THE NEED AND THE NETWORK’s MISSION

The field of oncology is more exciting and more challenging today than it has ever been before. Today’s oncologists are charting new territory on both the patient-management and the practice-management fronts. They face the dual challenge of having to keep up with clinical advances in their field and manage their practices productively in an ever-changing health care-delivery system. The Network For Oncology Communication & Research was founded in 1994 to assist medical oncology professionals in successfully meeting this dual challenge.

By providing a forum in which practicing oncologists can interact with their peers as well as with leading experts, the Network helps clinicians maintain steady practice growth while optimizing medical benefits for their cancer patients. Network meetings offer up-to-the-minute education about new cancer diagnostics and treatments, information on research opportunities, and practical advice on coping with the cost-management-driven changes that are sweeping the United States and the world. Network meetings also offer oncologists, nurses and administrators the opportunity to interact with leading pharmaceutical company representatives, manufacturers of medical therapies and equipment and others who are involved in supportive areas of cancer management.

PARTICIPANT EVALUATION

Organized and chaired by the Network’s Medical Director, Stanley H. Winokur, M.D., these biannual meetings have earned high praise from practicing oncologists such as:

Martin Weltz, M.D., Greenbelt, MD. “Hands-down the most informative and enjoyable meeting, reviewing state-of-the-art and beyond medical oncology management, business, politics and relative legal issues.”

Richard Just, M.D., Escondido, CA. “I enjoy the relatively small numbers of attendees, as compared to ASCO, for example, allowing for more personal interaction with speakers. The quality of the lectures is outstanding. The interactive format promotes a more open discussion among speakers and audience, which I’ve not experienced at other meetings. In addition, meeting locations and facilities have been superb.”

Gary Kay, M.D., Arlington Heights, IL. “The Network meeting, in addition to being educational, provides a superb opportunity to interact with, and benefit from, the experience of like-minded individuals, both from a clinical and business perspective.”

SUMMARY OF BOCA RATON MEETING

On February 21 and 22, 1997, more than 150 physicians, nurses and industry representatives attended the Network For Oncology Communication & Research meeting at the Boca Raton Resort & Club in Boca Raton, Florida. Clinical case studies, practice management issues and state-of-the-art health care products and services were discussed. Attendees were also eligible to receive 11.5 credit hours in Category 1 of the Physician’s Recognition Award of the American Medical Association.

In keeping with the theme, “The Practice of Oncology: Transitioning for the Future,” the invited faculty reviewed the most recent data on cancer treatment and their application to the clinical practice of medical, surgical and radiation oncology and oncology nursing. In recognition of the timeliness of the information, attendees were equipped with a computerized audience response system. Using the system, they could instantly respond to questions and ideas presented by the faculty. Their responses were tallied and used as a springboard for discussion. “The Great Debate” gave the faculty panel and audience the opportunity to discuss actual clinical cases in oncology. The following abstracts were chosen to reflect the breadth and the depth of some of the presentations. Regrettably, a paucity of space precludes the transcription of the superb discussions.
MULTIMODALITY MANAGEMENT OF PANCREATIC CANCER

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Many patients with a diagnosis of pancreatic cancer are not offered any therapeutic intervention other than surgical bypass due to very poor prognosis, poor patient tolerance to current therapeutic regimens, and a dismal tumor response to therapy. In view of these circumstances, an acceptable treatment regimen for pancreatic cancer must first demonstrate an ability to obtain a rapid tumor response with a regimen that will be well tolerated enabling the patient to maintain a good quality of life with full ambulatory status. The following multimodality trial was, therefore, undertaken in collaboration with my colleagues: Roman Franklin, M.D., Rajan S. Krishnan, M.D., Ralph W. Richardson, M.D. and Christopher Conlin, M.D.

Nine unresectable pancreatic cancer patients (4/9 had liver metastases) with an average age of 62 (range: 41-79) were treated with a concurrent regimen consisting of continuous infusion 5-fluorouracil (200-250 mg/m²/24 h) and continuous infusion cisplatin (5 mg/24 h: 2 weeks on, 1 week off) given simultaneously with 3-D planned BID hyperfractionated radiotherapy to the pancreas (5940 cGy/66 fractions/6.5 weeks), and whole liver (1980 cGy/22 fractions/2 weeks), plus additional dose to the partial liver in metastatic disease. Continuous infusion combination chemotherapy was continued alone after radiotherapy for a total of six months. Chemotherapy was delivered by dual lightweight portable external pumps. Hyperalimentation was used as needed to maintain nutritional status and warfarin thromboembolic prophylaxis was also utilized. Tumor response was monitored by monthly abdominal CAT scans, serum markers (CEA, CA 19-9), weight gain, and symptomatology. Full radiographic resolution of tumor mass was considered to be a complete response (CR), whereas 50% or greater radiographic decrease in size was considered a partial response (PR). Evaluation was done by independent diagnostic radiologists.

CR and PR of the pancreatic mass were achieved in 88% of all patients (8/9). CR was achieved in 44% of all patients (4/9). Patients with liver metastases exhibited 75% (3/4) PR in liver masses and either CR or PR in the primary site. All radiographic responses were achieved within one to three months after completion of the radiotherapy portion of the concurrent treatment regimen. One-year survival was achieved in 78% of patients treated (7/9). Two-year survival was achieved in 44% of patients treated (4/9). These response and survival rates were achieved with minimal complications and side-effects and patients predominantly maintained ambulatory status throughout the entire course of treatment and follow-up.

Concurrent continuous infusion combination chemotherapy in low daily doses with BID hyperfractionated radiotherapy is effective in achieving dramatic local response and improved survival with minimal side-effects. These results suggest that a significant synergistic effect exists with concurrent chemoradiotherapy in complimentary low-dose regimens for the treatment of pancreatic cancer. Additional studies are suggested for further exploration of the optimal integration of well tolerated concurrent chemoradiation combinations; however, it is evident that concurrent chemoradiotherapy is significantly superior to chemotherapy alone in the treatment of advanced pancreatic cancer.

LYMPHOMA UPDATE: 1997

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The Role of Salvage Therapy in Malignant Lymphomas

Three modalities are available for second line therapy of the malignant lymphomas and Hodgkin’s disease. They include: A) chemotherapy at increased or conventional doses; B) high-dose therapy with autologous stem cell support, and C) biologic therapy with immunotoxins or adoptive immunotherapy. Biologic therapy is still in the developmental...
phase and has not had a wide application. The first two approaches have had extensive testing.

In non-Hodgkin’s lymphomas, as well as in Hodgkin’s disease, the benefits of salvage therapy are determined by a variety of clinical factors, including: A) the tumor burden at the time of presentation for second-line treatment; B) the extent of prior response to conventional-dose therapy; C) the duration of first complete remission (if achieved)—this is especially true in Hodgkin’s disease; D) response to second-line therapy, especially prior to consideration of high-dose therapy with stem cell support, i.e., sensitive relapse, and E) possibly the nature of second-line therapy, i.e., high-dose versus standard-dose treatment. Since dose-response is an important component of first-line induction chemotherapy, it would be reasonable to assume that it would also apply to second-line therapy. Relapse of drug-sensitive lymphoma, especially after long remission detected early, clearly represents a favorable circumstance for second-line therapy, whereas primary refractory or incomplete responses represent an order of tumor cell resistance that is unlikely to be impacted upon by standard-dose second-line chemotherapy and, possibly, high-dose therapy if there is drug resistant relapse or primary refractory lymphoma. There remains to be explored a group of patients who achieve a good but definite partial response to initial therapy. They may represent a subgroup in whom sensitive imaging techniques can detect incomplete response and for whom a change in treatment to high-dose induction therapy would be appropriate for investigational treatment. Similarly, a clear-cut definition of presenting prognostic factors which predict for an unsatisfactory long-term disease-free remission would justify the application of high-dose therapy early in the treatment plan. These principles would apply to both non-Hodgkin’s lymphoma and Hodgkin’s disease.

Second-line chemotherapy regimens given at standard dose have been less extensively applied. It would appear that no more than 20%-30% of patients with Hodgkin’s disease in relapse achieve long-term benefit from second-line chemotherapy when all patients are considered. However, the circumstances are more favorable the longer the first remission, so that a first remission lasting over 12 months has a very high likelihood to respond completely to a second-line or even the same first-line chemotherapy regimen, resulting in long-lasting second remission with ~50% progression-free survival at five years (Milan series). The Cancer and Leukemia Group B has advanced a Hodgkin’s disease trial comparing MOPP to ABVD up front with a crossover to the alternate regimen at relapse or initial incomplete remission provided a database to examine prospective salvage chemotherapy. The failure-free survival is similar (25% and 34%) at three years. In the lymphomas, especially the large cell non-Hodgkin’s lymphomas, relapse usually occurs in the first two years, if it is to occur.

It is unclear whether very long second remissions can be achieved with standard-dose chemotherapy, although some trials suggest that no more than 20%-25% of previous complete responders may be relapse-free at two to three years after second-line therapy. It is unclear whether any relapsing large cell lymphomas can be cured by second-line standard-dose chemotherapy, especially if they have been primarily treated intensively with a third generation regimen. The role of high-dose therapy is still being defined. In Hodgkin’s disease, the complete response rate in 240 patients (published in 1989) was 46%, with 35% continuously free of disease at three years. The criteria which predicted a good result include 0 performance status, sensitive relapse and failure of no more than two prior regimens. In non-Hodgkin’s lymphoma the accumulated results are similar, with a clear message that the remission status and presence of a sensitive relapse correlate with the final results. It is unclear whether the results are affected by the type of induction high-dose regimen or by marrow purging. Most series represent clear-cut patient selection. One trial in a patient with large cell lymphoma in relapse from a complete remission suggests that the benefits of high-dose therapy with stem cell support will result in two- to three-year progression-free benefit in about 25% of eligible patients. Newer programs, including multiple high-dose regimens supported by hematopoietic growth factors, may offer an effective approach to cancer cell reduction.

**SYSTEMIC THERAPY FOR ADVANCED HODGKIN’S DISEASE**

The introduction of combination chemotherapy, especially the MOPP (nitrogen mustard, oncovin, procarbazine, and prednisone), was a pivotal event in the treatment of Hodgkin’s disease presenting in a disseminated stage or in relapse from primary radiation therapy. This regimen and its analogues are still used, but a series of randomized trials has shown that MOPP alternating with ABVD (doxorubicin-Adriamycin, bleomycin, vinblastine, DTIC) or a hybrid of MOPP-ABV was superior to MOPP in progression-free survival. A number of randomized trials has shown no difference between the “hybrid” and MOPP alternating with ABVD.

The choice of primary combination chemotherapy should be based on efficacy and toxicity. When ABVD (with or without radiation therapy) is compared to MOPP alone, there is a superiority in progression-free survival for the non-alkylating agent containing regimen, ABVD. The absence of male/female sterilization and secondary myelodysplasia/acute myeloblastic leukemia, both known to occur with MOPP, has led to a wider use of ABVD, especially in earlier stage disease with radiation therapy. It is unknown (and under investigation) whether hybrid is superior to ABVD alone. Another factor which complicates the...
use of MOPP is the particularly toxic effect of this regimen on bone marrow stem cells, which limits the doses of drugs that can be given in subsequent cycles.

At the present time, ABVD or hybrid are the most commonly used regimens in North America. A number of variants for MOPP and ABVD exist which attempt to reduce some of the acute toxicities. The British developed a regimen, ChlVPP (chlorambucil, vinblastine, procarbazine, prednisone), which reduced the hair loss, neuropathy and nausea/vomiting of MOPP with equal efficacy. Modifications of the ABVD regimen tend to omit the bleomycin to reduce pulmonary toxicity, but have not been widely tested.

The expected benefits of chemotherapy are based on clinical prognostic factors. They include age, stage, number of extranodal sites, B symptoms when in stage IV, and performance status. Age is the most significant factor in most series. About 50%-60% of patients in stage III/IV will be cured of Hodgkin’s disease after first-line therapy. In the poor prognostic subgroups, such as those >50 years of age or Stage IV with more than one extranodal site, the outcome is poorer, in the range of 30%. Other series have used elevated serum alkaline phosphatase with elevated sedimentation rate to predict a poor outcome in Stage III/IV.

REMAINING ISSUES IN GERM CELL TUMORS

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Testis cancer has become a model for a curative neoplasm. The past two decades have witnessed major surgical and medical advances that have significantly improved the cure rate and simultaneously decreased morbidity from therapy. Cisplatin combination chemotherapy truly revolutionized the cure rate as no other regimen has ever done in any solid tumor.

Despite the advances of the last two decades, there are still remaining clinical issues which are outlined below.

POST-CHEMOTHERAPY SURGICAL DECISIONS

The indication for post-chemotherapy surgery in patients with non-seminomatous germ cell tumors has been controversial. The goal of the surgery is to resect residual teratoma and/or carcinoma. If a patient achieves a radiographic complete remission, at Indiana University, no surgery is offered.

The more complicated issue is what to do when patients have multiple anatomical sites of persistent disease post-chemotherapy. There is evidence that if a two- or three-stage operation is done, and there is only necrosis in the retroperitoneal lymph node dissection, the probability of there being anything other than necrosis above the diaphragm is extremely low.

Another complicated area is what should be done in patients who have greater than 90% radiographic regression in a clinical scenario where the probability for teratoma is very low (e.g., no teratoma in the orchiectomy specimen). This is an evolving field and there are no definitive solutions for this complicated group of patients.

Finally, patients that have bulky pure seminoma will virtually never normalize their CT scan after completion of chemotherapy. It has been the policy at Indiana University to not do surgery; instead, the patients are watched with serial CT scans and no intervention is done unless there is evidence of radiographic progression.

PROGRESSIVE UNRESECTABLE TERATOMA

Most patients who have poor (advanced) germ cell tumors represent a struggle of chemotherapy versus cancer. However, some patients have biologic as well as radiographic reasons for incurability. These are patients who have bulky unresectable teratoma in multiple sites. Standard chemotherapy or radiotherapy has been unsuccessful in these patients and new strategies are clearly needed.

MANAGEMENT OF ADVANCED DISEASE

An international consensus has been reached with new definitions for poor risk disease. This will include serologic markers (i.e., HCG >50,000; alphafetoprotein >10,000), or LDH values greater than 10 times the upper limit of normal. In addition, this will include any patient with primary mediastinal non-seminomatous germ cell tumor, or bone, liver or CNS metastases. Previous randomized studies in the United States for advanced disease included BEP versus the same chemotherapy, but with double dose (40 mg/m² per day for five consecutive days) cisplatin and BEP versus VIP. Unfortunately, neither of these approaches improved the cure rate and, instead, were both associated with increased toxicity. The current intergroup study will address the issue of very high-dose chemotherapy with peripheral blood stem cell rescue. The control arm will consist of four courses of BEP, and the experimental arm will be two courses of BEP followed by two courses of very high-dose chemotherapy.
Late Relapse

Testicular cancer is a rapidly proliferating and uniquely chemosensitive tumor. It is now recognized that approximately 2%-3% of patients who are disease-free at two years will experience a late relapse and about half of those will be beyond five years. This is often manifested by a rising alpha-fetoprotein on a routine determination. Unfortunately, with very rare exceptions, these patients are not curable with chemotherapy. Proper management for these patients is to find where their disease is radiographically and attempt to surgically resect their disease.

It is a luxury in germ cell tumors to address the above issues rather than the fundamental issue of successful primary chemotherapy for disseminated disease. Testicular cancer has been a success story and, hopefully, these and other remaining issues will be appropriately addressed and answered as we approach the year 2000.

Navelbine: How I Use It

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Vinorelbine (Navelbine) is a new vinca alkaloid with superior efficacy compared to older drugs such as vincristine, vinblastine, and vindesine. Unlike the older vinca alkaloids, neuromuscular toxicity is not a major problem. However, myelosuppression (especially granulocytopenia) is the major dose-limiting toxicity. Nonmyelosuppressive toxicity is minimal, although venous irritation can be a major problem. This can be mitigated with shorter infusion times of 5 to 10 minutes.

Vinorelbine is the first drug in over 20 years to be FDA-approved for NSCLC. The older approved drugs, nitrogen mustard, methotrexate and doxorubicin, are not felt to have clinical value. The approval was based upon two phase III studies. An industry-sponsored American study compared Navelbine 30 mg/m^2 weekly versus 5-FU plus leucovorin in 216 patients. MST was 30 versus 22 weeks, with one-year survivals of 25% versus 16% (p = 0.03). Response rates were 12% versus 3%. The second study was a three-arm European study comparing vinorelbine (30 mg/m^2) versus cisplatin (120 mg/m^2) and either vinorelbine or vindesine. Six hundred twelve patients were entered. Response rates were 14%, 30%, and 19%, with MST. 31, 40, and 32 weeks (p = 0.04 favoring cisplatin + vinorelbine). Post-FDA approval, SWOG reported a phase III study comparing cisplatin (100 mg/m^2) every four weeks with or without vinorelbine (25 mg/m^2/week). Response rates (in 432 patients) were 10% versus 26% and MST six versus eight months with one-year survivals of 16.4% versus 35.4%.

Two other vinorelbine phase III studies are noteworthy. A Japanese study evaluated weekly vinorelbine (25 mg/m^2) versus vindesine (3 mg/m^2). Response rates were 29% versus 9% in 150 patients, with MST 12 versus 10 months. Finally, a phase III study of 231 patients compared vinorelbine (30 mg/m^2/week) ± cisplatin (80 mg/m^2 q 3 weeks). Response rates were 16% versus 43%, but no difference in survival (32 versus 33 weeks: p = 0.48).

Current cooperative group studies will compare cisplatin + vinorelbine to carboplatin + paclitaxel (SWOG), evaluate cisplatin + vinorelbine with XRT in stage III disease (CALGB), and evaluate cisplatin + vinorelbine as postoperative adjuvant therapy for stage I (T2N0) and stage II NSCLC (NCI-Canada and ECOG).

Vinorelbine also has activity in ovarian and breast cancer, and possibly prostate cancer. A study from Argentina evaluated vinorelbine 30 mg/m^2/week as first-line chemotherapy in metastatic breast cancer. There was a 41% response rate in 44 patients. An industry-supported multi-institutional American study had similar results. Vinorelbine has also been evaluated in metastatic breast cancer patients with prior chemotherapy. Most studies demonstrated activity with mild toxicity.

Gemzar (Gemcitabine): How I Use It

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Gemcitabine is a nucleoside analog related to Ara-C. However, compared to Ara-C, it has substantial activity in multiple solid tumors. It has greater cell membrane permeability and longer intracellular retention.
Numerous doses and schedules were evaluated in early phase I-II trials. Slight alterations in schedule caused major alterations in toxicity and efficacy. At the present time, standard doses are 1,000 to 1,250 mg/m² as a 30-min infusion weekly × 3 every four weeks. In pancreatic cancer, the phase III study that led to FDA approval utilized 1,000 mg/m² × seven weeks, one week of rest, and then 1,000 mg/m² weekly × 3 every four weeks. Chemotherapy with gemcitabine is very well tolerated, with minimal myelosuppression, nausea, myalgias, edema, and rash.

Gemcitabine was recently approved by the FDA on the basis of a phase III study in symptomatic pancreatic cancer patients. One hundred twenty-six patients randomized to gemcitabine versus 5-FU (600 mg/m²/week). Clinical benefit response (pain reduction, improved KPS or weight gain) was prospectively evaluated as the primary study endpoint, with values of 23.8% (gemcitabine) versus 4.8% \( (p = 0.002) \). In addition, there was a statistically significant survival advantage for gemcitabine, including a one-year survival of 18% versus 2%. Gemcitabine was also evaluated in a separate phase II study in patients with prior 5-FU, and 17 of 63 (27%) had a clinical benefit response.

Gemcitabine is one of the most studied single agents in NSCLC, and worldwide has a reproducible response rate of 20% with only minimal toxicity. A recently published phase I dose escalation study was conducted at M.D. Anderson. The authors demonstrated tolerability of 2,400 mg/m²/week (three of four weeks) in NSCLC. It is unknown whether there is any advantage to this “double dose” gemcitabine.

Numerous phase II trials have evaluated the logical combination of cisplatin + gemcitabine in NSCLC. There is preclinical evidence of synergism.

There are several interesting studies in NSCLC. The CALGB will evaluate cisplatin + gemcitabine with XRT. There is potent radiation sensitization, requiring attenuated doses of gemcitabine if given concurrently. ECOG is conducting a phase III study of cisplatin + paclitaxel or docetaxel, CBDCA + paclitaxel, or cisplatin + gemcitabine.

Gemcitabine has significant activity in numerous other solid tumors, including impressive activity in bladder cancer, ovarian cancer, and breast cancer.

Non-cisplatin (or XRT) combinations are considered investigational. At Indiana University, phase I trials of weekly paclitaxel + weekly gemcitabine are currently being conducted.

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**Paclitaxel/Carboplatin: How I Use Them**

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I. Early Development of the Combination

A. *Langer et al.* 24 h Paclitaxel infusion (135 → 175 → 220 mg/m²) Carboplatin AUC 7.5 Day 2. Severe myelosuppression. Response stage IV NSCLC 58%; one-year survival: 56%

B. *Natale et al.* 3 h infusion Paclitaxel (up to 225 mg/m²); AUC 6, 7, 9. Lower doses Carboplatin same day (AUC 6). No severe thrombocytopenia. Moderate neutropenia (no worse than with Carboplatin alone). Response >50% (stage IIIB and IV) NSCLC; one-year survival: 58%

C. *Greco et al.* 1 h infusion Paclitaxel (135-200 mg/m²) with Carboplatin AUC 5 and 6; plus oral etoposide 50/100 daily × 10 days. Very active regimen — small cell lung cancer. Survival probably better with higher doses

D. *Greco et al.* 1 h infusion Paclitaxel 225 mg/m² plus Carboplatin (AUC 6) Stage IIIB and IV NSCLC. 100 patients, response 48%; one-year survival 49%

E. Pharmacodynamic studies: There is no obvious pharmacologic interaction to explain the less-than-expected thrombocytopenia, and neutropenia, seen with this combination

II. Paclitaxel/Cisplatin

A. Superior to Etoposide/Cisplatin in Stage IV NSCLC—ECOG study

B. Why is Cisplatin used in 1997, given the comparative information with Carboplatin?

III. Several Randomized Studies in Progress (Stage IV NSCLC)

A. Bristol; Paclitaxel/Carboplatin versus Etoposide/Cisplatin; results pending. European study is similar (teniposide); results pending

B. SWOG; Paclitaxel/Carboplatin versus Nalvalbine/Cisplatin

C. ECOG; Paclitaxel/Cisplatin versus Gemcitabine/Cisplatin versus Taxotere/Cisplatin versus Paclitaxel/Cisplatin

D. CALGB; Paclitaxel/Carboplatin versus Paclitaxel

IV. Current Therapy with Paclitaxel/Carboplatin at Sarah Cannon-Minnie Pearl Cancer Center

A. Stage IB, II, IIIA NSCLC

- Neoadjuvant × 3 courses every 3 weeks
A. Resection → RT plus weekly Paclitaxel and Carboplatin for 6 weeks
B. Unresectable → RT plus weekly Paclitaxel and Carboplatin for 6 weeks
C. Adjuvant IB → 3 courses only; II, IIIA × 3 courses, then RT and weekly chemotherapy as above

D. Esophageal carcinoma
   ▲ Neoadjuvant: Paclitaxel, Carboplatin, infusional 5-FU plus RT, then resection
E. Locally advanced head and neck cancer and other advanced squamous cancers and urothelial cancers
   ▲ Paclitaxel 200 mg/m² plus Carboplatin (AUC 6) and infusional 5-FU 225 mg/m²/day for 6 weeks
   ▲ RT with weekly chemotherapy after induction for head and neck
F. Carcinoma of unknown primary site
   ▲ Paclitaxel 200 mg/m², Carboplatin (AUC 6) and oral Etoposide 50/100 mg daily × 10 days q 3 weeks × 4 courses
   ▲ Response rate 50%; 13% CR; all subsets responding; median survival 13 months; accepted for publication in Journal of Clinical Oncology

G. Ovarian cancer—Stage III, IV
   ▲ Paclitaxel 200 mg/m², Carboplatin (AUC 6) and oral Etoposide 50/100 × 10 days q 3 weeks × 6 courses → second look laparotomy

ORAL VP-16 (ETOPOSIDE): HOW I USE IT

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I. Background
   A. Variable absorption, but bioavailability is better; (70%-80%) with low daily doses.
   B. Data highly suggest that low plasma levels are as effective as higher levels, and with less myelotoxicity.
   C. Duration of therapy is key element not studied enough. Twenty-one days of oral etoposide appear too long; increases myelosuppression and no increase in activity. Optimal duration appears to be 7-15 days.
   D. Efficacy seems similar when using low doses daily for many days, i.e., 10 p.o. Very low doses can be given i.v. infusion for weeks without major toxicity in most patients.
   E. We use Etoposide incorrectly in nearly all settings; doses too high, duration not quite long enough. Solution: use low doses, 50-100 p.o. qd for 10 days only.

II. Use of Oral Etoposide in Combination
   I think low dose oral etoposide, 50/100 mg daily for 10 days can be substituted in any standard regimen using higher doses of etoposide except germ cell tumors. (I do not have the nerve to do this, but intellectually think it would be as effective and less toxic than 100 mg/m² daily i.v. × 5 days). We have used oral etoposide as part of a combination for elderly patients with aggressive lymphomas and results are good. Published in JNCI. Until and if further study refutes this, I think the best dose is 50 mg alternating with 100 mg orally for 10 days (the “optimal” dose and schedule).

III. Use as Single Agent for Palliation—a Long List
   A. Recurrent small cell lung cancer
   B. Recurrent lymphomas
   C. Recurrent germ cell tumors
   D. Recurrent advanced ovarian cancer
   E. Recurrent advanced breast cancer
   F. Recurrent medulloblastoma
   G. Untreated mesothelioma
   H. Untreated advanced gastric cancer
   I. Untreated advanced NSCLC
   J. Kaposi’s sarcoma with AIDS
**Taxotere: How I Use It in Breast Cancer**

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The clinical development of taxotere has resulted in an agent with substantial single-agent activity in women with both untreated and resistant metastatic breast cancer. The drug is thus currently being rapidly integrated into the oncologists armamentarium. In a study of taxotere as first-line therapy, Hudis and colleagues from Memorial Sloan-Kettering reported an overall response rate of 54% in 37 patients treated with 100 mg/m² every three weeks and the median duration of response was six months. A response rate of 63% in a similar population was observed by Trudeau and colleagues from the NCI-Canada Clinical trials group. In that study the median progression-free survival was 4.5 months. In this latter trial a second group of 16 patients was subsequently treated with a lower dose of taxotere (75 mg/m²) because of the high rate of admission for febrile neutropenia in the initial population treated at 100 mg/m². In this second cohort the response rate was 40%, a result which was not statistically significantly lower than in the cohort who received taxotere at 100 mg/m².

The development of novel agents for the treatment of metastatic breast cancer in the past few years has focused on drugs with activity in patients with resistant disease. While definitions of resistance may vary between studies, the recently reported phase II studies of taxotere have clearly identified a population of patients with disease which is resistant to anthracyclines and have observed response rates in these patients of up to 50%. Ravdin and colleagues noted complete and partial responses in 20 of 35 women with measurable breast cancer which had progressed on an anthracycline (administered either adjuvantly or for metastatic disease), who were treated with taxotere 100 mg/m² every three weeks. In a similar population, Valero and colleagues observed a 53% response rate. These initial studies have established the activity of this agent in patients with breast cancer which is truly refractory to anthracyclines. Neutropenia is the major side-effect of single-agent therapy with taxotere. In both studies mentioned above, grade IV neutropenia occurred in the majority of courses in which the drug was administered at full dose. Admissions for neutropenic fever and subsequent dose reductions were common.

Combination regimens containing taxotere are in early stages of development. Preliminary data suggest that taxotere and doxorubicin is an extremely active combination when administered as first-line therapy for metastatic breast cancer. Combinations with vinorelbine, cyclophosphamide and a variety of other agents are also under evaluation. No information is yet available on the role of taxotere in the adjuvant setting.

Taxotere is an active agent in the treatment of refractory breast cancer. Neutropenia may limit its use in heavily pretreated patients, for whom a starting dose of less than 100 mg/m² may be considered. Combination therapy with other agents both in the metastatic and adjuvant settings should be pursued in the context of clinical trials and several such trials are ongoing and will be discussed.

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**HIV Infection: An Oncologic Model of Pathogenesis and Treatment**

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**Insights into HIV Replication in Man Reveal That There Are:**

- Rapid rounds of viral replication in vivo with large numbers of virions produced and cleared daily. This explains the prognostic power of the viral load measurement.
- Slower second phase of viral decay with the identification of viral compartments and pool sizes with varying rates of decay. Can HIV be eradicated with current therapeutic approaches?
- If not, are there viral compartments with slower rates of decay (i.e., CNS, testicular)?

**Therapeutic Implications:**

- Rapid unchecked rounds of viral replication allows for the generation of genetic variants with reduced susceptibility to individual antiviral agents.
- Therapy with one or even two agents selects for the emergence of multidrug resistance.
- Combination antiviral therapy with three or four drugs has achieved prolonged aviremia as defined by plasma RNA and culture.
- Subjects with high viral loads and prolonged courses with exposure to multiple agents introduced sequentially do worse than those with lower viral loads, minimal drug exposure and perhaps earlier aggressive intervention.
Several recent trials of monoclonal antibodies for patients with B-cell lymphomas have been sufficiently successful to anticipate the more widespread availability of these agents in the near future. Several features that are fairly unique to monoclonal antibody therapy will be discussed, including: A) the allergic and immunologic manifestations that can occur with monoclonal antibodies, including the HAMA (human anti-mouse antibody) response with murine antibodies; B) issues for toxin conjugates, such as the need for internalization of the delivered toxin; C) dosimetry issues for radioimmunoconjugates, particularly when there is bone marrow involvement, and the associated risk of myelosuppression, and D) the consequent possible need for stem cell support.

Clinical results using the anti-CD20 antibody IDEC C2B8 will be discussed in some detail. IDEC C2B8 is a chimeric antibody with a human constant region of IgG1 kappa isotope; it is not conjugated to any isotope or toxin, so it probably acts largely through normal effector mechanisms such as complement-mediated lysis. This antibody has been found in a multi-institutional pivotal phase III trial to be both safe and effective. The overall response rate was 50%. The tolerance was very good. By virtue of its being a chimeric antibody, the HAMA response was negligible. On the schedule used (once weekly for four weeks), the treatment was completed in 22 days and was feasible on an outpatient basis.

LIPSOMES TECHNOLOGY FOR SOLID TUMORS: WHERE DOES IT WORK?

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PRECLINICAL BACKGROUND

The expectations from preclinical data that liposomes improve the therapeutic index of anthracyclines has now been verified in clinical studies of several liposomal preparations. The liposomes that have been used have varied in size, lipid composition, stability when injected in-vivo and pharmacology. Liposomes coated with polyethylene glycol on the surface are protected from the attack of lipoproteins and opsonins, and consequently have prolonged circulation. Based on superior activity to free doxorubicin against a number of xenografts, clinical studies with Doxil were initiated.

PHASE I CLINICAL STUDIES

Doses between 20 and 80 mg/m² in free-doxorubicin equivalents were explored with Doxil. The toxicity has been well characterized to consist primarily of hand-foot syndrome and other skin manifestations, which may get progressively more severe when the drug is dosed at three-week intervals. At four weeks, cumulative toxicity is exceptional. At the higher doses, stomatitis becomes increasingly more common, and some myelosuppression is observed, particularly in patients who have received much prior treatment. Activity was seen against a number of solid tumors that are classically anthracycline-sensitive (e.g., breast and ovarian cancers), and also some that are known to be refractory (e.g., renal) and others with intermediate degrees of sensitivity (e.g., head and neck cancers). Some very durable responses, and lack of radiation recall reactions, were also noteworthy features of these studies.

PHARMACOLOGY

Studies with radioactively tagged liposomes of the ‘Stealth’ variety, and of Doxil have shown half-lives of 50 to 100 hours. The kinetics of this agent fit an open, two-compartment structural model with linear distribution between the central and peripheral compartments, and a nonlinear elimination from the central compartment. The volume of distribution is equivalent to the blood volume. Factors that alter the clearance have been insufficiently studied, but the status of the reticuloendothelial system and presence of large tumors may play a role.

PHASE II STUDIES

Both DaunoXome and Doxil were approved for use against Kaposi’s sarcomas at doses lower than the recommended dose for solid tumor studies. In solid tumors, reports of activity of DaunoXome against lymphoma will be covered earlier. In our studies, activity against platinum- and paclitaxel-refractory ovarian cancer has been documented. The nine
of 35 objective responses (26%) were characteristically durable. We have extended these series to other patients with consistent results, and have also begun to study combinations:

paclitaxel is ongoing, and cisplatin began accruing March 1997. The toxicity profile as well as activity predict some of these combinations will prove attractive against a number of solid tumors.

TOPOTECAN IN OVARIAN CANCER

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I. Standard Therapy for Advanced Untreated Ovarian Cancer:
   A. Cisplatin (75 mg/m²) plus paclitaxel (135 mg/m² - 24h):
   B. Carboplatin (AUC = 7.5) plus paclitaxel (175 mg/m² - 3h)

II. Results of Initial Treatment:
   A. 70%-80% will be in clinical complete remission following cytoreductive surgery and chemotherapy with paclitaxel plus a platinum compound
   B. Most patients will recur; overall survival is 30%-35%

III. Management of Recurrent Ovarian Cancer:
   A. Treatment decision based on clinical drug response
     1. Drug sensitive: responded to therapy with DFI>6 months
     2. Drug resistant: responded to therapy with DFI<6 months
     3. Drug refractory: no response
   B. Treatment options for drug-sensitive patients
     1. Retreatment with agents used in initial therapy
     2. Single agents
     3. Use of non-cross-resistant agents
   C. Treatment for recurrent ovarian cancer: drug resistant
     1. Drugs used as part of initial therapy not useful
     2. Non-cross-resistant drugs:
        Topotecan
        Oral Etoposide
        Gemcitabine
        Navelbine
        Encapsulated Doxorubicin (Doxil)
        Hexamethylmelamine
        Ifosfamide
   D. Topotecan
     1. Topoisomerase I inhibitor
     2. Phase I Trials

DLT - hematologic
Non-hematologic toxicity generally mild: alopecia, N/V, fatigue
Hematologic: predictable, manageable, non-cumulative and primarily neutropenia

3. Schedule: 1.5 mg/m² qd × 5 every 3 weeks
4. Results of topotecan in ovarian cancer
   a. Response rate depends on prior response to initial chemotherapy:
      Platinum sensitive: 26%
      Platinum resistant: 18%
      Platinum refractory: 6%
   b. Randomized comparison with paclitaxel in recurrent ovarian cancer:
      Response: 23% versus 14%
      Response duration: 32 weeks versus 20 weeks
      TTP: 23 weeks versus 14 weeks
   c. More hematologic toxicity than paclitaxel

5. Future directions with topotecan
   a. Different schedules
   b. Combinations with other agents
   c. As part of initial therapy

E. Oral Etoposide
   1. GOG trial in 70 Patients
      Response: Platinum resistant: 27%
      Platinum sensitive: 34%

F. Gemcitabine
   1. 19% response rate in platinum-resistant tumors
   2. In vitro synergy with cisplatin

G. Other new active agents include Doxil and Navelbine

H. Selection of second-line therapy
   1. No objective criteria have established any non-cross-resistant agent as “drug of choice”
   3. Recommendation: Select drug and evaluate after two courses of treatment
Despite a rapid and often dramatic response to total androgen ablation, nearly all patients with metastatic prostate cancer will relapse. The median time to progression is 18 to 24 months, and the median survival after progression is six months. Approaches to the treatment of hormone refractory diseases include second hormonal manipulations, systemic chemotherapy, and palliation of bone pain with isotopes of external beam irradiation. Clinical trials of systemic chemotherapy for hormone-resistant prostate cancer have been disappointing; a recent review of 22 clinical trials demonstrated a complete and partial response rate of 8.7%. Clearly, there is a need to identify new active agents and drug targets which improve bone pain, quality of life and, ultimately, prolong survival.

Recent trials have identified active drugs and combinations such as suramin, estramustine + vinblastine, estramustine + etoposide, estramustine + Taxol. Another agent which has demonstrated both preclinical and clinical activity is liarozole, an inhibitor of retinoic acid hydroxylation. In a randomized study which evaluated three different doses (75, 150 and 300 mg p.o. b.i.d.) in 135 men with hormone-resistant prostate cancer, PSA declines of >50% were observed in 7%, 20%, and 24% of patients treated. Toxicities were dose-dependent, and included nausea, fatigue, dry mouth, pruritus, and skin rash. Clinical trials are currently evaluating the combination of liarozole + interferon, and liarozole + prednisone.

**TREATMENT OF HORMONE-RESISTANT PROSTATE CANCER**

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Surgery remains the mainstay of curative treatment for non-small cell lung cancer (NSCLC). Cisplatin-based chemotherapy regimens of the 1980s have been shown to have a small, but significant, impact on survival for patients with stage III and IV disease. New agents have shown encouraging single-agent activity in NSCLC and the cisplatin combination regimens may further advance the treatment of this disease. Docetaxel is one such new agent which has shown promising single-agent activity in NSCLC. The results of six single-agent phase II trials and three cisplatin combination trials are described below.

Three hundred and seventy-nine (379) patients with advanced or recurrent NSCLC have been enrolled into nine trials of docetaxel administered intravenously every 21 days. Seven of the trials enrolled 291 chemotherapy-naive patients (four single-agent phase II trials, n = 160; and three phase I/II cisplatin combination trials, n = 131), and two of the trials enrolled 88 patients who failed prior platinum-containing chemotherapy. Response rate in the intent-to-treat analyses for single-agent phase II trials of 160 chemotherapy-naive patients was 27% (95% confidence interval: 20%-34%). The median and one-year survival for the single-agent phase II trials was 9.2 months and 39%. Response rate for 88 platinum-treated patients was 17% (95% confidence interval: 10%-27%) and the median and one-year survival for these previously platinum-treated patients was 9.0 months and 38%. Response rate for 131 patients treated in the phase I/II cisplatin combination trials was 38% (95% confidence interval: 30%-46%). The median and estimated one-year survival for the docetaxel and cisplatin combination trials was 10.0 months and 40%. Leukopenia, alopecia, fluid retention, infusion-related reactions, onycholysis, and rash were adverse events observed in these trials. Dexamethasone premedication lessens the frequency and severity of fluid retention, infusion-related reactions, and rash. Docetaxel, as a single agent and combination with cisplatin, demonstrates significant activity in NSCLC. Trials of docetaxel in combination with carboplatin, cisplatin, vinorelbine, gemcitabine, irinotecan, and thoracic radiation are in progress. Trials of docetaxel, as primary chemotherapy for stage III NSCLC, are warranted.

**TAXOTERE (DOCETAXEL): HOW I USE IT IN LUNG CANCER**

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Camptosar is the first new agent approved by the Food and Drug Administration for the treatment of advanced colorectal cancer in 40 years. The drug, previously known as CPT-11, is a derivative of camptothecin, a chemical isolated from the stem wood of the Chinese tree *camptotheca acuminata*. Camptothecin was shown in early clinical trials to have antitumor activity, but also to have severe and unpredictable toxicities. In the mid 1980s, camptothecin was shown to be a potent inhibitor of the nuclear enzyme topoisomerase I (topo I). This understanding of the unique mechanism of action led to a flurry of investigations aimed at identifying water-soluble derivatives of camptothecin which would retain or improve upon its clinical activity and which would have more manageable and predictable toxicities. Two such derivatives have now reached the market: topotecan (Hycamtin) and irinotecan (CPT-11, or Camptosar).

It is important to recognize that these camptothecin derivatives do not necessarily share the same spectrum of activity. Topotecan, which is approved for use in cisplatin-refractory ovarian carcinoma, is essentially inactive in colorectal cancer. Irinotecan, or Camptosar, on the other hand, is highly active in colorectal cancer. In one study done by our group at Memorial Sloan-Kettering Cancer Center, 32% of colorectal patients with no prior chemotherapy achieved a major (>50%) reduction in tumor size. Perhaps as importantly, roughly 20% achieved a more modest tumor regression and another roughly 20% achieved a stabilization of disease, with only about a quarter of the patients treated showing overt progression of disease. In a trial published from the University of Texas, San Antonio, a 23% major objective response rate was reported in patients whose disease had progressed through 5-FU-based therapy. This antitumor activity in previously treated patients has led to Camptosar’s current approved clinical indication.

The standard treatment regimen for Camptosar in North America involves 90 minute intravenous infusions of 125 mg/m² weekly for four consecutive weeks followed by a two-week rest. More rapid intravenous infusions at this dose may lead to acute cholinergic reactions resulting in early-onset diarrhea. This type of cholinergic reaction, involving diarrhea and/or diaphoresis in the period during or within 12 hours of drug administration, is self-limiting, can be controlled or prevented with atropine, and does not require specific antidiarrheal agents for treatment. Decadron 10-20 mg i.v. is adequate antiemesis treatment for the majority of patients, but approximately one-fourth of patients will require Zofran or Kytril in addition. Compazine should be avoided within 24 hours of Camptosar administration since the combination has been reported to cause jitteriness and agitation.

The two major side effects of Camptosar are neutropenia and diarrhea. The drug is relatively platelet-sparing. The key to management of diarrhea is early recognition and aggressive therapy. Patients must be instructed to begin loperamide (Imodium) therapy at the very first sign of diarrhea (increase in stool frequency, soft or liquid stools). If a watery stool is experienced, patient should take loperamide 2 mg (one tablet) every two hours until they have gone twelve hours without a liquid stool. All too often, despite specific instructions to the contrary, patients may follow the directions on the box of loperamide, which limits the dose to four tablets daily. It must be emphasized to your patients that they are taking this over-the-counter medication according to your specific directions, and not according to the directions on the box.

The most important factor influencing clinical results with Camptosar is appropriate patient selection. Patients with a good performance status, good caloric intake, and ability and desire to cooperate with complex instructions, are good candidates for treatment with Camptosar. Patients who are severely debilitated, with ECOG 3-4 performance status, and/or patients with poor gut function and poor p.o. intake, appear to tolerate Camptosar poorly, are less likely to benefit from treatment, and should be seriously considered for supportive care rather than aggressive chemotherapy. Proper patient selection can greatly increase the likelihood of success, and decrease the risk of severe or life-threatening complications.

Issues under active investigation include the use of Camptosar as a first-line agent, combination regimens of Camptosar plus 5-FU and leucovorin, and Camptosar plus radiation therapy. Camptosar will be entering clinical trials in the adjuvant treatment of locally advanced colon cancer as well.
Liposomal encapsulation of Daunorubicin markedly alters the toxicity profile usually seen with anthracyclines. The initial phase I/II clinical work with DaunoXome was performed at the University of Southern California School of Medicine in Los Angeles. The maximum tolerated dose was between 100 mg/m² and 120 mg/m² given every three weeks. The dose-limiting toxicity was myelosuppression. However, other characteristic anthracycline toxicities were markedly diminished or absent. For example, there was little or no nausea and vomiting; alopecia and mucositis were rarely seen. Most notably, patients were able to remain on therapy for prolonged periods of time, after cumulative doses in excess of 2,000 mg/m² without evidence of cardiac toxicity. Phase II trials of DaunoXome showed good antitumor activity in patients with AIDS-related Kaposi’s sarcoma (KS). Thus, a pivotal phase III trial was conducted in AIDS-related KS. The result of this study showed DaunoXome had comparable activity to standard treatment with combination chemotherapy (ABV) and with a more favorable toxicity profile. Based on the results of this study, DaunoXome was recently licensed by the FDA for first-line therapy in AIDS-KS.

Due to the favorable profile and antitumor activity of this formulation, we have conducted a phase II study to evaluate the safety and efficacy of DaunoXome in patients with low- and intermediate-grade NHL with refractory disease or relapse from prior chemotherapy. Patients were treated with DaunoXome at a dose of 100 mg/m² given intravenously over two hours every three weeks. If hematologically stable, dose escalations of 20 mg/m² per cycle were allowed up to a maximum of 140 mg/m². Thus far, 14 patients have been enrolled (11 males, 3 females), with a median age of 67 (range 39-75). Twelve had low-grade histologies; two had intermediate-grade (follicular large cell and diffuse small cleaved in one patient each). Eleven (79%) had stage IV disease with bone marrow involvement. Eight (57%) had received two or more prior regimens while the others received one prior regimen. Four (29%) patients had received prior anthracycline therapy. Thus far, a median of two cycles of DaunoXome has been delivered (range 1-11). Of the 14 patients, six attained a partial response, three have stable disease and the remaining five have progression of disease. Three of the responders received prior anthracycline therapy. Six patients experienced grade 3 or 4 neutropenia. There was no other grade 3 or 4 toxicities. Other related side effects were all mild and consisted of fatigue, nausea, vomiting and alopecia. We conclude that DaunoXome at 100 mg/m² every three weeks is an active agent in this patient population. Further accrual is ongoing and additional data will be reported.
Chemotherapy remains the treatment centerpiece for small cell lung cancer. It has forged a role in the treatment of stage III disease, either before surgery, before radiotherapy, or together with radiotherapy before surgery. The exact role, what drugs and the timing remain the subject of trials. Platinoid drugs form the foundation of today's successful chemotherapy combinations. A second drug is almost always added, and there are debates about the value of adding a third, or even fourth drug. For small cell, the second drug is VP-16, etoposide. In non-small cell lung (NSCLC) the second drug commonly begins with the letter “V”—vinodesine, vinblastine, VP-16, vinorelbine, but not vincristine, and many argue that VP-16 has a poor response rate as a single agent, even though survival with cisplatin-VP-16 is as good as with any other combination. Other drugs that have been used include ifosfamide and mitomycin C. Others have been tried and were formerly popular, but are no longer regularly used. There are promising new drugs—gemcitabine, the taxanes, topotecan, irinotecan—all have already shown evidence of activity in lung cancers, but their use with radiotherapy is still unfolding.

Radiotherapy is perhaps the most versatile and least understood modality. It has been the treatment of choice for lung cancer when surgery cannot be used. It has been used like surgery, as a local treatment, but also like chemotherapy, as a regional treatment, attempting to include contiguous lymph node-bearing regions. The dose of radiotherapy has been limited by the volume, and an inability to understand three-dimensional dose-volume relationships, particularly in tobacco-abusing patients. We do not know how to predict for lung toxicity. A challenge for today is to escalate doses depending on volume of normal tissue irradiated. Radiotherapy had been restricted to doses in the 60-65 Gy in the past, but this was for volumes that included prophylactic treatment of lymph nodes. Re-defining doses and treatment volumes will allow better use of radiotherapy by itself, but, more importantly, as a partner in multimodal therapy.

Timing of the modalities provides a variety of choices, each with different potential benefits and liabilities. The sequential methods have the longest history. Pre-operative radiotherapy is a classic form of sequential therapy. Today we refer to “neoadjuvant” or “proto-adjuvant” therapy relating for the most part to chemotherapy before surgery, or before radiotherapy. Adjuvant therapy, or additional therapy after the more important therapy, has been extensively tested with older chemotherapy combinations and has not demonstrated great improvements in any measure of effectiveness. Post-operative radiotherapy has also not proven beneficial to survival, but there are recent retrospective trials that again raise the issue, and others that underscore the potential toxicity. A study of concurrent chemoradiotherapy in the post-op setting is just completed. It will show that therapy has toxicity, but the improvement in survival, if any, has not yet been detected. Consequently, the post-operative radiotherapy strategy does not enjoy universal popularity today, but there is increased enthusiasm for testing some of the newer drugs in this setting. Sequential therapies allow for assessment of the benefits and risks of each component of therapy.

Concurrent treatment uses at least two modalities at the same time. This strategy invites interactions between the modalities looking for the elusive “synergism” of effects, hopefully exclusively against the cancer, but usually it is less discriminating and causes additive or even synergistic toxicity. Large and unresected tumors harbor resistant cells. It is reasonable to anticipate that these are more likely to require more aggressive approaches.

Alternating modalities in swift sequence of days or weeks was tried in the 1980s with the promise of increasing antitumor effects without excess toxicity. Unfortunately, it seems that the toxic effects were not sufficiently reduced and the antitumor effects were not sufficiently improved. The radiotherapy used in these programs introduces gaps or “splits” in the treatment. These gaps allow for repopulation of tumor, which may explain in part the failed efficacy of this approach.

Small cell proves to be a very responsive tumor to either chemotherapy or radiotherapy. For disease confined to the thorax at presentation, local failure is a surprisingly high first sight of failure, even with the addition of thoracic radiotherapy. For disease disseminated at presentation but achieving a complete response, local failure occurs in 60%. By two meta-analyses, the addition of thoracic radiotherapy causes improved survival (and local control). Although there remains controversy, early and concurrent therapy seems to be associated with better survival than delayed and later treatment with radiotherapy. The role of surgical treatment is limited to odd cases with peripheral nodules without nodal or distant metastases. The problem of local failure needs attention, whether it be with improved drugs, altered thoracic radiotherapy dose or fractionation strategies, or timing of modalities alone or in combination.

Combined modality therapy is better for Stage III-a lung cancer (NSCLC), but Stage III-b remains unsettled. These combined modalities for Stage III provide the setting for clinical trials in the 1990s. Two surgical adjuvant trials have shown that surgery alone is poor treatment, and the standard of radiotherapy alone has fallen to very modest doses, added to only five weeks of chemotherapy before the thoracic radiotherapy. Studies now exist showing reduced systemic failure when even modest doses of chemotherapy are used. Concurrent cisplatin reduced local failure in a few studies but not consistently; a number of studies have shown no
benefit. The critical III-a question is the value of surgery in these patients. Surgery trials have selected patients capable of the rigors of surgery, but many try to apply these observations to less-fit patients. We are obliged to clarify these facts by clear clinical trials. These efforts are hampered by the allure of new drugs crying like sirens, seducing us away from our duty to answer difficult questions. New drugs are clearly needed, but so are clarifications of how we combine modalities.

Brain failure and brain prophylaxis pose special questions for combined modality therapists. Judicious use of surgical therapy in select patients is warranted. The value of adjunctive radiotherapy is under test. For patients with multiple metastases, we have little to offer. Prophylactic (PCI) therapy in both small cell and non-small cell are very contentious subjects. There is recent information suggesting a net benefit, and a very modest frequency of late effects when PCI is sequenced after completion of systemic therapy. Also, NSCLC patients completing chemotherapy, radiotherapy, and surgery seem to have a higher-than-expected frequency of brain metastasis. Since these patients have achieved good outcomes, this group might offer a reasonable cohort to test the value of adjuvant brain treatment.

Combined modality management of lung cancer has made major strides in the last decade. There is a great deal of work to do to clarify how best to manage these patients while we await new clues from the bench.

CURRENT THERAPY WITH INTERFERONS

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INTERFERONS

Interferons (IFN) have been in clinical use in the United States since the early 1980s when large-scale trials by the National Cancer Institute and the American Cancer Society identified activity for these compounds in solid tumors that were otherwise refractory to cytotoxic drugs. Interest in these compounds was also generated by the observations that the IFNs could stimulate natural killer cell activity, suggesting that these compounds could combine the specificity of biologic agents with the absence of unacceptable toxicities associated with cytotoxic drugs. The initial enthusiasm for IFN has been tempered by recent evidence which suggests that the toxicities of IFN are comparable, although different, from that of cytotoxic agents. Furthermore, the mechanism of action of IFN remains to be identified precisely, and immunologic effects may be secondary, rather than primary mechanisms.

The clinical spectrum of activity for IFN has continued to expand over the past 20 years. Nevertheless, the optimal utility of these agents remains to be identified. Current clinical uses for IFNs are described below.

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<tr>
<th>FDA-approved indications for IFN:</th>
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<tr>
<td>IFNα-2b</td>
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<td>Hairy-cell leukemia</td>
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<td>Condyloma acuminata</td>
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<td>AIDS-related Kaposi’s sarcoma</td>
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<td>Hairy cell leukemia</td>
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<td>AIDS-related Kaposi’s sarcoma</td>
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<td>Chronic myelogenous leukemia</td>
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MELANOMA

Adjuvant Therapy

Patients with early-stage melanoma (<1.5 mm in depth) will have an 85% survival at 10 years. The prognosis for patients with lesions >4 mm is substantially worse, with survival <50%. Based on the results of a randomized trial conducted by the Eastern Cooperative Oncology Group (EST 1684), IFNα-2b has recently been approved for the adjuvant treatment of melanoma by the FDA. In this trial, patients with locally advanced melanoma at high risk for recurrence were randomized to either observation or to high-dose adjuvant therapy with IFNα-2b for one year. Patients at high risk included those with Breslow thickness >4 mm or patients with primary or recurrent lymph node involvement. Treatment consisted of high-dose daily intravenous therapy for one month, followed by maintenance therapy. With a median follow-up of over seven years, there was an increase in the median survival duration for patients receiving IFN of 12.4 months (33.4 months versus 45.8 months, p = 0.02) and an increase in the median relapse-free survival of 8.8 months (11.8 months versus 8.8 months, p = 0.002).

Quality-of-life assessments were performed using the Q-TWIST instrument during the ECOG trial. The IFN arm had a significant gain in quality-of-life adjusted time, and that this was greatest in the node-positive strata, suggested that clinical benefits of the treatment could significantly offset the side effects of treatment.

Renal Cell Carcinoma

Single-agent IFN has modest activity in the treatment of renal cell carcinoma, with objective response rates in the
15%-20% range. Low- or intermediate-dose combinations of IL-2 and IFN have been employed in the out-patient setting. Recent trials from Europe using intermediate-dose IL-2 + IFN have suggested a survival or progression-free survival advantage for combination therapy versus either agent alone. This observation remains to be confirmed. While the severe toxicities observed in some studies do suggest caution in administering these regimens in the out-patient setting, this approach is clearly of interest in ameliorating the toxicities observed with high-dose IL-2 and with improving quality of life in this patient population.

**Non-Hodgkin’s Lymphoma**

IFN as a single agent has demonstrated clinical activity against follicular lymphomas in patients who have failed prior chemotherapy, with response rates of 30%-50%. Several clinical trials conducted by the ECOG, the EORTC and GELA have demonstrated a benefit in time to failure to combinations of IFN and cytotoxic agents. These results should be interpreted cautiously, however. The patient populations were often heterogeneous, with some patients having non-follicular lymphomas and some including both low-grade and intermediate-grade patients. In addition, only one trial demonstrated a clear survival advantage for the IFN group; there was no clear plateau in the survival curves. Additional studies are warranted to confirm these findings and attempt to improve the constitutional symptoms associated with IFN.

**Chronic Myelogenous Leukemia**

IFN has substantial clinical activity against CML. Response is highly dependent on stage of disease, however. In patients in blast crisis, a major cytogenetic response is almost never achieved, whereas in early chronic phase IFN treatment results in a major cytogenetic response in 20%-30%, with late chronic phase and accelerated phase being intermediate. In comparison with conventional chemotherapy, IFN treatment has demonstrated a survival advantage, and low-dose therapy may be as effective as high-dose therapy.

**Multiple Myeloma**

Several randomized trials have tested the role of chemotherapy with or without the addition of IFN. In addition, IFN has been studied in the maintenance setting following induction chemotherapy in patients with multiple myeloma. While not definitive, these trials suggest there may be benefits for selected patients with myeloma.

**NEXT MEETING OF THE NETWORK: OCTOBER 16-18, 1997**

The next Network meeting will be held in Atlanta, Georgia, October 16-18, 1997, at the Grand Hyatt Atlanta. Attendees will again be eligible for Category 1 CME credits. Invited speakers include: Bruce Chabner, Derek Raghavan, Franco Cavalli, Vincent DeVita, Patrick Loehrer, William Wood, Eric Rovinsky, and Craig Henderson. Many important topics will be covered, including contemporary and developing treatments of breast, lung, and colon cancers, genetic technologies and new drugs. A separate meeting will be held for nurses and administrators to discuss practice management issues, such as defining cancer care or how to determine what services to include in a capitated contract; how the regulatory environment affects capitation; obtaining the best capitated rate for cancer care, and creative contracting and direct contracting strategies.

Network membership is free. A cordial invitation is especially extended to European oncologists. For membership information and/or meeting registration, contact Network For Oncology Communication & Research, 1450 S. Johnson Ferry Road, Atlanta, GA 30319 (telephone: 404-252-9979; fax: 404-847-0409).