

Advances in Drug Development

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Current Developments in Oncology Drug Research

New Antimitotic Agents

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What is the current state of antimitotic drug research?

Natural product antimitotic cytotoxics have been the mainstay of cancer therapeutics since they were identified. Although much is known about molecular biology and our understanding of cancer has advanced greatly over the past few decades, the disease is mainly diagnosed in its advanced stage, and novel, more effective types of nonspecific cytoreductive therapies, as well as specific targeted therapeutics, are needed.

How are already approved taxanes continuing to be explored?

The taxanes confirmed that targeting the microtubule using chemotherapy is an effective therapeutic approach. Each year, taxanes are approved for new indications. Recently, docetaxel was approved for use as adjuvant therapy for breast cancer.

One of the interesting areas of taxane research at the moment is scheduling. There are not many agents whose therapeutic index is dependent on schedule of administration. However, it appears that with the taxanes, particularly paclitaxel and docetaxel, scheduling affects the toxicologic profile and possibly antitumor activity. When given on a weekly schedule, hematologic toxicity appears to be substantially reduced but efficacy is maintained. At the 2004 annual meeting of the American Society of Clinical Oncology, the results of a Cancer and Leukemia Group B study comparing 2 different schedules of paclitaxel for women with metastatic breast cancer were reported. The findings showed that efficacy was superior with the weekly schedule compared to the traditional every-3-week schedule.

Are higher doses also being evaluated?

Several randomized studies in various cancer types, including lung, breast, ovarian, and head and neck, have found that higher doses do not result in greater efficacy. New taxane analogs are currently being studied, many of which are said to deliver higher doses. However, tissue concentrations of the taxanes are very high with conventional doses and the results of randomized trials in patients with advanced non-small-cell lung, head and neck, ovarian, and breast cancers indicate

that higher doses do not result in greater efficacy compared to conventional doses. Therefore, it is difficult to foresee that taxane analogs that offer the possibility of delivering higher taxane doses will be much more efficacious on this basis.

Why don't higher doses increase drug efficacy?

The reason why both scheduling and dosing are probably not very important is that antimitotic agents, including the taxanes as well as the vinca alkaloids and epothilones, bind very highly and avidly to tissues. Studies conducted in the late 1980s/early 1990s in animal models using autoradiography found very high concentrations of antimicrotubule drugs in almost every tissue, except for the brain. This high, avid, and protracted tissue binding means that increasing the dose or prolonging the infusion time would not be likely to increase efficacy.

On the other hand, as just mentioned, a weekly schedule does appear to be more efficacious than an every-3-week schedule with certain taxanes. Since it takes approximately 1 week for the drug to come out of tissues completely, weekly administration is like "filling up the sink" each week. However, if the sink is filled too high, toxicity occurs.

How else are currently available taxanes being altered in an effort to improve outcomes?

Alternate formulations of taxanes were initially developed with the goal of eliminating polyoxyethylated castor oil (Cremophor EL), which produced a great deal of toxicity, mainly hypersensitivity reactions. However, we have learned to ameliorate those problems, which are not a major concern in the clinic anymore, and thus the need for alternative formulations has diminished.

Some data do suggest that some alternate formulations produce somewhat better results than the older formulations. However, ongoing studies have not yet reached definitive conclusions. ABI-007 (Abraxane, American Bioscience) is an albumin-bound formulation of paclitaxel that might be able to be given in higher doses, and is claimed to penetrate tissues better than standard paclitaxel. However, tissue binding is not problematic, so it is not certain that this agent will

offer significant improvement. Polyglutaminated paclitaxel (paclitaxel poliglumex, Xyotax, Cell Therapeutics), which has no polyoxyethylated castor oil, is also being developed. This agent may be less neurotoxic than the standard formulation, and it may improve efficacy. This drug is currently being evaluated in phase III trials in several tumor types.

Could you describe the epothilone class of antimetabolic agents?

The epothilones are one of a number of new classes of microtubule polymerizing agents currently being studied, all of which derive from natural products. There are several epothilones in clinical trials. These drugs appear to be more potent than the taxanes and do not seem to be substrates for the P-glycoprotein pump or the multidrug resistance phenotype. Responses to epothilones have been observed in some patients with taxane-refractory breast cancer and prostate cancer. There was a great deal of enthusiasm about EPO-906 (Novartis) early on in its clinical development because it was producing responses in colon cancer, which no other antimicrotubule agent had done. However, this agent also causes diarrhea, and activity and toxicity are both observed only at higher doses. The manufacturer is continuing research efforts to improve this drug. Ixabepilone (Bristol-Myers Squibb) is in phase III trials for breast cancer and is showing activity in that setting, and discodermolide (Novartis), which comes from sponge, is also showing activity. These drugs are mainly being studied as single agents right now, as part of early clinical development.

Are there other potential targets within the microtubule?

Yes, there are several targets currently being studied and several classes of agents against these targets are being evaluated. One of these is the kinesins, which are motor proteins, which transmit chemical energy into mechanical force, and align the microtubules properly during mitosis. Approximately 40 kinesins, some of which are very specific to proliferating cells and are not found in nerve cells or normal cells to the same extent, have been identified in humans. An agent in development by Cytokinetics and GlaxoSmithKline, SB715992, targets kinesin spindle protein and is currently in phase II clinical trials. The major toxicity observed with this agent is myelosuppression; no neurotoxicity has been observed.

Several drugs that target specific mitotic kinases or enzymes, called polo kinases, that are important to the mitotic cycle are being developed. Another target is the set of aurora kinases, which includes aurora A, aurora B, and aurora C, which are important in aligning the centrosome and mitotic spindles. One agent against the aurora kinases that is entering the clinic is VX-680, being developed by both Vertex Pharmaceuticals and Merck.

From what types of natural products are these various agents derived?

In addition to the sponge-derived product mentioned above, other natural sources include weeds, plants, tree bark, and

other vegetation. There exists in nature a variety of compounds that are very similar in mechanism but which look very different from one another.

How are these compounds identified?

The vinca alkaloids were found by scientists at Lilly. These agents come from *Vinca rosia*, the common vinca bush that grows in the yard. This plant was known to contain a hypoglycemic agent, but as it turned out, it is far more effective as a neoplastic drug. The taxanes were found through natural product screening against thousands and thousands of extracts of plants, fungi, weeds, and other vegetation. Rapamycin, an agent approved for renal transplant rejection, was found in the dirt on Easter Island, and is one of the most potent drugs available.

Are natural products continuing to be screened in this manner?

No, and this question raises an important concern. The current approach to drug development is to identify targets and then develop drugs against those targets. But in many cases the unique agent already exists in nature, and points us in the direction of discovering a new target or process such as mTOR for rapamycin and microtubule polymerization for paclitaxel.

Why is the random natural products screening approach not being pursued?

Screening is very inefficient. The process is both cumbersome and costly. The oceanographic laboratory at Bell Harbor is one of the only oceanographic groups searching for natural products, with a particular emphasis on searching for rare species so that extracts can be made. This research highlights another concern: as diversity decreases, the potential of finding novel compounds also decreases. Pharmaceutical companies are unlikely to pursue the screening approach because it is expensive and uncertain; it is impossible to make projections for this type of research. If the screening of natural products is going to continue, it will most likely require government funding.

Suggested Reading

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