%). In this group of patients, 33% had microbiologically documented infections with 21% (108 patients) having gram-positive infections attributed to staphylococci (13%), streptococci (7%), or both (0.7%). Thirty-day mortality rates were comparable in those with gram-positive infections (7%) and other types (5%). Multivariate analysis pointed out that the major risk factors associated with streptococcal infection were use of proton pump inhibitors, high dose cytosine arabinoside and oral colimycin as well as diarrhea and non-absorbable decontamination. In the case of staphylococcal infections, there was significant association with mucositis and inflammation of the catheter insertion site (Cordonnier C, etal, ICAAC97, Abs. J-89:304).

Capnacytophaga Bacteremia

A retrospective review strongly suggests that capnacytophaga bacteremia is associated with specific clinical symptoms in neutropenic patients, particularly children. While *Capnocytophaga sp.,* a capnophilic gram-negative rod, is known to cause periodontal and respiratory tract infections in immunocompetent hosts, the pathogenic significance of bacteremias reported in such hosts has not been elucidated. In an attempt to gain insight, a retrospective study was carried out in 13 patients with hematologic cancers such as acute leukemia (n=11) or lymphoma (n=2) who were found to have 16 episodes of capnocytophaga bacteremia. Positive blood cultures were collected 1 to 22 days after the beginning of aplasia. In 10 of the 13 patients, oral mucositis (WHO Grade II to IV) was observed and capnocytophaga was occasionally cultured from mouth samples. Predisposing factors for capnacytophaga bacteremia appeared to be treatment with cytosine arabinoside and broad-spectrum antibiotics.

Several of the isolated capnocytophaga strains were resistant to cefotaxime (Claforan; Hoechst Marion Roussel), ceftazidine, aztreonam (Azactam; Bristol-Myers Squibb), amikacin, and netilmicin (Netromycin; Schering). In these strains, further studies suggested presence of an extended broad spectrum β-lactamase. Empiric antibiotic treatment with a third generation cephalosporin and an aminoglycoside was initiated before capnacytophaga isolation in 12 of the 16 episodes. In 8 of the episodes, specific secondary antibiotic treatment was initiated with imipenem (Primaxin; Merck) and an aminoglycoside. All of the patients recovered from aplasia, and outcomes of the infections were all favorable, albeit, there were two late relapses (Lancry L, etal, ICAAC97, Abs. J-90:304).

The Growing Problem of Vancomycin-resistant Enterococci

Over the last 5 years, vancomycin-resistant enterococci (VRE) have disseminated throughout the USA and Europe. Between 1989 and 1995, prevalence of VRE increased 30-fold, from 0.3% to 10.8% of all nosocomial infections, mostly occurring in immunosuppressed or post-surgical patients, or in patients exposed to those infected with VRE. Although most VR *E. faecalis* still remain relatively susceptible to penicillin and ampicillin that are treatment mainstay, VR *E. faecium* are often resistant to β-lactams and most other antimicrobials making them virtually untreatable and resulting in extremely high mortality rates. Indeed, occasional infec-

tions caused by these organisms are now seen that are resistant to all commercially available antimicrobial agents. Although these instances are relatively rare, they are undoubtedly the beginning of an ominous trend.

Risk factors associated with VRE include prolonged hospitalization, prior antibiotic use, and serious underlying illness (Noskin GA, J Laboratory and Clinical Medicine, 1997 Jul, 130(1):14-20). In an analysis of 102 patients with vancomycin-sensitive enterococcus (VSE) and 100 patients with VRE, significant risk factors for VRE included hospitalization prior to infection (92% versus 74%), length of hospital stay prior to infection (19 days versus 5 days), antibiotic use prior to infection (92% versus 67%), concomitant infection (72% versus 59%), invasive procedure prior to infection (53% versus 35%), nosocomial acquisition (91% versus 73%), duration of ventilation (18 days versus 0.5 days), and location in respiratory unit at time of infection (10% versus 3%) (Curbelo DE, etal, ICAAC97, Abs. J-38:295).

The Minnesota Department of Health conducted a statewide hospital-based surveillance for VRE isolates from normally sterile sites or wounds. From July 1995 to March 1997, 142 cases were reported with results available for 105 (74%). Fifty-one different subtypes of VRE were found. Sixty-two of the cases fit into clonal Group A which includes *E. faecium* isolates with a VanA phenotype and were found in 10 hospitals in the Twin Cities metropolitan area; 15 isolates fit into 6 smaller clonal groups, and 28 were not clonally related, indicating the emergence of multiple clones of VRE (Lexau CA, etal, ICAAC97, Abs J-29:293).

In February 1994, an outbreak of VR *E. faecium* occurred in cancer patients at a hospital in Dublin, Ireland. Within 5 months, this pathogen was isolated from 18 patients, one staff member and 14 sites within the unit. Isolates exhibited high-level aminoglycoside and penicillin resistance. A retrospective study of enterococci isolated from blood cultures between January 1991 and January 1994, revealed that incidence of high-level gentamicin resistance increased from 17% to 60% and ampicillin resistance from 22% to 51% (Lavery A, etal, Journal of Medical Microbiology, 1997 Feb, 46(2):150-6).

Treatment options for VRE are becoming increasingly limited. A variety of regimens incorporating combinations of cell-wall active antimicrobials, among them vancomycin (Vancocin; Eli Lilly), ampicillin, penicillin, or imipenem, have been used but there are no published data on their effectiveness in humans. Teicoplanin (Hoechst Marion Roussel), usually used in combination with an aminoglycoside, was successfully used in 27 cases of wound infections and bacteremia caused by VRE exhibiting the VanB phenotype (highly resistant to vancomycin, sensitive to teicoplanin). Bacteriological eradication and/or cures was achieved in 23 individuals. However, resistance emerges when teicoplanin is used alone in this setting.

In addition to antimicrobial therapy, other interventions may also be important in the management of infections attributed to VRE. In point of fact, removal of foreign objects such as intravenous catheters and other prosthetic devices that often serve as a focus of infection, may even result in a cure. Many studying the epidemiology of infections in hospitalized patients believe that increased use of intravascular devices is the primary reason for the rise of CNS blood stream infection, as well as bacteremias, in intensive care units. Also, surgical debridement is crucial in the therapy of intra-abdominal, pelvic, and wound infections caused by enterococci.

The Centers for Disease Control and Prevention (CDC; Atlanta, GA) have issued guidelines restricting use of vancomycin to prevent emergence of resistance. However, it appears that these guidelines are not fully and uniformly implemented in hospitals across the country. Also, better infection control could limit spread of these deadly organisms.

Quinupristin/dalfopristin (Synercid, Rhône-Poulenc Rorer), an investigational drug combination, has shown considerable promise in the treatment of infections caused by VRE, demonstrating good activity against VR *E. faecium* (see FO, pp 159-164 and 402-407). This new injectable streptogramin, representing a new class of antimicrobial agent, has been successful, to date, in approximately 70% of more than 400 patients with VR *E. faecium* infection enrolled in open-label, emergency-use studies. Based on findings from these studies involving 1,199 patients treated in the USA, Canada, and Europe, an NDA was filed with the FDA on September 8, 1997 for use in a variety of infections including pneumonia, bacteremia, and skin infections, as well as for the treatment of infections caused by VR *E. faecium,* methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis,* and drug-resistant *Streptococcus pneumoniae,* in patients allergic to penicillins, cephalosporins, quinolones, or glycopeptides.

LY 333328, a new glycopeptide developed by Takara Shuzo (Otsu, Shiga, Japan) and licensed to Eli Lilly outside Japan, has shown *in vitro* activity in a variety of vancomycin-resistant gram-positive organisms including VR *E. faecium* (Cheron M and Boivison A, ICAAC97, Abs. F-8:147). In serious MRSA infections in animal models, activity of LY 333328 was found to be equivalent to that of vancomycin (Kaatz GW, etal, ICAAC97, Abs. F-11:148). When the *in vivo* efficacy of LY333328 and vancomycin against VRE were compared in a neutropenic mouse model, LY333328 eliminated mortality and significantly reduced the amount of bacteria present in the blood to the point of no detection at 48 hours in all 27 mice. In contrast, vancomycin was ineffective in 12 of the 13 mice in this treatment group were bacteremic at 48 hours, and 2 mice died at 96 hours. These results are consistent with the *in vitro* data (Schwalbe RS and Iarocci TR, ICAAC97, Abs. F-13:148).

Daptomycin, a natural product that exerts its antibiotic action by inhibiting cell wall synthesis and disrupting membrane permeability, was shown effective against gram-positive bacteria. Originally under development by Eli Lilly, it was licensed, in November 1997, to Cubist Pharmaceuticals (Cambridge, MA) that plans to develop an oral formulation of the drug for treatment of VRE infections.

Linezolid, an oxazolidinone, is under development by Pharmacia & Upjohn for treatment of serious staphylococcal, streptococcal and enterococcal infections, including resistant organisms such as VRE. An intravenous formulation of the drug, administered every 12 hours for 16 doses to 17 males and 1 female, was well tolerated in both 500 and 625 mg doses. The only adverse effect was possible discoloration/coating of the tongue and a fine papular rash predominantly on the trunk. The drug's elimination half-life was about 4.5 hours for both single-dose and steady-state conditions, and was independent of dose (Stalker DJ, etal, ICAAC97, Abs A-116:23). An oral formulation of the drug is also being investigated.

Ziracin (SCH 27899), an everninomycin with activity against gram-positive bacteria, is a novel oligosaccharide antibacterial under development by Schering-Plough, in a phase I clinical trial against VRE and MRSA infections.

Other agents include the fluoroquinolones trovafloxacin (Trovan; Pfizer) and oral and IV versions of clinafloxacin (CI-960; Warner-Lambert). Trovafloxacin is currently awaiting FDA action for a variety of indications, including severe infections but it is not expected to be launched until 2000. Clinafloxacin is currently in phase III clinical trials. MDL63246, a novel thiazolopeptide under development by Hoechst Marion Roussel, has also demonstrated activity against staphylococci and enterococci.

Vancomycin-Intermediate *Staphylococcus aureus*

The first isolation of a strain of *Staphylococcus aureus* with intermediate resistance to vancomycin has been reported, pointing to the need for stringent surveillance and control measures. The gram-positive microorganism, labelled *S. aureus* SA 14342, was isolated from a 59-year-old man with metastatic lung cancer and end-stage renal disease on peritoneal dialysis, with a history of repeated episodes of peritonitis while on a 6-month vancomycin therapy. Cultures also yielded other strains of staphylococci with low (2.0 μg/ml) and intermediate (8.0 μ/ml) MICs, as well as VR *E. faecium*. For *S. aureus* SA 14342, MICs to vancomycin by tube dilation, Microscan, and E-test were 8.0 μg/ml. The isolate was susceptible *in vitro* to low concentrations of a number of antimicrobial agents including trimethopim/sulfamethoxazole (Septra; Glaxo Wellcome and Bactram; Roche) with MIC less than .05 μg/ml, rifampin (Rifadin; Hoechst Marion Roussel), Synercid (MIC 0.5 μg/ml), tetracycline (MIC 1.0 μg/ml), clinafloxacin (MIC 1.0 μg/ml), and arbekacin (MIC less than 0.12 μg/ml), a drug on the market in Japan, supplied by Meiji Seika Kaisha (Tokyo, Japan). It was resistant to all other agents including teicoplanin (MIC 16.0 μg/ml) (Robinson-Dunn B, etal, ICAAC97, Late Breaker 14).

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is usually nosocomial, but incidence in the community is increasing. Between 1975 and 1991, nosocomial prevalence increased from 2.4% to 29% of *S. aureus* infections. The National Nosocomial Infection Surveillance data shows that MRSA currently causes 40% of nosocomial *S. aureus* infections in large hospitals in the USA. Infection commonly occurs within 2-3 days of admission to an institutional setting. Transmission of MRSA usually occurs from the hands of health care professionals, and is greatly enhanced with nasal carriage if the worker develops an acute viral respiratory infection (Boyce JM, etal, ICAAC97, Abs. S-40:390).

Treatment of MRSA consists of vancomycin, quinolones or rifampin or trimethoprim/sulmethoxazole (TMP/SMX), or newer agents such as teicoplanin or streptogramins. However, patients with MRSA may also be resistant to many of the standard therapies including clindamycin and although most infections are susceptible to vancomycin, low-level resistance has been reported in Japan and the USA (Alangaden GJ and Lerner SA, Infectious Diseases, Sep 1997; 4(1): 1-2).

Other Bacterial Infections in Cancer Patients

Penicillin-resistant Streptococcus pneumoniae (PRSP) prevalence has grown 60-fold, from 2% of *S. pneumonia* infections in 1979 to 30% in 1992. Hospitalized and immunosuppressed cancer patients are at high risk for this infection. Penicillin-resistant cases who acquire pneumococcal meningitis must be treated with vancomycin and cefotaxime or ceftriaxone as initial empiric therapy. However, 10% of PRSP patients are resistant to cefotaxime and ceftriaxone. Further treatment is based on modified penicillin and third generation cephalosporin therapy with meropenem used, if necessary, as an alternate agent. In the case of pneumococcal pneumonia or bacteremia, treatment consists of high-dose penicillin G or another appropriate β-lactam antibiotic.

Stenotrophomonas maltophilia is an opportunistic gram-negative pathogen infecting immunocompromised hosts. *S. maltophilia* is an emerging pathogen in cancer patients with hematologic conditions and is associated with high morbidity and mortality. Immediate administration of TMP/SMX or piperacillin-tazobactam is the best chance to improve outcome in these patients. Ninety episodes of *S. maltophilia* in 88 cancer patients were analyzed to determine relevant clinical factors that may be associated with immunosuppression. In 57% of the episodes infections arose during neutropenia; 35% involved the bloodstream, 14% the skin and soft tissues, 15% the urinary tract or lungs, and 19% were disseminated.

There was a 71% response rate to TMP/SMX or ticarcillin-clavulanate (Vartivarian SE, etal, ICAAC97, Abs. J-92:305).

Among 44 cases of *S. maltophilia,* identified in patients with hematologic malignancies at the University of Rome La Sapienza, acute leukemia was the underlying disease in 65% of patients who were treated with intensive cytotoxic chemotherapy within one month preceding onset of bacteremia. Of the 50% of patients who were not treated with an agent to which the isolate was susceptible, 59% (13/22) survived and 41% (9/22) died. However, of the 15 patients treated with an antimicrobial agent that demonstrated *in vitro* activity against the isolate, 12 survived (80%); all other patients died within 14 days of onset of *S. maltophilia* (Micozzi A, etal, ICAAC97, Abs J-208:327).

Pseudomonas aeruginosa, a gram-negative organism, has also been seen in cancer patients. In a review of 246 episodes of *P. aeruginosa bacteremia* in hospitalized patients at M. D. Anderson Cancer Center between 1991 and 1995, the bacteria was most commonly observed in patients with acute leukemia. Of those, 72% had been treated with chemotherapy during the last month, and 36% had been treated with antibiotic therapy for another infection during the previous week. Shock occurred in 21% of the patients and pneumonia in 40%. The cure rate was 84% for patients receiving the appropriate antibiotic and 38% for those receiving an inappropriate antibiotic. A 1- to 2-day delay in administering the appropriate antibiotic caused the cure rate to decrease from 85% to 48%. Patients with shock or pneumonia had a significantly lower response rate than those without either condition. Patients treated with an antipseudomonal β-lactam antibiotic with or without an aminoglycoside had a significantly higher cure rate than patients administered only an aminoglycoside (Chatzinikolaou I, etal, ICAAC97, Abs. J-91:305).

FUNGAL INFECTIONS

Invasive fungal infections currently represent a serious health problem because they are becoming increasingly common in immunocompromised hosts. Numerous fungi with clinical significance have been identified, but the primary offenders are *Candida albicans* and aspergillus infections which are uniformly fatal when they invade the central nervous system. Fungal infections in immunocompromised hosts are difficult to prevent/treat and are associated with significant morbidity and mortality.

Candida Fungi

Candida fungi, more than half of which are *Candida albicans,* are responsible for up to 28% of microflora contaminations, either as monoculture or in association with bacteria, which cause infection in cancer patients undergoing therapy (Smolianskaia AZ, etal, Klinicheskaia Laboratornaia Diagnostika, 1996 Jan-Feb;(1):30-2).

Over the last 7 years, the reported incidence of *Candida krusei fungemia* (CKF) in immunocompromised cancer patients has increased dramatically. Between 1989 and 1996, 60 cases were identified at University of Texas M.D. Anderson Cancer Center, and medical records were obtained on 58. Researchers attribute the increase in admissions from 2.5/100 patients in 1989-1992 to 5.7/100 patients in 1993-1996 to the widespread use of fluconazole prophylaxis. Indeed, 92% of the identified cases were administered fluconazole prophylaxis prior to onset of fungemia (90% were neutropenic, and 76% had leukemia as the underlying cancer). Disseminated infection occurred in 43% (24/58) of these patients, septic shock in 13% (18/58) and death related to CKF occurred in 48% (28/58) of patients. Most of the patients were treated with amphotericin B and failure to respond to this regimen was directly related to persistence of neutropenia and presence of disseminated infection. It is, therefore, important to recognize the opportunity of CKF infection in immunocompromised patients treated with fluconazole prophylaxis because the infection is associated with serious complications (Abbas J, etal, ICAAC97, Abs. J-63:300).

A study was done to evaluate the outcome of neutropenic cancer patients with candiduria for which recommended therapy includes systemic antifungals. In 173 cases of neutropenia, 52 (30%) of patients who presented with at least 1 positive urine culture of *Candida* species, were treated with empirical amphotericin B more often than patients without candiduria (38% versus 18%). Among those infected, 75% developed fever. Of 20 patients empirically treated with amphotericin B, 3 developed systemic candidiasis whereas none of the other 32 infected patients who were not treated with amphotericin B developed candidiasis (Nucci M, etal, ICAAC97, Abs J-181:322).

Zygomycosis

In zygomycosis that is most commonly (60% of cases) attributed to *Rhizous arrhizus,* pathogens invade vascularly to produce immediate tissue thrombosis and necrosis. The host sites for infection are at the nasal sinus, brain, lung, eye, kidney, skin, subcutaneous tissue, and multiple systemic sites, presenting as rhinocerebral infection (Kwon-Chung KJ and Bennett JE, Medical Mycology 1992:524-559). Most infections occur in immunocompromised patients who must be treated with aggressive antifungal therapy.

Fusarium

Fusarium is an emerging ominous pathogen in patients with hematologic malignancies. Fusarium which may mimic aspergillosis causes serious morbidity and mortality. In a retrospective study of invasive fusarial infections in 43 immunocompromised patients with hematologic malignancy with disseminated or invasive lung infection, 13 patients responded to therapy but two

subsequently relapsed. Response was noted in 4 patients administered granulocyte transfusions, 4 administered amphotericin B lipid formulations, and 2 administered an investigational triazole. Resolution of infection was observed in patients who recovered from myelosuppression. This infection responds only to newer therapeutic approaches in patients who ultimately recover from myelosuppression, but relapse is common if neutropenia recurs (Boutati EI and Anaissie EJ, Blood, 1997 Aug 1, 90(3):999-1008).

Antifungals in Development

Numerous antifungals are in development to meet the emerging need to combat fungal infections in immunocompromised patients.

Nyotran (AR-121), a liposomal intravenous formulation of the topical antifungal nyastatin, is under development by Aronex Pharmaceuticals (The Woodlands, TX) in collaboration with M. D. Anderson Cancer Center, for empiric therapy of presumed fungal infection. Phase I clinical trials demonstrated that Nyotran may be administered at doses that may be effective in treating aspergillus and candida infections. In a phase II/III clinical trial, Nyotran was administered to 33 seriously ill hospitalized patients at a dose of 2 mg/kg daily for a median of 13 days; 74% of the evaluable patients treated with Nyotran responded to therapy and remained free of infection 6 weeks after treatment. Multi-center phase III clinical trials, designed to compare Nyotran to amphotericin B in approximately 200 immunocompromised cancer patients with presumed systemic fungal infections, were in progress in Europe and USA as of August 1997. In May 1997 Aronex signed an agreement with Grupo Ferrer Internacional (Spain) to commercialize Nyotran in Spain and Portugal.

Echinocandin derivatives are lipopeptide antifungals that inhibit the synthesis of (1,3)β-D-glucan, an essential cell wall homopolysaccharide present in many pathogenic fungi. These compounds, that appear to be active against systemic candidiasis and aspergillosis, lack mechanism-based toxicity and may prove effective against drug-resistant strains.

LY303366, under development by Eli Lilly, is a semisynthetic lipopeptide antifungal related to echinocandin B (ECB), which exhibits broad-spectrum antifungal activity (Pfaller MA, etal, ICAAC97, Abs. F-68:157). This drug is in phase II clinical trials.

L-743,872, a water-soluble pneumocandin, is another echinocandin derivative with potent antifungal activity under development by Merck. This drug is in phase II clinical trials. *In vitro* antifungal activity of L-743,872 was demonstrated against a variety of clinically important fungi, including various aspergillus species but appeared to lack significant *in vitro* inhibitory activity against fusarium and *Rhizopus arrhizus* (Del Poeta M, etal, Antimicrobial Agents and Chemotherapy, 1997 Aug, 41(8): 1835-6). This antifungal was also effective against candida species in animal models and *in vitro* (Graybill JR, etal, Antimicrobial Agents and Chemotherapy, 1997 Aug, 41(8):1775-7 and Vazquez JA, etal, Antimicrobial Agents and Chemotherapy, 1997 Jul, 41(7):1612-4). L-743,872 was also shown to enhance the activities of amphotericin B and fluconazole *in vitro* against *Cryptococcus neoformans,* a difficult to treat pathogen in AIDS patients.

SCH 56592, a novel triazole derivative with a broad spectrum of activity is under development by Schering-Plough. It was highly effective in a neutropenic murine model of invasive aspergillosis (Oakley KL, etal, Antimicrobial Agents and Chemotherapy, 1997 Jul, 41(7):1504-7).

Sordaricin derivatives GM193663, GM211676 or GM 237354 that selectively inhibit fungal protein synthesis, under development by Glaxo Wellcome (Madrid, Spain), exhibit a broad spectrum of activity. GM 237354, a tetrahydrofuran sordarin derivative, was shown effective in animal models against *Candida albicans* (Martinez A, etal, ICAAC97, Abs. F-60:156) but showed modest activity at high concentrations in a neutropenic murine model of aspergillosis.

Novel Antifungal R&D Programs

RiboGene (Hayward, CA) focuses on the discovery and development of new classes of compounds that inhibit or interfere with translation, the downstream process by which genetic information stored in DNA is converted into functional units known as proteins. The company's proprietary technology targets proteins necessary for growth of pathogens and has established antibacterial, antifungal, and antiviral drug discovery programs. In its antibacterial program, RiboGene has two targets, deformylase and ppGpp degradase, that are in the lead discovery phase, and several others that are in the assay development phase. In its antifungal program, two targets, EF3 and GCN4, are at the lead optimization phase and several others are in various phases of development.

In April 1996, RiboGene entered into a collaboration with Abbott Laboratories (Abbott Park, IL) in its antifungal program. As part of this collaboration, Abbott has agreed to provide RiboGene with $5.0 million in research support payments and fund additional research and development at Abbott, including lead optimization. RiboGene is also entitled to milestone payments upon the achievement of mostly late-stage regulatory milestones in the amount of up to $9.0 million for each product developed through the collaboration. Abbott also made a $3.5 million equity investment in RiboGene and agreed to purchase an additional $4.0 million of the company's shares at the initial public offering price. RiboGene has also entered into agreements with ArQule (Medford, MA), Pharmacopeia (Rockville, MD), and Trega Biosciences (was Houghten Pharmaceuticals; San Diego, CA) to gain access to additional compound libraries for its drug discovery programs.

Millennium Pharmaceuticals (Cambridge, MA) recently merged with ChemGenics Pharmaceuticals (was Myco Pharmaceuticals; Cambridge, MA), a company involved in the development of novel antifungals. The merger closed in February 1997 with the shareholders of ChemGenics receiving 4.8 million unregistered shares of Millennium common stock in exchange for all of ChemGenics outstanding stock.

ChemGenics focuses on delineating the genetic structure of fungi. Using information on fungal genes essential for the viability of pathogens, provided by ChemGenics, scientists from both companies are collaborating to design new broad spectrum fungicidal drugs that are less susceptible to resistance. ChemGenics is also collaborating with researchers at Imperial College (London, UK) and Colorado State University (Fort Collins, CO) on one antifungal, papuamine, which is in preclinicals. In March 1995, ChemGenics and Pfizer entered into a 4-year agreement to develop therapeutics to treat various infections including cryptococcal meningitis and systemic candidiasis. Pfizer's total equity investment and R&D funding is estimated at more than $20 million and milestone payments could exceed $30 million, depending on the number of drugs developed. ChemGenics will also receive royalties on sales of commercialized products as well as options for future manufacturing and marketing rights.

In December 1996, ChemGenics also entered into a 5-year strategic alliance with Wyeth-Ayerst in the area of antibacterial drugs which included $20 million in committed funding with additional payments for achieving research and product development milestones and royalties on the sale of products derived from the collaboration. As of October 1997, Wyeth-Ayerst Research had accepted three antibacterial drug targets and paid Millennium milestones for each target drug and a bonus for delivering the targets in less than one year.

Alpha-Beta Technology (Worcester, MA) develops novel classes of proprietary drugs composed of complex carbohydrates. In addition to Betafectin PGG-glucan, a proprietary carbohydrate immunotherapeutic for infectious disease indications, the company is pursuing a discovery program in immunomodulation as well as direct inhibition of fungal and cell-wall synthesis.

In October 1997, Alpha-Beta's wholly-owned subsidiary MycoTox (Denver, CO) was awarded four phase I Small Business Innovation Research (SBIR) grants by the NIH, totaling $400,000, to identify and develop novel chemical entities exhibiting antifungal activities against pathogenic fungi. Two of the grants are for the development of novel *in vitro* screens that target two signal transduction kinases identified by Alpha-Beta that are essential for cell-wall assembly and cell viability. With the first grant, the company will develop *in vitro* enzyme assays to screen compounds for inhibitors of each novel kinase activity. With the second grant, Alpha-Beta/MycoTox will develop novel screens that target the expression of each of two genes essential for cell-wall assembly, (1,3)β-glucan synthase and an osmosensor histidine kinase.

The third SBIR grant, which was awarded in collaboration with Montana Biotech (Belgrade, MT), is part of Alpha-Beta/MycoTox's natural product screening program to identify new chemical entities exhibiting antifungal activities from extremophiles (microorganisms that are adapted to living in a broad range of extreme and harsh habitats). These extracts provided by Montana Biotech have never been screened for antifungal activity and, therefore, represent a rich source of diverse bioactive compounds. Alpha-Beta/MycoTox is using its comprehensive screening program, MycoSelect, to detect antifungal activity in these extracts which will be purified for use in Alpha-Beta/MycoTox's antifungal drug development program.

Alpha-Beta/MycoTox is also engaged in developing zeamatin, a novel antifungal cationic protein belonging to the thaumatin-like pathogenesis-related (PR)-5 protein family, produced by *Zea mays*. Zeamatin, causes fungal membrane permeability changes and has potent *in vitro* fungicidal activity. Researchers at MycoTox have obtained zeamatin from the fungus *Neurospora crassa,* by introducing a chimeric gene construct comprised of a DNA plasmid, pGEZ, that was constructed by inserting zeamatin-encoding cDNA into an expression cassette containing the promoter, a truncated open reading frame, and the terminator sequence of the *N. crassa* glucoamylase gene. Zeamatin-encoding cDNA was modified at the N terminus to include a kex-2 protease site, allowing cleavage of the chimeric product in the secretory pathway. Secreted zeamatin was active in inhibiting the growth of *Candida albicans in vitro*, indicating that zeamatin was correctly synthesized, processed, and secreted by *N. crassa* (Rasmussen-Wilson SJ, etal, Applied and Environmental Microbiology, 1997 Sep, 63(9):3488-93). The company has received an SBIR grant to test the antifungal activity of zeamatin in animal fungal infection models.

THERAPEUTIC APPROACHES FOR OPPORTUNISTIC INFECTIONS

Bacterial Infections

Cefepime (Maxipime; Bristol-Myers Squibb), a fourth generation injectable cephalosporin is administered as first-line monotherapy in the treatment of acute febrile neutropenia. Maxipime was shown to be as effective and better tolerated than imipenem-cilastatin (Primaxin IV; Merck) in a large-scale study conducted by 17 French centers involving 400 febrile patients with neutropenia of short duration, to compare the effects of cefepime and imipenem-cilastatin as empiric monotherapy on febrile episodes following chemotherapy for solid tumors, lymphoma, or myeloma. All patients were randomly assigned to cefepime (2.0 gm) twice daily or imipenem-cilastatin (1.0 gm) thrice daily (50 mg/kg/day) and response to monotherapy was assessed 7 days post-treatment. Response

was based on resolution of fever, signs and symptoms, eradication of pathogens, absence of new infection, relapse, and death attributable to infection.

Among 344 (86%) patients evaluable for response, successful monotherapy was reported in 79% treated with cefepime and 72% by imipenem-cilastatin; additional antibiotics, mostly glycopeptides, were administered in 20% and 21% of patients, respectively. The overall response rate to therapy, with or without added antibiotics, was 95% in the cefepime group and 90% in the imipenem group. Survival was similar in both groups (95% versus 98%). Interestingly, cefepime was significantly better tolerated, with 9% of patients on cefepime experiencing adverse events compared to 19% of those treated with imipenem-cilastatin. In this regard, nausea and vomiting were significantly more frequent in the imipenem-cilastatin group, 15% versus 5% for cefepime (Biron P, etal, ICAAC97, Abs. LM-48:373).

In May 1997, Maxipime was approved for the supplemental indication of monotherapy for empiric treatment of febrile neutropenic patients (based on the dose regimen discussed above), and is the first antibiotic to be approved for this indication. Empiric therapy is necessary in immunocompromised hosts because they often go into septic shock and die before the offending pathogen is definitively identified. Cefepime is approved in more than 20 countries for this indication. It was approved in the USA in early 1996 and entered the market during the third quarter of 1996, for treatment of moderate to severe pneumonia, including pneumococcal bacteremia, and urinary tract and skin and skin-structure infections.

Ciprofloxacin (Cipro; Bayer Pharmaceuticals), administered in combination with piperacillin (Piperacil; Lederle) for the empiric treatment of fever in neutropenic cancer patients, is as effective as the commonly used combination approach of tobramycin (Nebcin; Lilly) and piperacillin, without concerns of aminoglycoside-induced ototoxicity or nephrotoxicity. In a prospective, randomized, double-blind, multi-center trial, 543 febrile and neutropenic patients under treatment for leukemia, lymphoma, or solid tumors, or undergoing BMT, were randomly assigned to IV piperacillin (50 mg/kg), every 4 hours, plus either IV ciprofloxacin (400 mg) every 8 hours, or IV tobramycin (2 mg/kg) every 8 hours. Serum concentration of all agents was monitored.

Overall, 470 patients, 233 in the ciprofloxacin/piperacillin group and 237 in the tobramycin/piperacillin group, were evaluable for efficacy. The success rate was statistically equivalent between the 2 treatment groups, 27% in those treated with ciprofloxacin and piperacillin compared to 22% for those on tobramycin and piperacillin. In addition, no difference in survival was noted (93% versus 92%). Median time to fever resolution, however, was significantly lower in the ciprofloxacin/piperacillin group (Peacock JE Jr., etal, ICAAC97, Abs. LM-49:373).

Thirty oncology patients with solid tumors treated with high dose chemotherapy and ciprofloxacin prophylaxis were assessed for suspected emergence of quinolone resistant *E. coli* in faecal flora. Ciproflaxacin prophylaxis lasted for a median period of 7 days (range 2-12). Quinolone-resistant *E. coli* emerged in 11 (36.6%) patients, however, in 81.8% of those patients, colonization by resistant *E. coli* was transitory, lasting only up to 3 months before becoming susceptible again. The presence of *E. coli* resistance did not correlate with a worse outcome (Perea S, etal, ICAAC97, Abs. E-10:115).

Viral Infections

Penciclovir (PEN, Vectavir; SmithKline Beecham), administered intravenously every 12 hours, is a well tolerated and effective therapy for mucocutaneous herpes simplex virus (HSV) infection in immunocompromised hosts. Furthermore, on this schedule, PEN offers a reduced frequency dosing regimen compared to standard dosing of every 8 hours for acyclovir (Zovirax; Glaxo Wellcome). To ascertain the efficacy and safety of PEN for the treatment of HSV infections, 342 immunocompromised patients with mucocutaneous HSV infection were enrolled into a double-blind, acyclovir-controlled, multicenter study and randomized to either IV PEN (5 mg/kg) every 8 or 12 hours or IV acyclovir (5 mg/kg) every 8 hours. Treatment was initiated within 72 hours of lesion onset and continued for up to 7 days. The main reasons for the hosts' immunocompromised state were hematologic disorders (63%) or transplantation plus hematologic disorders (16%). The primary endpoint was new lesion formation, with secondary endpoints being viral shedding, healing, and pain.

Either PEN regimen (every 8 or 12 hours) proved to be equivalent to acyclovir administered every 8 hours, with respect to the proportion of patients who developed new lesions during therapy (approximately 20% in each treatment group). In addition, for all 3 treatment regimens, the median time to cessation of viral shedding was 4 days and the median time to complete healing was 8 days. Furthermore, there were no statistically significant differences between PEN every 12 hours, PEN every 8 hours, or acyclovir every 8 hours, with respect to resolution of pain. PEN was well tolerated at both dosages, with an adverse event profile comparable to acyclovir (Lazarus H, etal, ICAAC97, Abs. H-72: 226).

Reusser and colleagues (ICAAC97, Abs. H-77:227) investigated the antiviral activity of PEN and its oral prodrug famciclovir (FAM) against cytomegalovirus (CMV), following allogeneic bone marrow or peripheral blood stem cell transplantation. Eleven patients were administered IV PEN (10 mg/kg) as a 1-hour infusion every 8 hours, from 7 days prior to transplant to 30 days after, at which time IV PEN was replaced by oral FAM (750 mg tid) for 2 additional months. Five of the 11 patients were treated with subsequent FAM for a median duration of 5 weeks. Severe adverse events during both treatments

included graft-versus-host disease (n=6), stomatitis (n=3), veno-occlusive disease (n=2, fatal in 1 case), and anxiety (n=2); all side-effects were judged to be unrelated to the study drugs. Although none of the patients developed CMV disease during PEN or FAM treatment, CMV antigenemia occurred in 55% (5/11) of patients at a median of 33.5 (range 25-54) days after transplant.

Fungal Infections

In a review of 24 randomized trials (2,758 patients, 434 deaths) comparing antifungal agents, prophylactic or empirical treatment with antifungals had no effect on mortality. However, results from some small studies indicate that amphotericin B may significantly decrease mortality, but further investigation is needed to confirm these findings. On a positive note, antifungal therapy decreased incidence of invasive fungal infection and colonization (OR 0.47, 95% CI 0.35-0.64) (Johansen HK and Gotzsche PC, ICAAC97, Abs. LM-89:381).

Liposomal amphotericin B (AmBisome; NeXstar and Fujisawa) proved to be as therapeutically successful as conventional amphotericin B (Fungizone; Apothecon) for empirical antifungal therapy in persistently febrile neutropenic patients, with the added advantages of being superior in reducing proven treatment-emergent fungal infections, nephrotoxicity, and infusion-related toxicity.

To determine the efficacy and safety of AmBisome compared to conventional amphotericin B, 687 neutropenic patients with persistent fever present after 96 hours of antibacterial therapy, were randomly assigned to at least one dose of AmBisome (3 mg/kg/day) or conventional amphotericin B (0.6 mg/kg/day), with a mean duration of therapy of 10.8 days for AmBisome and 10.3 days for conventional amphotericin B. The baseline profile (demographic baseline characteristics, underlying neoplasia, antifungal prophylaxis) of the two groups were comparable.

The composite success rate was equivalent, being 50% in the AmBisome-treated patients and 49% in those on conventional amphotericin B. Comparable responses also were observed in the two groups for survival rate (93% versus 90%), resolution of fever during neutropenia (58%), and premature drug withdrawal because of toxicity or lack of efficacy (14% versus 19%). By contrast, there were significantly fewer proven treatment-emergent fungal infections in patients treated with AmBisome (16 patients or 5%) compared to those on conventional amphotericin B (32 patients or 9%), as assessed by independent blinded investigation. This reduced risk was independent of risk of infection, age group, or prior use of antifungal prophylaxis.

With respect to the drugs' adverse event profiles, there was a significant reduction in the frequency of infusion-related fever (17% versus 44%), chills and rigors (18% versus 54%) and cardiovascular events such as dyspnea, hypotension, tachycardia, hypertension, and hypoxia (13.1% versus 45.6%) in the AmBisome and conventional amphotericin B groups, respectively. Furthermore, there was a significant reduction in development of nephrotoxicity in AmBisome-treated patients (19%) compared to the conventional amphotericin group (34%) (Walsh T, etal, ICAAC97, LM-90:381).

AmBisome, developed by NeXstar Pharmaceuticals (Boulder, CO), was approved by the FDA for empiric therapy of presumed fungal infections in immunocompromised patients as well as treatment of patients with fungal infections refractory to amphotericin B. It is marketed in Europe by NeXstar and co-marketed in the USA with Fujisawa, a co-developer of the drug. Other liposomal formulations of amphotericin B include Amphocil (Sequus Pharmaceuticals) and Abelcet (Liposome Company; Princeton, NJ). Abelcet was approved in the USA for treatment of invasive aspergillosis in November 1995 and, in October 1996, for expanded indications, including candidiasis, cryptococcal meningitis, zygomycosis, and fusariosis in patients refractory to or intolerant of conventional amphotericin B. Worldwide sales of Abelcet were $52.8 million in 1996, $44.8 million in the USA and $8 million abroad. Amphocil, one of the first liposomal formulations to be approved and launched worldwide (in the UK in 1994), was launched in the USA in December 1996 after gaining FDA approval in November 1996. It is marketed in Europe by Zeneca.

Aerosol amphotericin B prophylaxis did not confer benefit in an unblind prospective clinical trial of 227 neutropenic patients randomized to 20 mg aerosol amphotericin B for the prevention of invasive aspergillus infection, and 155 to no inhalation prophylaxis. Fewer pneumonias resulted in the first group (19% versus 30%). The overall incidence of infection was 4% and 7%, respectively, with 4 proven, 5 probable and one possible episode(s) occurring in the first group compared to one proven, 9 probable, and one possible occurrence in the second group. Neither infection-related mortality nor overall mortality differed between the two study arms. Thirty-two percent of the patients in the treated arm discontinued aerosol amphotericin B early, because of nausea, cough, or "bad taste" (Heinemann V, etal, ICAAC97, Abs. LM-87:381).

Fluconazole (Diflucan; Pfizer) is the leading systemic antifungal with worldwide 1997 sales forecast at $930 million, up from $910 million in 1996. Fluconazole prophylaxis decreases *Candida albicans* colonization, preventing acquisition and persistence of yeasts in the lower gastrointestinal (GI) tract and reducing occurrence of invasive fungal infections in neutropenic cancer patients. To evaluate the impact of fluconazole prophylaxis on fungal colonization in cancer patients with neutropenia, 304 individuals were enrolled in a prospective, randomized, double-blind, placebo-controlled, multi-center trial, and were randomly assigned to oral fluconazole (400 mg) once daily or placebo, initiated at the beginning of intensive cytotoxic therapy and lasting until marrow recovery or prophylaxis failure.

Among 270 evaluable patients, *Candida albicans* colonization was reduced from 29% to 11% by fluconazole prophylaxis compared to an increase from 33% to 58% in the placebo group. Colonization by non-albicans candida increased from 8% to 22% and from 8% to 18% in the fluconazole and placebo groups, respectively. Definite or probable invasive fungal infections were documented in 41 patients, 9 of whom were on fluconazole prophylaxis and 32, who were on placebo. Relative risks for definite or probable fungal infections in placebo and fluconazole-treated patients with colonized rectal swabs were 3.79 and 1.70, respectively. Surveillance cultures of different body sites indicated a colonization index at the end of prophylaxis of 0.39 in the placebo group and 0.15 in those on fluconazole prophylaxis (Laverdiere M, etal, ICAAC97, Abs. LM-85:380).

Granulocyte-macrophage colony stimulating factor (GM-CSF, Leukine; Immunex) administered subcutaneously, in combination with traditional surgical and medical treatment, is highly effective in achieving resolution of rhinocerebral and disseminated mucormycosis (RDM) in immunocompromised patients. RDM, a rare opportunistic infection, occurs exclusively in immunocompromised patients with severe neutropenia, diabetes, or corticosteroid therapy being major risk factors. Despite aggressive surgical treatment and use of amphotericin B, RDM is associated with a greater than 50% mortality rate. Because several case reports had pointed to successful use of GM-CSF plus conventional antifungal therapy for several other fungal infections, 4 consecutive patients with RDM were treated with subcutaneous GM-CSF in combination with aggressive surgery and a formulation of amphotericin B. Three of the 4 patients were treated successfully (Palau LA and Pankay GA, ICAAC 97, Abs. LM-55:374).

Voriconazole (UK-109,496), an antifungal under development by Pfizer, is in phase III clinical trials. Voriconazole inhibits the growth and alters the morphology of fluconazole-susceptible and resistant *Candida spp.* (Belanger P, etal, Antimicrobial Agents and Chemotherapy, 1997 Aug, 41(8):1840-2. In *in vitro* studies, when voriconazole was compared to amphotericin B, fluconazole, and itraconazole, voriconazole MICs were lower than those of fluconazole in all instances and in most instances, MICs were lower than those of amphotericin B and itraconazole (McGinnis MR, etal, Antimicrobial Agents and Chemotherapy, 1997 Aug, 41(8):1832-4).

Voriconazole exhibited potent activity against clinical isolates of *Aspergillus spp. in vitro*. Also, in an animal model of invasive pulmonary aspergillosis, daily oral voriconazole (30 mg/kg) significantly delayed or prevented mortality (Murphy M, etal, Antimicrobial Agents and Chemotherapy, 1997 Mar, 41(3):696-8). An anecdotal report of successful treatment of cerebral aspergillosis with voriconazole in a patient with acute leukemia illustrates the potential of this fungicide (Schwartz S, etal, British Journal of Haematology, 1997 Jun, 97(3):663-5). Also, voriconazole was 10 to 100 times more potent than fluconazole when tested against 249 isolates of *Candida spp.* representing 6 species. Strains with decreased susceptibility to fluconazole were inhibited by relatively low concentrations of voriconazole (Barry AL and Brown SD, Antimicrobial Agents and Chemotherapy, 1996 Aug, 40(8):1948-9).

Itraconazole oral solution (IOS) was compared with placebo in a randomized, double-blind study involving neutropenic patients with hematologic malignancies. A total of 405 patients were enrolled with 201 assigned to IOS (2.5 mg/kg bid) and 204 to placebo; all patients were also treated with oral nystatin (500 IU qid) and ciprofloxacin (500 mg bid). Suspected deep fungal infections were detected in 21% of those administered IOS and 29% of those on placebo. Fifteen (7.5%) IOS patients died during the trial and 33 (16%) stopped therapy because of adverse effects, compared to 8.8% and 14%, respectively, among those on placebo. IOS reduced incidence of deep fungal infections and appeared to be safe and well tolerated (Del Favero A, etal, ICAAC97, Abs. LM-84:380).

Azole-based prophylaxis was effective in substantially reducing superficial and invasive fungal infection and fungal infection-related mortality, according to a meta-analysis of 4,147 neutopenic cancer patients (Bow EJ, etal, ICAAC97, Abs. J-91:380).

New Spectrum of Opportunistic Infections in Fludarabine-Treated CLL

Although fludarabine (Fludara; Berlex) is generally well tolerated, its use in pretreated chronic lymphocytic leukemia (CLL), particularly in combination with prednisone, has increased the risk of infection with pathogens associated with T cell dysfunction, including listeriosis and *Pneumocystis carinii* pneumonia. Advanced CLL and prior cytotoxic therapy appear to be predisposing factors for increased susceptibility to infection.

To determine the risk factors for infections in patients with CLL treated with fludarabine, a retrospective evaluation was carried out on 402 patients with CLL (not previously treated or treated with standard therapy) who were treated at 4-week intervals with fludarabine, with or without prednisone. Risk factors were determined by multivariate analysis. Infections occurred more frequently in those pretreated with cytotoxic chemotherapy (47%) than in untreated patients (24%). In addition, involved pathogens that were not traditionally associated with CLL included *Listeria monocytogenes, P. carinii,* varicella zoster virus, fungi, and mycobacteria. Furthermore, fungal infections and infections caused by unusual pathogens such as *P. carinii, L. monocytogenes,* cytomegalovirus (CMV), and mycobacteria, occurred more frequently in pretreated patients. Listeriosis and pneumocytosis occurred in 6% of the 170 pretreated patients administered

Exhibit 3
Cost comparison of Inpatient Antibiotic Regimens in Neutropenic Patients

Outcome	Treatment Regimen		
	Ceftazidime	Ceftriaxone	Imipenem
Drug failure	10%	45 %	9%
Adverse effects	9%	23%	40%
Successful treatment	55%	41%	64%
Average direct cost ($)	4,582	5,271	4,294
Cost difference from imipenem treatment ($)	288	977	N/A

fludarabine plus prednisone but in none of the 154 untreated individuals and in only 1 of 78 pretreated patients administered fludarabine alone.

Also, among 158 patients whose CD4 counts were measured after 3 cycles of therapy, 5 of 19 (26%) with CD4 counts under 50 cells/ml developed cutaneous zoster compared to only 9 of 139 (6%) with a CD4 count greater than 50 cells/ml. Univariate analysis of risk factors identified prior chemotherapy, advanced Rai stage, failure to respond to fludarabine, elevated serum β_2 microglobulin, low serum albumin, elevated serum creatinine, and poor performance status, as risk factors for these infections. After multivariate analysis, risk factors were identified as advanced Rai stages, prior treatment, and elevated serum creatinine (Anaissie EJ, etal, ICAAC97, Abs. J-88:304).

Fungal Pneumonia

Over a 5-year period, 767 neutropenic patients with unexplained fever (<1,000 neutrophils and 38.5ºC) following intensive chemotherapy for hematological malignancies, were assessed for suspected fungal pneumonia to determine the effect of antifungal therapy. Patients were randomized to either piperacillin/aminoglycoside treatment or a third generation cephalosporin (ceftazidime or cefotaxim) with an aminoglycoside. Response to initial therapy was 65.3% (including 14% with modification); 2.2% died and no significant difference was observed between initial treatment regimens. If no response was observed within 72 hours, patients were randomized to imipenem/glycopeptide (IMI+GLP) or IMI+GLP + amphoterin B + 5-flucytosine (5FC), or IMI+GLP + fluconazole. In the 155 patients treated with antifungals in addition to IMI+GLP, response rates were significantly higher (55.6% versus 77.8% and 62.5%, for additional antifungals, respectively). However, the response rate between the two antifungal regimens was not significantly different, concluding that either empirical antifungal therapy improves the response rate in neutropenic patients with unexplained fever not responding to antibacterial first line therapy. Patients with lung infiltrates (n=98) were treated with amphoterin B or amphoterin B + 5FC added to initial therapy or IMI+GLP, respectively. The addition of 5FC did not significantly affect response rate (Link H, etal, ICAAC97, Abs. LM-47:372-373).

Costs Associated with Anti-infective Therapy in Neutropenic Patients

A retrospective cost-effectiveness analysis, including direct costs as well as treatment outcome, compared ceftazidime, ceftriaxone, and imipenem regimens administered to 176 hospitalized febrile neutropenic patients (see Exhibit 3). Despite a higher incidence of adverse effects, treatment of febrile neutropenia appears to be most effective and cost-efficient with imipenem (Dietrich ES, etal, ICAAC97, Abs. N-18:385).

A cost-benefit analysis comparing an inpatient versus outpatient treatment approach for low-risk cancer patients with febrile neutropenia was performed at the University Hospital of Heraklion in Crete, Greece. Patients were randomized to inpatient IV treatment (91 patients) of ceftazidime + amikacin, or outpatient PO treatment (92 patients) of ampicilin/sulbactam + ciprofloxacin. Outpatient therapy was as effective as inpatient therapy (92% and 91% response, respectively). However, outpatient oral antibiotic therapy was less costly (median cost $1,300, mean cost $1,130, range $375-$1,667 per episode) than inpatient IV therapy (median cost $1,750, mean cost $1,585, range $790-$2,500 per episode) (Anaissie EJ, etal, ICAAC97, Abs. LM-51:373).

To determine the cost-benefit of enhanced infection control strategies (EICS) for the prevention of VRE transmission within an adult oncology unit, the annual cost of EICS was compared to savings that would result from fewer patients with VRE infection, fewer VRE colonized patients, and less vancomycin use. The excess length of hospital stay associated with infection was calculated using a mixed effect ANOVA linear regression model for 37 infected patients matched with 37 controls. The annual cost of EICS was $116,813 and resulted in 8.5 fewer infected patients and 40 fewer VRE colonized patients per year. Length of hospital stay was 26.3 days for infected patients and 12.6 for controls. The reduction in infection and colonization resulted in a total annual savings of $157,977, concluding that EICS effectively reduced nosocomial transmission of VRE with a positive cost-benefit ratio of 0.74 (Montecalvo MA, etal, ICAAC97, Abs. J-84:303).

Editors Note: *Next three FO issues will cover primary and metastic CNS cancer.*

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