the degree to which they do so nor the significance of these effects is well known. Beyond that, each agent has its own specific effects, particularly if it is a manufactured peptide or synthetic. For instance, tumor necrosis factor has caused cerebellar ataxia (a muscle coordination problem originating in the brain). Marimastat has prompted tenosynovitis in the shoulder or hands; and, besides sedation, thalidomide causes peripheral nerve damage and constipation. Folkman, however, exults that certain of the compounds demonstrate low toxicity. He noted that in some trials, patients have used the drugs for a year without discontinuation. "Nurses report that patients don’t lose their hair. They’re not scared to come back [for additional treatment]," he said. Despite unsolved questions, the bubbling pace of angiogenesis research represents a sort of vindication for Folkman and other researchers who got into the game early on. When Folkman first began espousing his ideas, he inspired mostly ridicule. Folkman still has one grant application that was returned with the comment: "An angiogenic factor exists only in the mind of the principal investigator." He does not yet claim the last laugh. But he does admit, in an understated way, to the thrill of it all. "One cannot transmit the excitement," he said.

— Jan Ziegler

Topotecan: After FDA and ASCO, What’s Next?

Even standing room was scarce at the May meeting of the American Society of Clinical Oncology when James Carmichael, M.D., described the pivotal trial of topotecan that brought U.S. Food and Drug Administration approval of the drug for marketing on May 29. Carmichael, from the University of Nottingham, England, presented data comparing topotecan (Hycamtin®) to paclitaxel (Taxol®) for treatment of advanced, recurrent ovarian cancer. Topotecan produced a 21% overall response rate in the 226-patient, randomized trial compared with a 13% rate for paclitaxel; a median duration of response of 32 versus 20 weeks; and median time to progression of 23 versus 14 weeks.

While these data drew a large crowd, it may have been the next steps planned for topotecan that roused the most intense interest at ASCO. "It is exciting that oncology is finally getting an approved topoisomerase inhibitor," said David Alberts, M.D., of the Arizona Cancer Center, Tucson. "Now we can study it."

Carmichael said at a press briefing that one next step for the drug’s manufacturer SmithKline Beecham, Philadelphia, is a trial comparing topotecan against paclitaxel as the initial therapy for advanced ovarian cancer in combination with cisplatin. That multi center trial will enroll 400 patients, the first of whom was entered shortly after the ASCO meeting, Carmichael said in an interview.

Alberts, too, said that he sees topotecan “moving up very quickly to front-line treatment studies.” Chairman of the gynecologic cancer committee of the Southwest Oncology Group and member of the ovarian cancer committee in the Gynecologic Oncology Group, Alberts said a special SWOG/GOG subcommittee is now discussing study designs to look at initial treatment with topotecan. One possibility, he said, would be to use topotecan as a consolidation therapy — meaning soon after initial therapy, rather than waiting for the cancer to recur. In this scenario, topotecan might be used just a few months after a standard initial regimen such as paclitaxel and cisplatin. "I feel strongly about [trying topotecan soon after other therapies]," Alberts said. "We have to get away from the concept of six courses of treatment and then stopping, because we already know what happens when we do that." The cancer recurs in 75% to 80% of patients with advanced (stage IIIB and IIC) disease, he said. Consolidation therapy might reduce that recurrence rate substantially.

Oral Version

Another goal is to develop a form of topotecan that could be given orally instead of intravenously, and one such formulation is under study for treatment of recurrent ovarian cancer, Carmichael said. Other trials, still in the planning
stage, will look at the drug in combination with agents such as cyclophosphamide and etoposide.

Numerous drugs are now available for treating recurrent ovarian cancer, Alberts pointed out. Three of them — altretamine, etoposide, and liposomal doxorubicin — have, like topotecan, shown activity against platinum- and paclitaxel-resistant tumors, he said. Topotecan, developed initially by the National Cancer Institute, is the first drug approved that stops tumor growth by inhibiting the enzyme topoisomerase I.

Alberts, who was a discussant on the ASCO papers on ovarian cancer, noted that it is now important to look at topotecan versus longer infusions of paclitaxel. The SmithKline study used a 3-hour infusion of paclitaxel — the standard established by the Gynecologic Oncology Group trial published earlier this year — rather than the 24-hour infusion that some think may be more effective.

Further in the future might be trials looking at different schedules for administering topotecan. A paper presented by Howard Hochster, M.D., of New York University Medical Center, reported data showing that a continuous 21-day infusion of topotecan produced an overall response rate of 37% in a phase II study of 16 patients with recurrent ovarian cancer. “This is one of the highest response rates we’ve seen for any second-line therapy,” Hochster said.

— Caroline McNeil

Middle Eastern Nations Sign Milestone Pact to Collaborate

In a milestone scientific agreement in the Middle East, the Ministers of Health of Cyprus, Egypt, Israel, Jordan, and the Palestinian National Authority created the Middle East Cancer Consortium on May 20, 1996.

Building on the example of an earlier nongovernmental endeavor, this National Cancer Institute-led initiative sets a precedent, bringing together forces on an official level to combat a disease whose burden is expected to grow in the Middle East in the near future.

“This consortium will help build bridges of understanding and teamwork so that, together, we can defeat one of our greatest enemies: cancer,” said U.S. Health and Human Services Secretary Donna Shalala, who witnessed the signing as the official U.S. representative at the U.S. Mission in Geneva. “I am very pleased that our National Cancer Institute will play an important part in [it].”

National Cancer Institute Director Richard Klausner, M.D., who also attended, said “This is the first government-level, ministerial level agreement in the Middle East which will set up an infrastructure for epidemiology, for registries, for screening, for investigation, for cooperative groups, and for centers of excellence in that region of the world. I hope that this will be a model for other things we can do at this level.”

The consortium is an official intergovernmental organization aimed at increasing knowledge about cancer and decreasing its burden for the people of the area. To address common needs, the consortium’s main areas of focus will include cancer surveillance, information, and education. Efforts will also concentrate on training, basic research, public health and patient care, quality control, and international communications. Clinical cooperation may involve basic and applied research and include programs of clinical guidelines and protocols.

Earlier Cooperation

The consortium’s creation was inspired by the initial progress of another NCI-supported effort, the Middle East Cancer Society, a regional, scientific, non-governmental organization established in 1994. So far, the society has held four meetings and assigned task forces to draft projects on lymphoma and breast cancer (two predominant cancers in the region), cancer registration, epidemiology, pediatric oncology, and quality assurance.

Because most members of the Middle East Cancer Society are from countries belonging to the consortium, it is expected that the two organizations will work closely together, complementing and reinforcing each other’s work. However, while the society’s goal is to provide state-of-the-art knowledge of cancer, its membership is based on individual personal application. The consortium will function at the ministerial level, building a government-sponsored infrastructure. Its role will be to im-