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A REVIEW OF CURRENT CONCEPTS IN CANCER CHEMOTHERAPY

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Chemotherapy today is a modality predominantly used to treat metastatic or disseminated malignant neoplastic disease. Depending upon the primary site and stage (extent) of disease, chemotherapy can be geared to be curative or palliative in its intent.

Chemotherapy can lead to prolonged disease-free survival in a percentage of patients with certain stages of eleven different malignancies (Table 1)[1]. For some of these, chemotherapy can eradicate all malignancy by itself in advanced stages when macroscopic metastatic disease is present. For the three pediatric solid tumors on the list, chemotherapy is used as an adjuvant to surgery and/or irradiation to eradicate microscopic metastatic disease after the local modalities have removed or ablated the primary local and residual disease.

The roles of cancer chemotherapy in the treatment of metastatic tumor are manifold[2] with the diversity being dependent on:

1. whether the target is macroscopic (clinically evident) disease or microscopic disease;
2. the site of the primary tumor from which the metastases arose;
3. the clinical and pathologic stage of the disease at the time of treatment.

The intent of treatment can be curative or palliative depending upon the three factors just elucidated. Chemotherapy can be administered as single agent treatment, combination chemotherapy or within a combined modality setting with irradiation and/or surgery.

Cytotoxic cancer chemotherapy is an imperfect modality. Its imperfection rests in its inability to cause tumor regressions in all patients treated and its side effects. Some patients achieve dramatic benefits from cancer chemotherapy which more than offsets the toxicity risks associated with the drugs. Other patients obtain little or no therapeutic benefit from the drugs and therefore receive the toxicity risks without the benefits. The chemotherapy situation is further complicated by the reality of the heterogeneity of multiple sites for neoplastic primary disease and the multiplicity of drugs available for usage. Each of the many different diseases called cancer has its own natural history, patterns of spread and responsiveness to therapy. The established anti-cancer drugs have their own pattern of sensitive and resistant primary tumor types. In addition, the use of combination of drugs makes for an enormous complexity of possible regimens.

The choice of drugs for usage against metastatic tumors is exquisitely dependent upon the primary site of origin. Over the years, a data base has been established which links specific primary tumor types with drugs which have demonstrated reproducible clinical activity. This data base is far from complete and is replete with examples of differences of opinion among clinical investigators. Few, if any, of the commercially available anti-cancer agents have an adequate data base in the relevant malignancies to determine their activity.

The most successful chemotherapy of clinically evident metastatic disease has been combination chemotherapy[3]. The choice of drugs to be included in a disease-specific combination regimen has generally followed some empirically developed guidelines:

1. the drugs should be active when used alone against the disease in question;
2. the drugs should have different postulated or known mechanisms of action;
3. the drugs should not have overlapping toxicity patterns to the degree possible.

Since most drugs cause myelosuppression, the last aspect cannot be perfectly followed.

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This last aspect has made drugs which do not cause significant myelosuppression, e.g. vincristine and bleomycin, highly popular in combination regimens when even a hint of possible disease-specific activity can be found.

Activity against macroscopic metastatic disease is generally defined as some minimal rate of objective regression in a cohort of treated patients. An objective regression is either a complete or partial regression of measurable or evaluable tumor masses by criteria which are generally accepted in only a broad sense and open to wide variations in interpretation. The wide variation in the interpretation of what is an objective regression has led to a great lack of consistency in the chemotherapy literature and a major interpretive challenge for a busy clinician of clinical investigator.

TABLE 1 – The Varying Roles of Cancer Chemotherapy

A. Tumors in Which Chemotherapy Used Alone has a Curative Potential

Tumor	Stage	Representative Regimens	Comments
Acute Lymphocytic Leukemia	NA	*Induction:* Vincristine + Prednisone + Daunorubicin *CNS prophylaxis:* Intrathecal Methotrexate ± Craniospinal Irradiation *Maintenance:* Methotrexate and 6-Mercaptopurine with Periodic Re-induction	Curative potential in children under age 15. Complete remission induction about 90% but long-term maintenance required.
Hodgkin's Disease	III-IV	"MOPP" Nitrogen Mustard Oncovin (Vincristine) Procarbazine Prednisone or "ABVD" Doxorubicin Bleomycin Vinblastine Dacarbazine	Complete remission induction 65-80% Maintenance of no proven value. Important to pathologically restage.
Diffuse Histiocytic Lymphomas	III-IV	"CHOP" Cyclophosphamide Doxorubicin Oncovin (Vincristine) Prednisone or "BACOP" Bleomycin Doxorubicin Cyclophosphamide Oncovin Prednisone or "MACOP-B" Methotrexate (with rescue) Doxorubicin Cyclophosphamide Vincristine Prednisone Bleomycin	Complete remission 50-60%. Maintenance of no proven value. Important to pathologically restage complete remissions.

TABLE 1 (continued)

Testicular Carcinoma	III (disseminated disease)	"PVB" Cisplatin Vinblastine Bleomycin	Complete remission in about 75%. Can use surgery in patients with partial response to further induce complete remission. Long-term maintenance of no proven value. Data predominantly in non-seminomatous histologies.
Burkitt's Tumor	IV	Cyclophosphamide	
Uterine Choriocarcinoma	Metastatic	Single-agent Methotrexate or Actinomycin D + Methotrexate + Alkylating agent	Single agents giver 95% cure in low-risk patients while combinations give 70-80% complete remission in high-risk patients.

B. Tumors in Which Chemotherapy Increases the Cure Rates When Used as Adjuvant to Surgery and/or X-ray Therapy

Tumor	Stage	Local Control Therapy	Representative Regimens	Comments
Breast Cancer	II	Surgery ± X-ray	"CMF" Cyclophosphamide Methotrexate 5-Fluorouracil "CMFVP" Above 3 drugs + Vincristine and Prednisone	Data most persuasive for premenopausal women and suggestive for postmenopausal women.
Osteogenic Sarcoma	Clinically Localized	Radical Amputation	High-Dose Methotrexate + Vincristine ± Doxorubicin	Data suggestive from historically controlled studies but not proven in prospectively randomized studies.
Wilms' Tumor	Local or Regional Spread	Surgery and X-ray	Actinomycin D + Vincristine	
Embryonal Rhabdomyo-sarcoma	Local or Regional Spread	Surgery and X-ray	Cyclophosphamide + Actinomycin D + Vincristine	
Ewing's Sarcoma	Localized Disease	X-ray	Cyclophosphamide + Vincristine ± Actinomycin D	

C. Tumors in Which Chemotherapy Can Achieve Complete Remissions in More Than One Quarter of Patients Treated with Resultant Significant Prolongation of Survival and Occasional Long-Term Disease-free Survival

Tumor	Representative Regimens	Comments
Small Cell Anaplastic Lung Cancer	Cyclophosphamide + Doxorubicin + Vincristine or Cyclophosphamide + Doxorubicin + Etoposide (VP-16) or Etoposide + Cisplatin	In "limited" disease, combination chemotherapy plus irradiation gives complete response in 50% with 2-year disease-free survival of about 20%.

TABLE 1 (continued)

Ovarian Cancer	Cisplatin + Cyclophosphamide ± Doxorubicin	High complete response rate in patients with minimal residual cancer after surgery. Cyto-reductive surgery may be helpful. Pathologic determination of complete response with surgery indicates those with long-term survival benefit.
Nodular Lymphomas	"CVP" Cyclophosphamide Vincristine Prednisone or Single-agent Chlorambucil or Cyclophosphamide	Aggressive chemotherapy may have curative potential in nodular mixed lymphomas. In nodular lymphocytic, conservative therapy with single agents may be preferable.
Acute Non-lymphocytic Leukemia	Arabinosyl Cytosine + either Daunorubicin or Doxorubicin ± Thioguanine or Vincristine + Prednisone	Complete remissions in more than half the patients treated. Bone marrow transplantation in remission may offer curative potential.

D. Tumors in Which Chemotherapy Can Give High Response Rates with Survival Prolongation and Significant Palliation

Tumor	Representative Regimens	Comments
Breast Cancer	CMF ± VP Cyclophosphamide Methotrexate 5-Fluorouracil Vincristine Prednisone or Doxorubicin + Cyclophosphamide ± 5-Fluorouracil	Objective response rate in 50-70% of patients with complete responses in 10-20%.
Multiple Myeloma	Melphalan + Prednisone ± Vincristine Cyclophosphamide or ± Vincristine Doxorubicin	Objective response rates in 50-60% of patients treated with median survival 2 years.
Chronic Lymphocytic Leukemia	Chlorambucil + Prednisone	High response rates in patients with active disease. In patients with indolent disease, supportive care is best.
Chronic Myelocytic Leukemia	Busulfan	Diminishment of leukemic cells observed in most patients. Median survival is about 3.3 years. Chemotherapy may not actually prolong survival but is significantly palliative.

E. Tumors in Which Chemotherapy Achieves Objective Regression in 30-50% of Patients Treated with Drugs for the First Time

Tumor	Representative Regimens	Comments
Squamous Cell Carcinomas of Head and Neck	Cisplatin ± Bleomycin or 5-Fluorouracil or Methotrexate	Response rates nearly 50% with occasional complete response.

TABLE 1 (continued)

Soft Tissue and Bone Sarcomas	Doxorubicin ± Dacarbazine Vincristine	Response rates close to 50% with complete response in 10-20%
Gastric Cancer	5-Fluorouracil ± Doxorubicin + Mitomycin C	Response rates in about 40% of patients
Transitional Cell Bladder Cancer	Cisplatin ± Adriamycin Cyclophosphamide	Response rates in about 40% of patients.
Malignant Gliomas	Carmustine (BNCU)	Response rates in about 30% of patients.
Adrenocortical Carcinoma	Mitotane (Ortho para 'DDD)	Response rates in about 30% of patients.
Uterine Cervix Carcinoma	Cisplatin	Preliminary evidence of response rates in 40% range.
Islet Cell Tumors of the Pancreas	Streptozotocin ± 5-Fluorouracil	Objective response rates in about 50%. In functioning tumors, more than 50% have Symptomatic improvement.
Prostate Cancer	Doxorubicin or Cisplatin or Estramustine	Symptomatic improvement and stability of disease in nearly 50%. Actual objective response lower but the majority of patients do not have measurable disease.
Neuroblastoma	Cyclophosphamide + Vincristine ± Dacarbazine and Doxorubicin	Response in about 40% with two drugs. More aggressive combinations may give higher response rates.
Endometrial Adenocarcinoma	Progestational Agents	Response rates in about 30%.

F. Tumors in Which Chemotherapy Gives Response Rates in only 10-25% of Patients with Minimal Survival Benefit

Tumor	Comments
Non-oat Cell Carcinoma of the Lung	Some combinations in adenocarcinoma give higher response rates, but survival benefit in large scale studies not yet shown.
Colorectal Adenocarcinoma	5-Fluorouracil will give about 20% response rate.
Malignant Melanoma	Dacarbazine will give about 20% response rate.
Pancreatic Adenocarcinoma	5-Fluorouracil will give about 10-20% response rates. Some combinations give higher response rates in small series.
Renal Cell Carcinoma	Progestational agents giver 0-15% response rates. No active drugs to date.
Esophageal Cancer	Preliminary evidence that cisplatin may have activity. Further studies needed.

LUNG CANCER

Bronchogenic carcinomas, small cell (SCLC), and non-small cell (NSCLC), are aggressive tumors with 75% of patients inoperable at presentation, >50% mortality within the first year of diagnosis (especially SCLC) and an essentially unchanged 5 year survival. Small

cell lung tumors present as a perihilar of mediastinal mass on chest x-ray. Bronchoscopy and biopsy usually determine the diagnosis, though mediastinoscopy may be necessary for tissue diagnosis if bronchoscopy is negative. Due to the systemic nature of this disease, staging workup is important. Routine tests should include bone scan, though some would screen by alkaline phosphatase elevation, bone marrow aspirate and biopsy, liver function tests (LFT's) and brain scan. Patients with hepatomegaly or elevation in LFT's should have a liver scan.

Patients with limited disease (LD) are those with disease confined to the hemithorax with or without supraclavicular nodes. These patients have an improved chance of response and survival over patients with extensive disease (ED). Surgery. alone has been proven to be of no value as primary treatment for either limited or ED patients.

Treatment modalities for limited disease include radiotherapy (RT) + chemotherapy ± CNS prophylaxis. Moving from single agent to combination and combined modality therapy response rates have risen to current values where approximately 80% responses are seen with complete remissions (CR) of 20-25% for unselected patients (see table 2). Active agents against SCLC include cyclophosphamide, adriamycin and VP-16. Representative combinations include CAV (cyclophosphamide, adriamycin, vincristine), CAE (cyclophosphamide), EP (etoposide, cisDPP), and EP-CAV. Potential CR rates for limited disease patients is about 40% with less than half of these achieving a 2 year disease free survival. Alternating regimens have been shown to extend survival. In Osterlind's study comparing CCNU, cyclophosphamide, vincristine, methotrexate, continuous to alternating with doxorubicin, VP-16, response rates were similar (68% and 72% respectively) however, median duration of response was significantly longer for the alternating regimen (28 wks. vs. 16 wks.)[2]. Combined modality therapy, including mediastinal and prophylactic cranial irradiation has reduced

TABLE 2 – Treatment Regimens for SCLC

	Rx	Stage	CR (%)	Median Survival (A11)	1 year Survival
S.W. Oncology	Rad	L	41	52 wks	50%
Group	+	E	14	26 wks	
	VAC				
		Total	22	31 wks	
Indiana U.	Rad	L	–	78 wks	26% alive
	+	E	–	36 wks	at 26-45
	VAC				months
		Total	41	51 wks	
Radiation Oncology	Rad	L	79	2 yrs	
Branch, NCI	+	E	48	105 mos.	
	VAC				
		Total	66		
NCI-VA	Hi-dose	L	50	13 mos.	
Med. Onc. Branch	CMC	E	26	8.5 mos.	
Washington, D.C.					
		Total	30	10.5 mos.	
Baltimore Cancer	CAV +	L	57	11-12 mos.	
Research Prog.	Alternating	E	29	7.5 mos.	
NCI	Non-cross resist. Rx.				
		Total	41		
Johns Hopkins	CAV	L	40	65 wks.	
	Radio Rx	E	18		
		Total	26		

TABLE 3 – SCLC – Treatment of ED Patients

Investigator	Regimen	No. of Pts.	Median survival mos.	CR (%)	CR+PR (%)	Comments
Zelen et al[5]	Supportive care only	108	1.5	–	–	VA lung study gp.
Green et al[6]	High dose intermittent cyclophosphamide	200	4	4	22	1 year survival 5%
Edmonson et al[7]	CTX 700 mg/m^2 q 3 wks CCNU 70 mg/m^2 po q6 wks	106	4.5	12	43	Include 17% with LD
Hansen et al[8] Cohen et al[9]	CTX 500 mg/m^2 q 3 wks + CCNU 50 mg/m^2 q 6 wks + MTX 10 mg/m^2 x 2 wks	42	6.8	–	45-56	1 yr survival 10%
Hansen et al[10]	CTX 700 mg/m^2 q 3 wk + + CCNU 70 mg/m^2 q 4 wk + + MTX 20 mg/m^2 d18 and 21 q 4 wks vs CTX + CCNU + MTX + VCR weekly x4, then q 4 wk	47	65	–	75	randomized comparison p= 0.06 (one-test), 1 year survival 25%
		49	9	–	83	
Cohen et al[11]	CTX 1500 mg/m^2 dl, then 1000 mg/m^2 d21 CCNU 100 mg/m^2 dl + MTV 15 mg /m^2 x 2/wk for 5 wk – VCR 2 mg + ADR 60 mg/m^2 on d 42 and 63 + PROC 100 mg/m^2 d 10, days 42 and 63 – varied	42	13	40	90	CR in 6 wks, thymosin includes randomized in half of pts.
Livingston et al.[12]	ADR 50 mg/m^2 + CTX 750 mg/m^2 – VCR 1 mg, repeat ADR + CTX at 3 wks, VCR weekly x12, XRT to 1 and whole brain, 3000 rad in 2 wk given at 6 wks, then resume ADR + CTX	250	6	14	56	CR in 18% of fully ambulatory 10% of others, MTX 8 vs 4.5 mo fully ambulatory vs other

incidence of local recurrence and CNS metastases. In one study, CNS metastases decreased as the initial manifestation of recurrence from 22% to 2%[4].

Extensive disease patients have improved response rates with combination over single agent treatment although median survival rarely exceeds a year (Table 3). Patients may be treated with one of the aforementioned combinations with or without RT for local control. The CR rate for ED patients is reduced to approximately 15% with a 2 year disease-free survival (DFS) of 2%. Common side effects associated with these drug combinations include leukopenia, thrombocytopenia and pulmonary fibrosis.

Other treatment modalities that are under investigation include intensive chemotherapy with autologous bone marrow transplantation, immunotherapy plus chemotherapy, and debulking surgery. Although small cell lung cancer is very chemosensitive, the aggressive anti-leukemia-like protocols favor patients with limited disease and currently offer little to patients who relapse.

Diagnosis of NSCLC is usually made by chest

x-ray and bronchoscopy. Mediastinoscopy and exploratory thoracotomy may be necessary for a tissue diagnosis. CT scanning has also proven helpful in evaluating mediastinal involvement. Surgical resection is the treatment of choice for Stage 1 & 2 patients. Stage III patients with inoperable disease due to mediastinal involvement are divided into limited and extensive disease patients. Limited disease patients treated with RT alone achieve a 21% five hear survival[13] They generally have an increased median survival and improved local control over non-treated patients. Stage 3 patients with ipsilateral lymph node involvement may qualify for combined modality surgery and RT. Other surgical approaches include enbloc resections for peripheral lesions and superior sulcus tumors. Combination chemotherapy ± RT in NSCLC is considered in patients with distant metastases, mediastinal or pleural extension (extensive disease), paraneoplastic syndromes, or in patients medically inoperable due to severe chronic lung of heart disease. Resonse to chemotherapy largely depends upon performance status, disease extent, weight loss and history of prior treatment. In general, response is limited with low C.R. rates and short median survivals. Because of this low response rate, the decision to administer chemotherapy must be weighted by the significant toxicity associated with these treatments. Klastersky et al found significant hematologic toxicity in patients receiving cisDDP + VP-16, with severe grade III-IV granulocytopenia and leukopenia occurring in 23% and 12% of patients, respectively[14]. Diarrhea occurred in about 20%, and alopecia in 65% of patients receiving 60 mg/m² of cisDDP. Combinations producing responses of 35-45% include CAP (cyclophosphamide, adriamycin, cisDDP), MACC (methotrexate, adriamycin, methotrexate, CCNu), and CAMP (cyclophosphamide, adriamycin, methotrexate, CCNu). Data from several studies indicate that increased response rate is associated with improved survival. Question concerning improved quality of life still need to be more systematically evaluated although there is data which demonstrates relief of pain, dyspnea and improved performance status[14, 15] in these patients.

Tumors of this classification have a high propensity of micrometastasis and regional extension. Various groups have examined the use of chemotherapy, radiotherapy and immunotherapy in an adjuvant setting. The use of these modalities as adjuvant treatment for Stage I-II disease is still investigational.

LARGE BOWEL CANCER

Colorectal cancer has the highest incidence in North America and Northwestern Europe. Clinical presentations with acute obstructive symptoms or perforation are often the hallmark of advanced disease. Diagnosis is generally made, however, in the process of investigating constipation, abdominal pain or hemoccult positive stool samples.

OPERABILITY

Operable candidates are those who demonstrate a lack of distant metastases by chest x-ray, liver function tests, and physical findings. Patients with large lesions on barium enema and evidence of metastatic disease may undergo surgery for palliation to prevent obstruction or bleeding. Typical pre-operative tests include barium enema, colonoscopy, LFT's, liver scan (when indicated) CEA and stool for occult blood. All operable patients without metastatic disease are then staged by Duke's classification. Dukes A lesions are confined to the mucous membrane. Duke's B, divided into B_1 B_2, demonstrate incomplete and complete penetration of the muscularis propria and penetration of the serosa by B_2 lesions. Duke's C also divided into C_1 and C_2, are lesions with regional lymph node involvement with incomplete and complete penetration of the entire bowel wall. Duke's D lesions are those with distant metastases of those which have adjacent organ invasion or are irremovable altogether.

Early stage lesions are potentially curable. Dukes A + B resectable lesions experience a 5 year survival of 65%. Patients with lymph node involvement, however, have a significantly decreased 5 hear survival to the range of 30%.

TREATMENT

Adjuvant chemotherapy for colorectal cancer originated with the hopes of improving survival of patients with locally invasive tumors (Dukes B + C). 5-fluorouracil is the agent that has undergone most extensive testing. Randomized trials in the 1970's comparing 5-FU in various dose schedules vs. no chemotheraphy revealed no significant difference in survival for adjuvantly treated patients. Studies that looked at 5FU + MeCCNU were equally disappointing. In 1982 the GITS (G) conducted a trial for B_2 and C lesions. Four groups were formed: surgery alone, surgery + FU and MeCCNU, surgery + MER,

TABLE 4 – Randomized Trials of Adjuvant Chemotherapy for Colorectal Cancer (Taken from Carter S., et al, Principles of Cancer Treatment)

Author	Regimen	No. Pts.	Survival
Higgins et al[17] (1971)	5FU IV 2wk and 8-10wk post op vs no chemo	308	No significant difference
Higgins (1976)[1-8]	5FU IV q 6wk for 1 1/2 yr vs no chemo	522	No significant difference
Dwight et al[19] (1973)	FUDR IV and oral vs no chemo	548	No significant difference
Lawrence et al[20] (1975 and 1978)	5FU intraluminal ± q 2 mos. (oral) for 1 year vs no chemo	203	No significant difference
Grage et al[21,22] (1977)	5FU IV weekly for 1 year vs no chemo	189	No significant difference
Grossi et al[23] (1977)	5FU (intraluminal) vs no chemo	478	No significant difference

surgery + chemotheraphy + immunotherapy. After 47 month follow-up, 29% of patients had tumor recurrence which correlated only to stage and not to treatment arm[16]. No adjuvant treatment has been shown to be successful (table 4). Treatment options for patients with metastatic or inoperable disease may be determined by the absence or presence of symptoms. Asymptomatic patients can be reasonably observed off treatment, or undergo treatment with single agent 5FU or intra-arterial drugs if applicable.

Symptomatic patients may be treated similarly with single agent 5FU or intra-arterial drug.[24,25] Systemic chemotherapy with either single agent or combination treatment for metastatic disease produces minimal palliative results with almost no effect on survival. Commonly used single agents demonstrating activity against colon cancer include 5FU (21% response), mitomycin C (12-16% response), BCNU, CCNU and MeCCNU (10-15% response each). There is no data that demonstrates a significantly improved response rate with combination over single agent treatment. Methotrexate-5FU, for example, a combination with possible synergy in vitro has also demonstrated no significant benefit in clinical trials[26].

The most common site of metastases from colon cancer is the liver, usually resulting in rapid clinical deterioration. Hepatic artery infusion of chemotherapy selectively delivers drug to the liver. Continuous hepatic artery infusion of 5FU or FUDR takes advantage of the unique tumor blood supply arising from hepatic arterial circulation. The liver is also the main site of 5FU catabolism and, therefore, systemic toxicity should be markedly reduced while the tumor is directly bathed in cytotoxic drug. While a variety of investigators have explored this treatment modality, by far the most successful and currently irreproducible data comes from Einsminger's study. Here an 83% response was achieved in patients without extra hepatic metastases vs. 74% for those who had tumor outside the liver[27]. Toxicity specific to this treatment is chemical hepatitis and gastritis. Systemic effects are minimal. COG compared IA vs IV 5FU in a randomized trial where IA 5FU was given 20 mg/kg/d x 14d followed by 10 mg/kg/d x 7 days. Systematically treated patients received a loading dose of 12 mg/kg/d x 4 days + 6 mg/kg/d qod x 4 doses. All then received weekly IV 5FU. Response rates were 34% and 23% for IA and IV administration, respectively, which was not significant[28]. A recent prospective randomized trial of IA vs. IV FUDR yielded a 46% PR rate for those treated IA vs. a 23% PR rate for those treated by IV route. Toxicity for the intrahepatic route was confined to ulcer disease or gastritis in 21%, bilirubin > 3 mg/dl in 24% and biliary sclerosis in 9%. The systematically treated group experienced diarrhea in 66% of patients[29]. Despite the difference in interim response rates, survival between the

two groups was identical. Intra-arterial treatment of hepatic metastases does not offer significant benefit to patients and is associated with a variety of toxicities. It is a modality that should be considered but not recommended for routine use.

At the current time chemotherapy for 5FU failures is disappointing. Agents with some activity include BCNU, CCNU, MeCCNU and streptozotocin.

BREAST CANCER

Breast cancer attacks 1/11 women, exhibiting high dissemination potential and likelihood of late-recurrence[30, 31]. Diagnosis is usually made by phisician's exam, breast self-exam and/or routine mammography. Pertinent information in evaluating disease stage include tumor size, palpable lymph nodes, bone scan, and LFT's. Clinical Stage 1+ 2 patients undergo surgery with axillary node dissection to determine presence or absence of nodal disease. Those who are node negative at this time are not routinely given adjuvant chemotherapy. Node (+) patients shoued be considered for adjuvant treatment.

According to modern theories of cancer spread, malignant breast cancer cells spread to draining lymph nodes and distant sites at approximately the same time. Therefore, regional treatment of lymph node involvement will only help decrease local recurrence without effecting micrometastasis.

Patients with nodes (+) for tumor will have local-regional recurrence within 3 years[32]. Those with 1-3 positive nodes have a 50% 5 year relapse rate which rises to 80% 5 year relapse with 4 positive nodes[33]. Receptor status is an independent variable in terms of relapse potential. Patients with ER negative tumors have a higher likelihood or relapse[34]. It is accepted that patients presenting with axillary node involvement benefit significantly from adjuvant chemotherapy. In the mid-seventies, cytoxan, methotrexate, 5-fluorouracil (CMF) proved to be significantly better than single agent L-PAM yielding 53% vs 22% response rate[35]. The Milan NCI looked at adjuvant CMF vs no treatment, demonstrating a 5 year survival of 48% in controls vs 64% in the treated group[36]. Notably, this treatment was most beneficial for pre-menopausal patient with 1-3 nodes positive. In addition, there was no different in response when treated for 6 or 12 months. In terms of survival, in a review of 10,000 women in randomized trials presented by the UK Breast Cancer Trials Coordinating Subcommittee and Project on controlled therapeutic trials of the UICC (October 1984) it was determined that adjuvant CMF significantly reduced short term mortality (1-5 years). In pre-menopausal patients decrease in mortality was twice as great as that in post-menopausal patients[37]. In general, post menopausal patients are not benefitted by adjuvant chemotherapy. Those who are post-menopausal are usually treated with tamoxifen or other anti-estrogen compounds. A similar combination for pre-menopausal node (+) patients is CMFVP. A retrospective analysis of toxicity with this combination revealed significant toxicity associated with prednisone and perhaps enhanced by a prednisone-vincristine interaction. The list of prednisone related toxicities was extensive and included gastritis, hyperglycemia, cushingoid features, cataracts, osteoporosis and an unexpected increased frequency of subarachnoid hemorrhage and stroke[38]. Since there is no significant advantage of CMFVP over CMF, the use of this combination should be weighed against its toxicity.

Treatment of Stage III or locally advanced breast cancer is as yet unrewarding. Surgical treatment alone for those tumors is inadequate when local recurrence is 50%. Clinical features which deem these tumors inoperable include extensive edema over the breast, satellite nodules, inflammatory carcinoma, parasternal or supraclavicular node mets or arm edema. In these cases pre-operative radiotherapy ± chemotherapy is helpful in local control. Adequate RT of 6000 rads as well may obviate the need for mastectomy to achieve local control. However, these patients have a very high likelihood of developing micrometastases and systemic treatment is a reasonable consideration. Trials have been ongoing to determine the place of chemotherapy in these patients.

In a Milan prospective trial of patients with T_3b or T_4 lesions, all were treated with 4 cycles of AV, adriamycin and vincristine, followed by super voltage RT, 6000 rads in 6 weeks + an additional 1000 rads to residual tumor. Those who achievev CR with this combination were then randomized to no further treatment or 6 more cycles of chemotherapy. Overall, 89% of patients responded to AV. After RT 83% who responded to AV were considered CR. However, 3 year survival was 53% which was not dissimilar to that seen when patients were treated with RT alone[39]. Further studies are needed to determine better regimens to affect outcome in these patients.

Adjuvantly treated patients who relapse have similar patterns of relapse as those who were untreated or who have stage 4 disease at presentation. Fifty-sixty per cent of patients relapse in bone and lung. Relapsed patients after adjuvant therapy can be re-treated with the same regimen providing a 40-60% response rate.

The mainstay of treatment of metastatic breast cancer is combination chemotherapy[40]. Combination treatments may be divided into non-adriamycin and adriamycin containing compounds. Comparable non-adriamycin containing combinations are CMF, CMFP, CMFVP and CFP. Adriamycin containing combinations include AC, FAC, FACVP, AV. The addition of adriamycin to combination treatment does not significantly alter response rates or increase toxicity. In trials comparing CAF to CMF or CMFVP, response rates for CAF were 82% and 65% compared to 62% and 32% respectively[41, 42]. An improved response duration, however, was noted with CAF over CMFVP[41]. A recent look at CAF vs CMFP yielded similar results with no combination having an advantage[43].

Hormonal treatment of breast cancer is a vast and exciting branch of cancer therapy. Estrogen receptors are found in about 50% of primary breast tumors. Fifty to sixty per cent of patients with ER positive tumors experience tumor shrinkage when treated with hormonally active drug. Those with ER (—) tumors have a 10% response to hormonal treatment[44]. Pre-menopausal patients have a 30% incidence of ER + tumors compared to 60% in postmenopausal patients. Perimenopausal patients have the lowest incidence of ER (+) tumors at 20%[45]. Standard hormonal treatment include oophorectomy, hypophysectomy, bilateral adrenalectomy, tamoxifen citrate, megestrol acetate, aminoglutethimide, and DES. Those exhibiting the least side effects are megace and tamoxifen. These agents recently evaluated in a phase 3 trial revealed similar results in a group of premenopausal ER (+) patients[46]. Similar toxicities were also demonstrated including edema, nausea and vomiting, hot flushes, phlebitis, weight gain, and vaginal bleeding. As these agents are most appropriate for postmenopausal patients, the relative paucity of toxic effects are an important part of the therapeutic decision.

The challenge for systemic treatment for metastatic breast cancer is to affect survival. Currently, survival from first diagnosis of metastatic disease is unaffected by type of therapy received, menopausal status or treatment response[47]. This is not to say, however, that quality of life is unaffected. Metastatic breast cancer is a chronic disease, especially in the postmenopausal population where it is often slow growing and positively affected by treatment producing symptomatic relief, i.e. decreased bone pain. At best, however, these patients live symbiotically with their tumors until disease acceleration or vital organ involvement.

PROSTATE CANCER

The basis of treatment for localized prostate cancer is surgery and radiation therapy. Disease extent is determined by rectal exam, serum prostatic acid phosphatase, bone scan, and pelvic CT scan with or without lymphangiogram. Patients who are thought to have localized disease may be further classified by their clinical and pathological categories to determine risk for lymph node involvement. Patients with nodal involvement are treated with either lymph node dissection or external beam RT.

Those who cannot undergo surgery or who have incomplete prostate resections are candidates for I^{125} implants or external beam radiation. Management of metastatic disease is almost uniformly treated hormonally. This is based on the fact that prostatic tissue is androgen dependent and removal of this stimulus causes tumor regression. This manipulation can occur in one of several ways — surgical ablation of circulating androgens, removal or suppression of hypothalamic luteinizing hormone releasing factor, inhibition of androgen synthesis or blocking of androgen effect at the cellular level.

Bilateral orchiectomy reduces circulating androgens by 90%[48]. Tumor recurrence is not associated with an increase in secondary circulating androgens. As a result, estrogen treatment after orchiectomy is unsuccessful in relapse patients.

Hypothalamic inhibition of luteinizing hormone releasing factor by estrogen which occupies the hypothalamic binding site of testosterone is a controversial area. Patients treated with 1 mg/day of DES experience similar antitumor effects to those treated with 5 mg/day, with less cardiovascular effects. Effective suppression of testosterone levels to that of castrate range does not occur uniformly until doses of 3 mg/day are reached. Many argue that orchiectomy is the treatment of choise for metastatic disease since the removal of testosterone source is complete, there is less cardiovascular risk, and the need for medical compliance is eliminated. Other agents

that interfere with androgen synthesis such as aminoglutethimide, cyproterone acetate, spironolactone, have not been proven to be more effective than estrogens. Survival data obtained by the Veterans Administration Cooperative Urological Research Group (VACURG) revealed a 2 year median survival regardless of initial hormonal treatment[49]. Response to hormonal treatment is measured in terms of improved quality of life and decreased pain. Recent clinical trials have tested the efficacy of leuprolide, a gonadotropin-releasing hormone analogue, with presumably fewer side effects. The leuprolide study group compared DES 3mg daily to leuprolide 1 mg subcutaneously daily. Their results demonstrated equivalent efficacy in metastatic prostate cancer. The leuprolide treated group experienced less nausea, vomiting, gynecomastia and thromboembolism, all frequent side effects of DES. Patients on leuprolide did report more hot flushes[50].

Patients with hormonally resistant disease generally have soft tissue and nodal disease in addition to osteoblastic bone disease. Chemotherapy has not proven to be of benefit for the majority of these patients. Cytotoxic drugs with activity in prostate cancer include cyclophosphamide, adriamycin, DTIC, methotexate, and estramustine. Response rates with combination chemotherapy is in the 10-30% range. In one study, 62 patients treated with doxorubicin, 5-FU, and mitomycin C achieved a 48% response[51]. Another study of active agents doxorubicin and cisplatin vs. doxorubicin alone revealed a 53 and 59% response rate respectively[52]. Most of these patients, however, did not have measurable disease and response to treatment was determined by a reduction in alkaline phosphatase, improved performance status and decreased bone pain which may inflate responses somewhat. Despite some higher response rates, differences in median survival are not significant in any of the larger trials[53]. Improved local control of large B_2 and C tumors are a challenge for the future. Consideration of adjuvant treatment for clinical stage C patients is also necessary since the have a higher incidence of lymph node involvement and bone metastases. Combination treatment including surgery, external beam RT, interstitial implants and chemotherapy may improve local control and prevent metastatic spread.

LYMPHOMA

With the advent of aggressive high dose chemotherapy, combined modality therapy and non-cross resistant drugs, patients with Hodgkins and non-Hodgkins lymphoma may achieve complete remissions. Staging determines the course of treatment and prognosis for patients with Hodgkins disease and non-Hodgkins lymphomas. Important diagnostic tests in Hodgkins disease include CBC, LFT's, uric acid, chest x-ray, lymphangiogram, bone marrow biopsy and biopsy of accessible nodes. These tests are, of course, adjuncts to history and physical exam which will determine presence or absence of B symptoms, i.e., sweats, weight loss, fever and clinical extent of nodal and organ involvement. Staging laparotomy is important if the results will change the modality of treatment. In general, patients with suspicious lymphangiograms, splenomegaly, large mediastinal disease or anyone suspected of having disease below the diaphragm who would otherwise be treated with RT alone should undergo laparotomy.

Total nodal irradiation for stage I & II A disease produces long term disease-free survival of 80-90%[54]. The presence of B symptoms increases the likelihood of relapse and these patients should be considered for combined modality treatment. Treatment should be as definitive as possible up front since the treatment of relapses are less successful. Stage III and IV Hodgkins disease is treated with combination chemotherapy ± RT to major areas of involvement. MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) and AVBD (adriamycin, bleomycin, vinblastine, DTIC) are considered comparable primary treatments for advanced disease with somewhat different side effects. Non-cross resistant combination for Hodgkins disease such as MOPP-ABVD further increases response rates especially in patients with bulky disease[55]. Comparable results are achieved using 6 vs 12 cycles of the above alternating regimens. A similar combination without dacarbazine studied by Klimo and Connors demonstrated 96% Cr in 56 patients with 98% 3 year relapse-free survival. The 3 drug regimen was more tolerable due to less severe nausea and vomiting[56].

Patients who relapse within the first 12 months or who have not achieved CR are considered resistant. Salvage treatments that have been used include ABVD in MOPP resistant patients, yielding CR of 54% and PR of 14%[57]. Median duration of CR was 34 months. Improved CR rates were related to absence of systemic symptoms (77% vs 41%) and nodal involvement alone (68 vs 42%). Another possible treatment

after relapse from MOPP-ABVD is CEP (CCNU, VP-16, Prednimustine) a totally oral combination. After 6 cycles, 40% achieved CR and 14% PR[58]. Median relapse-free survival was 15 months. Other combinations for relapse patients include CAD and MIME (methyGAG, ifosfamide, methotrexate, VP-16) with response rates of 46% and 60%, respectively.

Common toxic side effects from combination chemotherapy for Hodgkin's disease include nausea and vomiting, vincristine neurotoxicity, sterility and leukogenesis. Combined modality treatment also increases the likelihood of pulmonary fibrosis. ABVD has been shown to have less germ cell toxicity than MOPP. In women over 30 years of age treated with MOPP, 6/14 had amenorrhea for 6 months. Out of 8 patients treated with ABVD, none had experienced this complication[55]. Similarly, combined modality treated using MOPP-RT vs ABVD-RT revealed superior response and less significant toxic effects in the ABVD treated group.

Favorable histology non-Hodgkins lymphomas, nodular diffuse lymphocytic well differentiated, nodular lymphocytic poorly differentiated, nodular mixed lymphocytic and histocytic lymphomas are generally treated with radiation for Stage I + II disease. Total lymphoid irradiation may be considered for patients with Stage 1-3 disease. There is no clear treatment for Stage III + IV patients. Single alkylating agent, combination chemotherapy such as CVP (cyclophosphamide, vincristine and prednisone) or C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisone), whole body RT, combined modality therapy, involved field irradiation or no treatment are all options. Complete responses in the range of 60-80% can be achieved with single agent therapy, combination therapy or whole body irradiation. In most studies 70-80% of patients are alive at 4 years. Asymptomatic patients may be observed until symptoms occur. Symptomatic patients may then undergo treatment with alkylating agents for RT for palliation.

Notable inroads have been made with aggressive treatment of the unfavorable histology diffuse large cell lymphomas—including diffuse large cell (Cleaved or non-cleaved), immunoblastic, lymphoblastic, and undifferentiated small cell, both Burkitt's and non-Burkitt's types. Factors associated with poor response include stage IV disease, bone marrow involvement, GI involvement and tumor mass >10 cm in a single location.

Regimens with highest responsiveness include those alternating non-cross resistant drugs such as Pro MACE-MOPP, MACOP-B programs designed to provide continuous treatment with alternating myelosuppressive and non-myelosuppressive agents[59]. In general, there is no need to administer the same drug for >3 months since resistant growth will develop. Agents such as doxorubicin, VP-16, MTX and Ara-C in alternating schedules have improved survival. Patients who have achieved CR by 2 years have a minimal likelihood for relapse beyond this time. Those with Stage I and II disease can achieve CR with combined modality treatment achieving a relapse-free survival of > 80%[60]. In a comparison trial of CVP + RT vs BACOP + RT the adriamycin containing regimen had improved freedom from progression, relapse-free survival and overall survival (97 vs 94%, 77 vs 57%, 79 vs 62%, respectively)[60]. Salvage regimens for non-Hodgkins lymphomas is presently less than satisfactory. Drugs such as VP 16, cisDDP and amsacrine have produced some of the more promising results with response duration of 3-13 months[61,62]. Amsacrine containing regimens are particularly interesting since patients who responded to this therapy had failed all known active drugs in lymphoma[61].

Current non-Hodgkins lymphoma trials are aimed at delivering high drug doses with minimum toxicity utilizing non-cross resistant agents and reducing length of treatment.

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