ADJUVANT THERAPY: IS IT NECESSARY?

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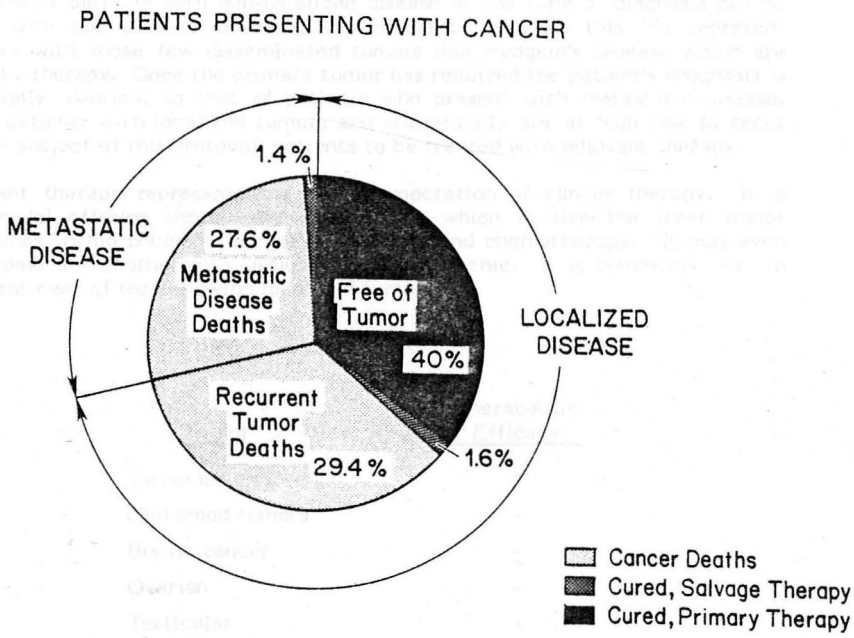
Figure 1



There are 700,000 new cases of cancer per year in the United States; i.e., exclusive of skin and in situ cancer of the cervix (1). Metastatic disease will be present at the time of diagnosis in 200,000 patients (29%) while 500,000 (71%) will have localized tumor. Of this latter group, 280,000 (40%) will remain free of disease, cured by the primary therapeutic approach. The remaining 220,000 (31%) will go on to develop either recurrent tumor at the site of primary therapy or metastatic disease. These patients have tumor which was not eradicated by the primary therapy. A portion of these patients failed primary therapy because the primary therapy did not kill or remove the localized tumor. This is an infrequent problem and it is usually detected by the oncologist or the pathologist at the time of therapy. Multicentric cancer is particularly common in carcinogen-induced tumors like bronchiogenic carcinoma, hereditary cancers as in colon tumors associated with familial polyposis and in tumors of endocrine

regulated tissue like breast cancer. It has been postulated that a portion fail because tumor emboli occur during the primary surgical procedure; this has been very difficult to substantiate scientifically; it probably occurs infrequently when primary therapy is carried out with the best technique. Most, if not all, patients will develop metastatic disease because the disease was present at the time of primary treatment but not detectable by available diagnostic techniques. These undetectable metastases are called "micrometastases".

Only 5% of patients with non-localized disease at the time of diagnosis can be cured with our present therapeutic armamentarium (2); this 5% represent patients with those few disseminated tumors like Hodgkin's Disease which are cured by therapy. Once the primary tumor has recurred the patient's prognosis is essentially identical to that of patients who present with metastatic disease. Those patients with localized tumors and statistically are at high risk to recur are the subject of this protocol; patients to be treated with adjuvant therapy.

Adjuvant therapy represents the great expectation of cancer therapy. It is multimodal offering therapeutic alternatives which involve the three major disciplines within oncology, surgery, radiation, and chemotherapy. (It may even encompass immunotherapy.) Adjuvant therapy is chic. It is commonly used in the treatment of the following localized tumors:

TABLE 1

Tumor	Therapeutic Efficacy
Sarcomas	?
Childhood tumors	+
Breast cancer	±
Ovarian	+
Testicular	+
Brain	–
Melanoma	–
Lung	±
Gastrointestinal	–
Hematologic	?
Head and neck	++

Many oncologists believe that adjuvant therapy may represent the breakthrough in curing cancer. These expectations and the attendant misconceptions will be explored in this protocol. To deal with these points, the protocol is divided into four sections: 1) Definitions and General Concepts, 2) Utilization of Adjuvant Therapy, 3) Principles of Adjuvant Therapy, and 4) Status and Future Considerations.

I. DEFINITIONS AND GENERAL CONCEPTS

To avoid augmenting pre-existing misconceptions or developing new ones, defining the terms which relate to adjuvant therapy is necessary.

Adjuvant Therapy

Adjuvant is defined in Webster's New World Dictionary as a "thing that helps" (3). The Random House Dictionary defines it as "anything that aids in removing disease especially a substance added to a prescription to aid the effect of the main ingredient" (4). Thus, in its broadest sense, it includes any therapy which is added to therapy directed at eradication of the localized tumor. The important connotation is that adjuvant therapy is helpful. (We will discuss this particular point in detail later in the protocol.) In its initial usage, adjuvant therapy represented either radiation and/or chemotherapy following surgical removal of the primary tumor. It is now conceived as any therapy directed towards undetected, but statistically likely residual disease which would not have been adequately treated by the primary therapeutic approach. The rationale behind adjuvant therapy is to treat "micrometastasis" or to treat the patient systemically when the tumor burden is the least.

Micrometastasis

These are metastatic foci of tumor which can not be detected by present diagnostic means such as physical exam, x-rays, radionuclide scan, computerized tomography, and biochemical studies. It is presumed that micrometastases develop prior to the eradication of the primary tumor and are responsible for metastatic disease which occurs after successful control of a tumor which appeared to be localized. Using the size, location, and pathological grade of a tumor as well as other risk factors, an oncologist statistically predicts when micrometastases are likely to be present and selects these patients for adjuvant therapy.

Tumor Burden

This represents the total mass of tumor present in the patient. It is thought to be important to adjuvant chemotherapy because of studies with animal tumor models. The efficacy of drug therapy in animal tumors is related to the tumor burden. When disease is less extensive, remissions and cures are more easily attained with chemotherapy whereas extensive disease responds poorly to therapy. As a general principle, this applies to human tumors as well. The scientific argument is based on principles of tumor growth too complex to extensively review (see Ref. 5,6,7). Briefly, the larger the tumor mass, the greater the amount of necrosis and avascularity present preventing drug delivery. Simultaneously, a smaller proportion of cells will be actively dividing reducing that proportion of cells sensitive to most chemotherapeutic agents. Another consideration is the relationship between tumor burden and sensitivity to therapy when avascularity and necrosis are not significant factors; e.g., diffuse micrometastasis. There are two models of cell growth and cell kill, the log-kill model of Skipper and Schabel (8,9) and the Gompertzian model of Norton-Simon (7). Both theorize that the smaller the tumor the more curable the lesion.

TABLE 2

ADJUVANT THERAPY: CELL KINETIC MODELS

Model	Cell Growth	Drug Action	Tumor Response	Drug Required (micro disease)
Log-Kill	Exponential	Log-Kill	Uniform	Little
Gompertzian	Gompertzian	Kill proportional to growth rate and tumor size	large: insensitive moderate: sensitive micro: insensitive but curable	Eradication difficult

The differences are related to tumor cell growth. In the log-kill, cell growth is assumed to be exponential. A drug will reduce the cell population by a fixed percentage; cells remain equally sensitive whether there are 10^4 or 10^{12} cells present. In the Gompertzian model, growth is exponential during a narrow range of tumor size. It is not exponential when few cells and bulky tumors are present. Norton and Simon predict that tumors of these sizes are relatively drug-resistant. Thus, the major difference between these two hypotheses is that adjuvant therapy requires less chemotherapy than the treatment of macroscopic disease in the log-kill since there are few cells to eradicate. The Gompertzian model states that the few micrometastases are stubborn and require aggressive therapy. This difference in theories is critical to the choice of agents, their dosage, and the duration of adjuvant treatment.

Survival and Disease Free Interval

To measure the efficacy of adjuvant chemotherapy, one must consider survival and the disease-free interval. The survival is measured from the time of therapy to the death of the patient. It may be compared to patients who have received no therapy throughout the course of disease (untreated controls), a different adjuvant therapy, or patients who have received therapeutic manipulations following the onset of overt metastatic disease. In studying survival, patients treated with adjuvant therapy can receive no further therapeutic manipulations (salvage therapy) with the onset of metastatic disease or, if they do receive salvage therapy, this should have no significant effect on survival. This is true of most therapeutic endeavors following relapse in patients treated with adjuvant chemotherapy. Survival studies require significantly longer periods of observation than those reporting changes in the disease-free interval (DFI).

The DFI is measured from the institution of therapy to the development of recurrent disease. Studies compare varying adjuvant therapies or no therapy. An underlying assumption is an increase in DFI relates to an increase in survival. This is not true in lesions with good salvage regimens like ovarian carcinoma, testicular cancer, and hematologic malignancies. It also implies that the presence of active disease effects the quality of the patient's life. This is frequently true but in diseases like regional melanoma this is often not the case. A study based on the DFI requires the ability to accurately measure disease parameters; in brain and pancreatic tumors the DFI cannot be evaluated. When studying tumors for survival and/or disease-free interval, it is critical to

understand the biology of the tumor. In breast cancer the DFI (10) and probably survival are increased in patients whose tumors contain estrogen receptors. Similarly, ovarian tumors of less malignant pathologic grade will effect response to therapeutic agents as well as survival independent of therapy (11). Thus, in small studies, patients must be stratified into control and treatment groups according to factors which influence survival and DFI (12,13).

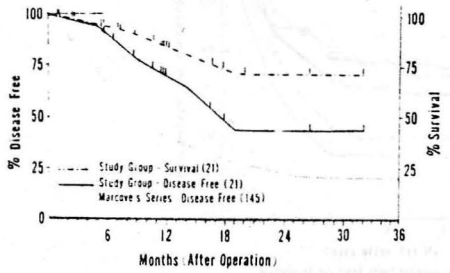
II. CLINICAL APPLICATIONS OF ADJUVANT THERAPY

To illustrate the types of response to adjuvant therapy as well as to define principles and misconceptions associated with adjuvant therapy trials, the following section will discuss results attained in osteogenic sarcoma, breast, ovarian, and testicular cancer.

Osteogenic Sarcoma

Although adjuvant therapy was probably first utilized in breast cancer, it began to achieve clinical notice and therapeutic importance with studies of osteogenic sarcoma. In an issue of the New England Journal of Medicine, two successful reports were presented for the adjuvant therapy with high dose methotrexate and citrovorum factor rescue[1] (14) and adriamycin (15).

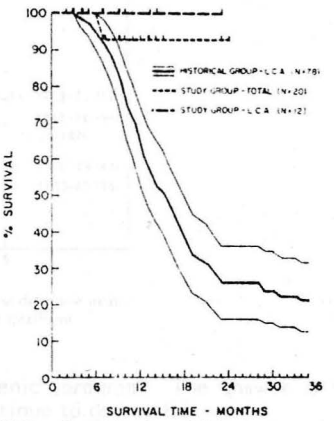
Figure 2a: Adriamycin



Percentage of Patients with Osteosarcoma Remaining Free of Disease or Alive after Operation.

Study group patients received adriamycin. Individual disease-free and surviving patients are indicated by vertical lines.

Figure 2b: Methotrexate



Here was a disease which was uniformly fatal in 80% of patients within two years with pulmonary metastasis developing within nine months (16). (See Marcove's series, a historical control, Figure 2a (. . . .)) With aggressive adriamycin chemotherapy (Figure 2a), the percentage disease-free at two years was 45%, with 71% surviving. The data was somewhat better with the high dose methotrexate but the sample was smaller and followed for shorter duration (Figure 2b). Since these two drugs were at best capable of inducing short-lived

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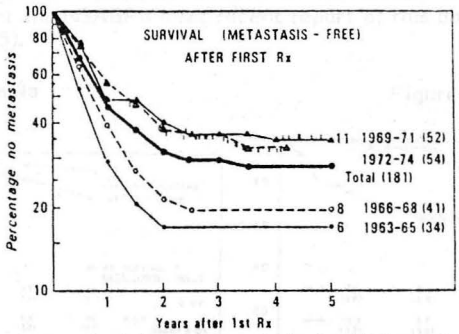
[1] to avoid marrow and renal failure caused by the high dose of methotrexate

remissions in only 40% of patients with metastatic disease, and little or no effect on survival (17), these studies appeared to support the cell kinetic data justifying adjuvant therapy. Burchenal, in an editorial in the same issue of the New England Journal of Medicine, suggests that if the data stands up, that this should be the approach in patients with high risk for metastatic disease (18). The gates were opened and adjuvant therapy of cancer was begun. Looking back on this data six years later, a number of significant reports have effected our interpretation of these results. A report from the Mayo Clinic suggested equivalent results can be attained with no adjuvant surgery (19). They conclude that the improved survival rates are based on better screening of patients for metastatic disease. They also suggest that the pathologic grade of the tumor and the location of the lesion within extremities predicts prognosis. A recent larger study from the National Cancer Institute (20), repeating the study of Jaffe et al. (14), has achieved similar results to the original study. When the NCI results are analyzed for pathologic grade, there is no difference between a historical control group and those patients with a more aggressive pathologic diagnosis (20). Unfortunately, no control group was included in this study.

Figure 3

Osteosarcoma: historical control



Survival to first metastasis after first definitive treatment for osteosarcoma by calendar year of treatment.

Is adjuvant therapy of any benefit in osteogenic sarcoma? The answer is not known, but the believers and non-believers continue to do battle.

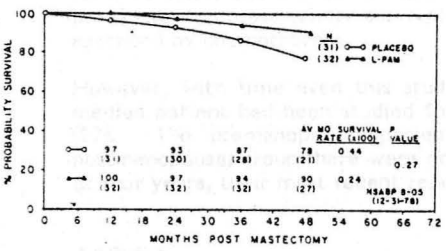
However, for our purposes, that is irrelevant. My reason for presenting this data is not to become bogged down in a controversy, but to illustrate principles and misconceptions. Historical controls are of value, but with continually changing treatment they may be of little value. In certain cancers, pathologic grade is a significant prognostic indicator and may reflect the patient's ability to respond to therapy (this point will be amplified in the section dealing with ovarian cancer). The adjuvant studies presented have convinced most investigators and practicing oncologists of their benefit, but some evidence indicates that this interpretation may not be valid. As a result, it is impossible to accrue patients for the most appropriate study on osteogenic sarcoma, a randomized study of

adjuvant therapy compared to a stratified control group receiving only primary therapy.

Breast Cancer

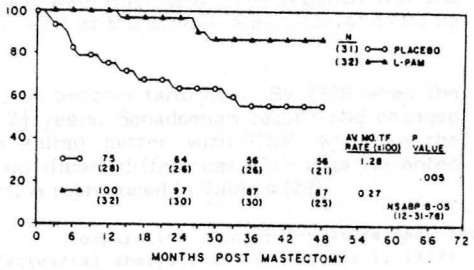
Breast cancer represents the first tumor to have been treated with adjuvant therapy. There are two early studies which suggested that chemotherpay could prolong survival in selected patients. The Thio-TEPA trial of the National Surgical Adjuvant Breast Project (NSABP) (21,22) and the cyclophosphamide trial of a combined Norwegian group (23) have demonstrated a 10-20% increase in the survival at 10 years of breast cancer patients. Patients in both groups were treated with chemotherapy given for just a few days either during or immediately following the mastectomy. By all modern criteria of cell kinetics, the amount of chemotherapy and the drugs selected were inadequate. The rationale for this therapeutic approach was to treat tumor emboli, not micrometastasis. During the 1970's there have been many successful adjuvant trials in breast cancer. The NSABP L-PAM (alkeran) trial established the criteria for evaluating results. Stratifying patients on the basis of nodal involvement and menopausal status (24). Phenlylalanine mustard was selected because it was simply taken with minimal, predictable toxicity; it was not the most effective drug available. The results reproduced below (Figures 4a and 4b) demonstrate that patients who were less than 50 years old faired significantly better than a group of patients treated simultaneously with a placebo. These figures represent the NSABP's most recent report of this data with follow-up now to four years (25).

Figure 4a



Life Table Probability (%) of Survival by Months After Mastectomy - Patients Age 49 or Younger With 1-3 Positive Nodes

Figure 4b



Life Table Probability (%) of Survival Without Disease by Months After Mastectomy - Patients Age 49 or Younger With > 3 Positive Nodes

The most important and widely discussed adjuvant study in breast cancer has been the use of CHF combination chemotherapy, consisting of cyclophosphamide, methotrexate, and 5-fluorouracil. Bonadonna used this combination in patients with operable breast cancer and regional disease involving axillary nodes (26).

TABLE 3

(Bonadonna, 1976)

Characteristics of 179 Control Patients and 207 Patients Treated with Cyclophosphamide, Methotrexate and Fluorouracil (CMF), with Observed Failure Proportions.

Characteristic	Evaluable Patients				P Value
	Control		CMF		
	no.	%	no.	%	
Total with recurrence:	43/179	24.0	11/207	5.3	$<10^{-6}$
Nodes:					
1-3	21/125	16.8*	5/139	3.6	$<10^{-3}$
≥4	22/54	40.7*	6/68	8.8	$<10^{-4}$
Age:					
≤49 yr	17/74	22.9	6/95	6.3	$<10^{-3}$
≥50 yr	26/105	24.7	5/112	4.4	$<10^{-6}$
Menopause:					
Pre	20/82	24.3	5/95	5.2	$<10^{-3}$
Post	23/97	23.7	6/112	5.3	10^{-6}
Mastectomy:					
Radical	26/132	19.6†	9/148	6.1	$<10^{-3}$
Extended	17/47	36.1†	2/59	3.3	$<10^{-4}$
Stage:					
T_1	4/22	18.1	1/18	5.5	0.23
T_2	31/136	22.7	7/153	4.5	10^{-5}
T_3	8/21	38.1	3/36	8.3	$<10^{-3}$
Histology:					
Ductal	39/158	24.6	9/180	5.0	$<10^{-6}$
Lobular	4/15	26.6	2/21	9.5	0.18
Other	0/6	—	0/6	—	
Mean follow-up period (mo)	14.0		13.7		

*1-3 nodes vs 4 or more: $P < 10^{-4}$. †Radical vs extended: $P = 0.03$.

This table represents their overall data presented after 27 months of study. With all the parameters examined except one, lesions (breast lesions less than 2 cm), patients treated with CMF were doing significantly better. Of particular note are the patients greater than 50 years of age and the postmenopausal group with probability values at the 0.0001 level. This study was the largest and the best controlled. The agents used which were effective inducing remissions in approximately 50% of patients with metastatic disease. They had no major long-term toxicity, and the combination was well tolerated. The regimen was the proof that in breast cancer survival as well as the disease-free interval could be extended by chemotherapy.

However, with time even this study has become tarnished. By 1978 when the median patient had been studied for $2\frac{1}{2}$ years, Bonadonna's results had changed (27). The premenopausal patients faired better with CMF while in the postmenopausal group there were no significant differences. The data presented at four years, their most recent report, is reproduced in Table 4 (28).

TABLE 4

(Bonadonna, 1979)

Comparative percent 4-year relapse-free (actuarial analysis as of February 1, 1979)

	Control	CMF	P*
Total	47.3	63.1	0.0001
1 node	58.0	76.7	0.02
2-3 nodes	47.3	67.1	0.01
> 3 nodes	35.2	44.8	0.03
Premenopause	43.4	70.0	0.00002
1 node	52.2	80.9	0.01
2-3 nodes	49.3	84.2	0.0005
> 3 nodes	26.7	45.4	0.005
Postmenopause	51.7	56.5	0.22
1 node	63.2	72.0	0.24
2-3 nodes	45.4	53.0	0.10
> 3 nodes	43.6	46.2	0.23

* On time distribution

The disease-free percentage in the postmenopausal CMF patients is greater than the control but the profound statistical significance ($\rho < 0.001$) has disappeared. In the group with greater than three positive nodes, there is truly no difference in response. Needless to say, these results have dampened the enthusiasm for adjuvant therapy in postmenopausal patients with breast cancer while encouraging premenopausal therapy. There are many retrospective arguments to explain the postmenopausal results: 1) breast tumors in postmenopausal patients are biologically different and may not respond to chemotherapy, 2) patients with hormone receptors may not respond to chemotherapy, 3) the postmenopausal patients over 65 years of age received about 60% of the chemotherapy that the other patients received because of a priori dosage modifications resulting in diminished efficacy, and 4) these results are a statistical error. All of the above are possibilities and are presently being considered in other trials but no data has been reported that substantiates. It must be pointed out that at the Adjuvant Therapy of Cancer Meeting (Tucson, April 1979), there were four studies presented which demonstrated that postmenopausal patients were doing as well as premenopausal (25,29,30,31). However, none of the studies had reached a median of three years, and when considered in light of Bonadonna's results (27), these studies are not worth more than mentioning. That these preliminary reports were presented and published simply demonstrates that some individuals never learn from the mistakes of others. The over-reaction to preliminary data is occuring once again in breast cancer. The duration of adjuvant therapy is being shortened from 12 months to 6 months on the basis of a randomized study which attained no difference in the DFI or survival at $2\frac{1}{2}$ years (28). It is obvious that small but significant differences are detected only with large numbers of patients studied over long periods of time, and to distinguish differences may take as long as 10 years.

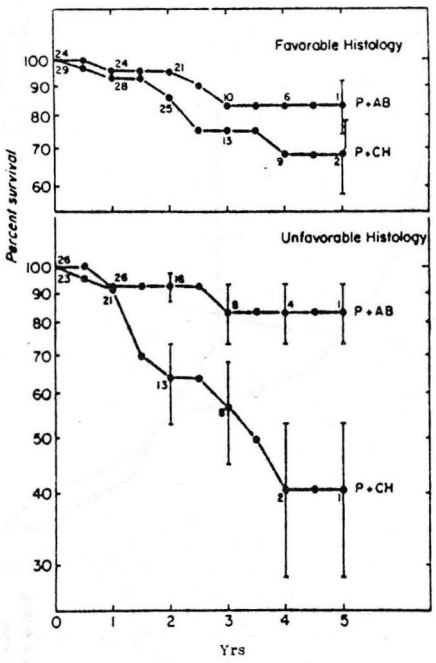
For purposes of this protocol, the following conclusions can be drawn from breast cancer studies. Certain subclassifications of breast cancer patients treated with adjuvant therapy have increased in both DFI and survival. However, it is not apparent that all patients with breast cancer respond. This once again demonstrates the importance of patient stratifications. Because of the multitude of potential stratifications in breast cancer, it is necessary to have exceedingly large clinical trials; Dr. Fisher (NSABP) finds it necessary to accrue greater than 1,000 patients per study. Since survival and the DFI varies considerably in breast cancer patients, patients must be observed for at least 10 years. The rapid publication of preliminary data is of little value in this disease.

Ovarian Cancer

In ovarian cancer the use of adjuvant therapy is relatively new; in 1974, there were only five prospective studies in ovarian cancer underway (32). In the subsequent years, three important concepts have been incorporated into the therapeutic approach which have defined prognosis and treatment groups. Surgical staging with good visualization of the entire abdomen, blind biopsies of the diaphragm and peritoneal gutters in conjunction with peritoneal washings have shown that most patients present with disease spread to the peritoneum (33). Identification of patients with disease truly confined to the ovary has greatly improved survival from 60% to approximately 80%. The gynecologic oncology group has preliminary data to suggest that adjuvant chemotherapy with melphelan prevents recurrence (34). Once again, the pathologic grade of the tumor reflects the prognosis for a given pathologic stage and the ability to respond to therapy. This applies to patients with limited (Figure 5a) and more

Figure 5a

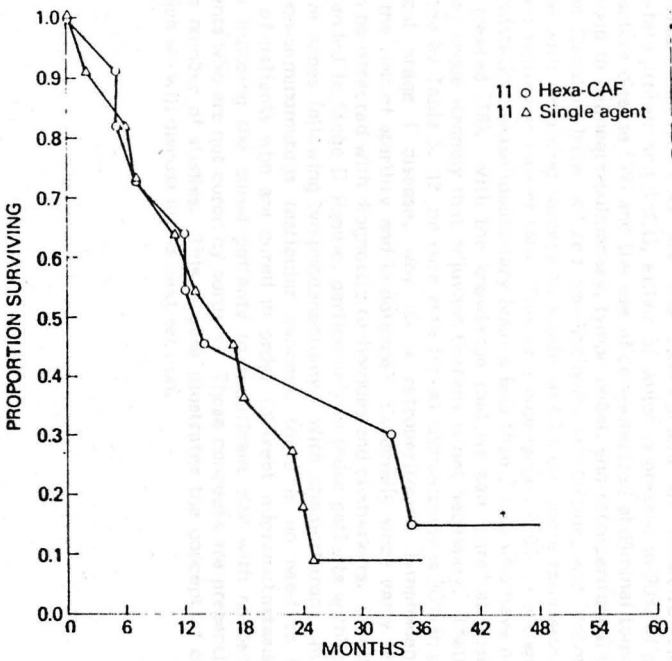
Figure 5b



Actuarial survival curves by treatment and histology in BSOH-completed stage IB, II, and asymptomatic III patients.

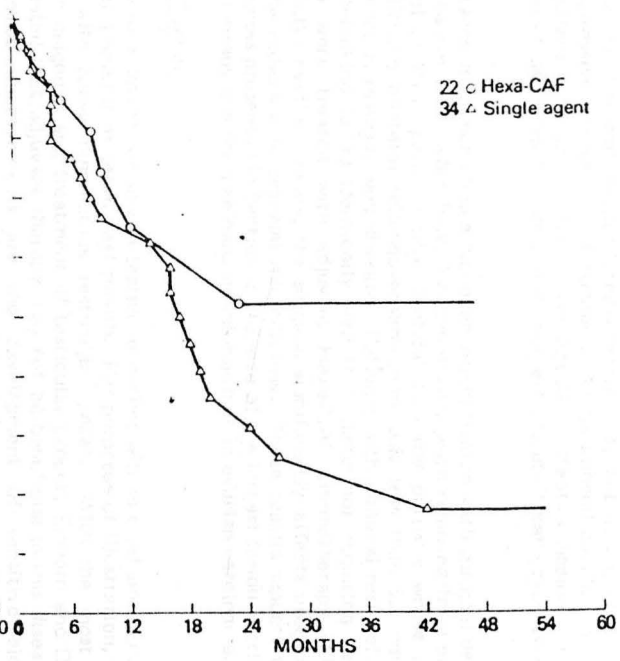
extensive disease (Figure 5b) as shown in this study from Toronto (35). In their study, pelvic irradiation (4,000 r) with a 2250 r boost by strip techniques to the entire abdomen (p + ab) was more successful than pelvic irradiation plus chlorambucil (p + ch) particularly in patients with the more unfavorable histology. This indicates that patients with more aggressive disease respond to more aggressive therapy. Somewhat dissimilar results were attained in a study of more advanced disease from the NCI (36). When one compares Hexa-CAF (Hexamethylmelamine, cyclophosphamide, aminopterin, and 5-fluorouracil) vs. single agent melphelan therapy in pathologic grade IV ovarian tumors, the differences in DFI are significant (Figure 6a) but the overall survival is uneffected. However, in the more benign grades both survival and DFI are improved with the combination chemotherapy (Figure 6b).

Figure 6a



Survival curves of patients with stage III–IV ovarian cancer and modified Broders' grade IV as a function of single-agent or Hexa-CAF combination chemotherapy.

Figure 6b



Survival curves of patients with stage III–IV ovarian cancer and modified Broders' grades II–III as a function of single-agent or Hexa-CAF combination chemotherapy.

This data shows that combination chemotherapy may not be better than single agent in aggressive disease. It illustrates a simple-minded conclusion which is often forgotten: one must have active agents to treat a disease. The best combination of drugs used to date does not effectively treat grade IV ovarian carcinoma.

The importance of tumor burden has been demonstrated with surgical debulking in ovarian cancer (37). When bulky ovarian masses were removed from patients, the survival in these patients was identical to those patients whose residual disease following bilateral salpingo-oophrectomy was less than 1.6 cm in its largest diameter, residual microdisease. Patients with minimal residual disease following debulking faired identically well to patients not requiring debulking when both were treated with adjuvant Hexa-CAF chemotherapy (33). By removing bulky ovarian tumors, the surgeon significantly affects prognosis and converts macrodisease to residual microdisease. These results support the cell kinetic theories presented in Section I: the size of the largest lesion is critical to successful therapy and the size must be microscopic in ovarian carcinoma.

Testicular Cancer

The review of adjuvant therapy in testicular cancer will be brief since Dr. James Strauss will discuss it in detail next month. For purposes of illustration, we will deal only with non-seminomatous testicular cancer. With the most recent advances in diagnosis and treatment of testicular cancer, Einhorn and Donahue have suggested that adjuvant therapy may not be beneficial in this disease (38). The diagnostic improvements are the development of sensitive biological markers, α-feta protein and βhCG, either of which is present in 90% of patients that have active disease (39) and the use of computerized abdominal tomography and ultrasound to delineate pulmonary, lymph nodal, and retroperitoneal disease. Einhorn and Donahue have utilized cis-Platinum, vinblastine, and bleomycin in combination with debulking surgery to attain an 80% complete remission rate in disseminated testicular cancer (40). This rate approaches 100% in patients with limited metastatic disease (pulmonary lesions less than 2 cm) who have not been previously treated (38). With the knowledge that we can "cure" all metastatic disease, they argue strongly that adjuvant therapy is not necessary. Their points are supported by Table 5. If the cure rate for an orchiectomy is 50% in patients with clinical Stage I disease, why do a retroperitoneal lymphadenectomy enhancing the risk of sterility and impotence? Especially since early recurrent disease can be detected with diagnostic techniques and biomarkers. Similar logic can be extended to Stage II disease, particularly in those patients with less than five positive nodes following lymphadenectomy. With chemotherapy which can cure all non-seminomatous testicular cancers, there is no need to treat a proportion of patients who are cured in order to treat micrometastasis. This constitutes exposing the cured patients to significant risk with no benefit to those patients who are not cured by surgery. These concepts are presently being tested in a number of studies. This disease illustrates the concept of cost and benefit which we will discuss in the next section.

TABLE 5

TESTICULAR CANCER

Stage	Disease	Treatment	Primary Cure Rate
I	Confined to testis	Orchiectomy	50%
		+	
		Retroperitoneal lymphadenectomy	90%
II	Subdiaphragmatic	Orchiectomy	60-80% (<5 nodes)
		+	
		Retroperitoneal lymphadenectomy	20-60% (>5 nodes)
III	Supradiaphragmatic	Orchiectomy	
		+	
		Chemotherapy	80%
		+	
		Debulking	

III. PRINCIPLES AND CONCEPTS

Study Design

The four examples of tumors presented illustrate the basic principles and concepts which should be employed in the design of adjuvant therapy. To do an adequate adjuvant study, one must be able to accrue a large population of patients which will discriminate efficacy from failure and, thus, answer the question which the investigator is posing. It is important to understand the natural history of the tumor so that appropriate stratification will be done. If the sample size is large, one can assume random distribution and stratification may be done retrospectively (13). Each point of stratification will increase the sample size geometrically and, hence, the requirement of the NSABP for often greater than 1,000 patients. Careful pathologic staging of the patient is critical, as we have reviewed in osteogenic sarcoma, ovarian, and testicular cancer; this will distinguish metastatic disease and impart a significant effect on survival. Similarly, in ovarian and osteogenic sarcoma the pathologic grade has a signifi- independent effect on prognosis, influencing the response to therapy. In breast cancer older age, post-menopausal status, and the presence of estrogen receptor, a biologic marker, impart favorable prognosis (41). The initial osteogenic sarcoma studies chose to use an historical control; with the continual progress in patient management and diagnosis, this is often unwise and may lead to invalid conclusions. This is contrary to the opinions of Dr. Freireich (42) and is the

rationale for randomized studies with adequate control populations. Bonadonna has demonstrated in breast cancer the preliminary reporting of data can be a potential source of confusion (27). As a result of this and the osteogenic sarcoma studies, the cancer journal editors have become much more suspect and are requiring longer follow-up and adequate control populations before acceptance of studies for publication. The last element, and probably the most important, is the selection of the appropriate therapeutic modality. Selection is easy in some diseases, like testicular cancer, where there are curative agents available and in others, like melanoma, where no therapeutic endeavor appears to improve survival. We have seen that the therapeutic efficacy requires agents which can treat the disease. There is no reason to suspect that a therapeutic manipulation which affects a 20% remission rate in metastatic disease will have a much greater effect when used in an adjuvant setting. Since most tumors have a dismal prognosis and established therapies are of little proven value, the tendency among oncologists is to use the newest approach. Many non-reviewed studies are taken as truth. These therapies may cause significant toxicity and cost to the patient offering little chance for success. Given the commitment of time and energy involved in an adjuvant study or just giving adjuvant therapy, it is appropriate to await the development of adequate therapy.

Risk:Benefit Accounting

As discussed briefly in the section on testicular cancer, there must be a means of selecting patients to be treated with adjuvant therapy. In testicular cancer, the question may be easily answered -- no one. This is a disease which appears to be curable by salvage therapy. Thus, the risks attendent with adjuvant therapy -- sterility, impotence, second malignancies, etc. -- may be unacceptable since only those patients who develop recurrent disease require therapy. No one would be against an adjuvant chemotherapy trial in oat cell carcinoma of the lung since the survival rates are zero. This is not the case in most other tumors because a proportion can be cured with primary therapy. In breast cancer, 25% of small localized lesions without lymph node disease will relapse. Since there is no curative salvage regimen, all relapsing patients will die from their disease. Does this justify treating 75% of the patients who will never relapse? Most oncologists feel that the risk of second malignancies is great from adjuvant therapy. As this complication may approach 15% (43), this mitigates against its use in Stage I breast cancer. When there is minimal nodal disease (less than four nodes) in addition to a small primary breast lesion, cure rates drop off to about 50%. With nodal disease almost all oncologists believe adjuvant therapy is justified and most would treat postmenopausal disease where there has been no good evidence to support its use.

There are a number of approaches to improve the risk:benefit accounting of adjuvant therapy. The first is to select patients who are most likely to benefit: 1) those free of other illness which would affect survival or tolerance of therapy; 2) younger patients since older patients more poorly tolerate therapy and their survival may not be significantly affected; 3) those patients at greater risk, higher histologic grade, vascular invasion by tumor, and absence of biologic markers. The second approach is to minimize the secondary toxicity associated with the therapy. This includes excluding ineffective drugs. By NCI criteria, a drug should have at least a 20% response rate as a single agent in treating the metastatic tumor. Where possible, avoid carcinogenic agents like procarbazine and nitrosoureas, and the use of agents with chronic toxic side effects, like adriamycin (cardiotoxicity) and bleomycin (pulmonary toxicity).

IV. ADJUVANT THERAPY: PRESENT STATUS, FUTURE CONSIDERATIONS

The role of adjuvant therapy in cancer treatment must be individualized from cancer to cancer. Consideration of patients for adjuvant therapy must be based on the pathologic stage of the disease, the grade of the tumor, and other biological information relating to tumor growth.

There are diseases where adjuvant therapy has no value; these are diseases like malignant melanoma with no successful salvage therapy. Testicular tumors appear to be the other extreme; salvage therapy is so successful that adjuvant therapy should not be considered. If these patients were treated with adjuvant therapy, those patients cured by primary therapy would be exposed to the multiple toxic effects of cis-Platinum, vinblastine, and bleomycin. Since patients who develop recurrent disease can be "cured" by these agents, adjuvant therapy would be treating cured patients unnecessarily. Selected patients with ovarian and breast cancers apparently should be treated with adjuvant therapy. In both diseases, the disease-free interval and survival have been prolonged by therapy. It is unfortunate in these diseases that the ideal study has not been done. No one has compared the disease-free interval and survival following adjuvant therapy to that with no therapy followed by salvage therapy at the time of recurrence. If adjuvant therapy is not effecting cure rate but is prolonging the DFI and survival, it is quite possible that salvage therapy without adjuvant therapy might yield an equivalent survival curve. This approach is particularly important since it would allow the oncologist to treat only those patients who relapse and not patients who are cured by primary therapy. In doing so, those cured would not be exposed to the inherent toxicity of adjuvant therapy and the true costs and benefits defined.

From the data I have presented, a number of conclusions can be drawn. An effective adjuvant program requires therapeutic endeavors which will induce a high rate of remissions in disseminated disease. One can't cure a disease that doesn't respond to therapy by treating earlier. The data in testicular tumors suggests that "in the best of all possible worlds" where salvage therapy is curative, adjuvant therapy will become unnecessary. There is a considerable risk in treating patients who have no obvious tumor following primary therapy; cured patients may develop mórbid complications of that therapy. The role of the oncologist is to select those patients who are at great risk in developing metastatic disease. These are the candidates for adjuvant therapy.

Since agents which cure malignancies are not available for most diseases, it is my opinion that adjuvant therapy should be considered experimental. The need for the ideal experiment comparing adjuvant therapy to no therapy followed by salvage therapy further supports this contention. And, finally, the risk of the morbidity of adjuvant therapy to which we may be exposing patients unnecessarily points out the need for definitive studies. This viewpoint is not widely held by practicing oncologists. Through precise studies the appropriate use of adjuvant therapy will be defined and the best agents selected. Eventually, adjuvant therapy may become unnecessary.

BIBLIOGRAPHY

1. Cancer Facts and Figures. American Cancer Society, Inc., 1977.

2. DeVita, D.T., Jr., Henney, J.E., and Stonehill, E., in Adjuvant Therapy of Cancer. S.E. Jones and S.E. Salmon, eds., Grune and Stratton, New York, 1979, p. xv-xx.

3. Webster's New World Dictionary of the American Language, D.B. Guralnik, ed., William Collins and World Publishing Co., Cleveland, 1976, p. 18.

4. The Random House Dictionary of the English Language, Jess Stein, ed., Random House, Inc., New York, 1967, p. 19.

5. Hill, B.T. The management of human "solid tumors: some observations on the irrelevance of traditional cell cycle kinetics and the value of certain recent concepts. Cell Biol. Int. Rept. 2:215-230, 1978.

6. Schabel, F.M., Jr. Concepts for systemic treatment of micrometastases. Cancer 35:15-24, 1975.

7. Norton, L., and Simon, R. Tumor size, sensitivity to therapy, and design of treatment schedules. Cancer Treat. Repts. 61:1307-1317, 1977.

8. Skipper, H.E., Schabel, F.M., Jr., and Wilcox, W.S. Experimental evaluation of potential anti-cancer drugs. XIV. Further study of certain basic concepts underlying chemotherapy of leukemia. Cancer Chem. Rep. 45:5-28, 1965.

9. Skipper, H.E., and Schabel, F.M., Jr. Quantitative and cytokinetic studies in experimental tumor models. In Cancer Medicine, J.F. Holland and E. Frei, III, eds., Lea and Febiger, Philadelphia, 1973, p. 629-650.

10. Allegra, J.C., Lippman, M.E., Simon, R.E., et al. Association between steroid human receptor status and disease free interval in breast cancer. Cancer Treat. Rep. 63:1271-1277, 1979.

11. Bzols, R.F., Garvin, A.J., Costa, J. et al. Histologic grade in ovarian cancer. Cancer Treat. Rep. 63:255-265, 1979.

12. Peto, R., Pike, M.C., Armitage, P. et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Brit. J. Cancer 34:585-612, 1976.

13. Peto, R., Pike, M.C., Armitage, P., et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Brit. J. Cancer 35:1-39, 1977.

14. Jaffe, N., Frei, E., III, Traggis, D., et al. Adjuvant methotrexate and citrovorum-factor treatment of osteogenic sarcoma. N. Engl. J. Med. 291:994-997, 1974.

15. Cortes, E.P., Holland, J.F., Wang, J.J., et al. Amputation and adriamycin in primary osteosarcoma. N. Engl. J. Med. 291:998-1000, 1974.

16. Marcove, R.C., Mike, V., Hajek, J.V., et al. Osteogenic sarcoma in childhood. N.Y. State J. Med. 71:855-859, 1971.

17. Cortes, E.P., Holland, J., Wang, J., et al. Doxorubicin in disseminated osteogenic sarcoma. JAMA 221:1132-1138, 1972.

18. Burchenal, J.H. A giant step forward -- if . . . N. Engl. J. Med. 291:1029-1031, 1974.

19. Taylor, W.F., Ivins, J.C. Dahlin, D.C., et al. Trends and variability in survival from osteosarcoma. Mayo Clin. Proc. 53:695-700, 1978.

20. Rosenberg, S.A., Chabner, B.A., Young, R.C., et al. Treatment of osteogenic sarcoma. I. Effect of adjuvant high dose methotrexate after amputation. Cancer Treat. Rep. 63:739-751, 1979.

21. Fisher, B., Ravdin, R.G., Ausman, R.K., et al. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigations. Ann. Surg. 168:337-356, 1968.

22. Fisher, B., Slack, N., Katrych, D., et al. Ten-year follow-up of breast cancer patients in a cooperative clinical trial evaluating surgical adjuvant chemotherapy. Surg. Gynec. Obstet. 140:528-534, 1975.

23. Nissen-Meyer, R., Kjellgren, K., Malmio, K., et al. Surgical adjuvant chemotherapy. Results with one short course with cyclophosphamide after mastectomy for breast cancer. Cancer 41:2088-2098, 1978.

24. Fisher, B., Carbone, P., Economore, S.G., et al. L-phenylalanine mustard (L-PAM) in the management of primary breast cancer: A report of early findings. N. Engl. J. Med. 292:117-122, 1975.

25. Fisher, B., Redmond, C., et al. Breast cancer studies on the national surgical adjuvant breast and colon project (NSABP). In Adjuvant Therapy of Cancer II, S.E. Jones and S.E. Salmon, eds., Grune and Stratton, New York, 1979, p. 215-226.

26. Bonadona, G., Brusemolino, E., Valagussa, P., et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N. Engl. J. Med. 294:405-411, 1976.

27. Bonadonna, G., Valagussa, P., Rossi, A., et al. Are surgical adjuvant trials altering the course of breast cancer? Sem. Oncol. 5:450-464, 1978.

28. Bonadonna, G., Valagussa, P., Rossi, A., et al. CMF adjuvant chemotherapy in operable breast cancer. In Adjuvant Therapy of Cancer II, S.E. Jones and S. E. Salmon, eds., Grune and Stratton, New York, 1979, p. 227-235.

29. Tormey, D., Falkson, G., Weiss, R., et al. Post-operative chemotherapy with/without immunotherapy for mammary carcinoma -- a preliminary report. Ibid., p. 253-260.

30. Buzdar, A., Blumenschein, G., Gutterman, J. Adjuvant therapy with 5-fluorouracil, adriamycin, cyclophosphamide, and BCG (FAC-BCG) for stage II or III breast cancer. Ibid., p. 277-284.

31. Wendt, A.G., Jones, S.E., Salmon, S.E., et al. Adjuvant therapy of breast cancer with adriamycin-cyclophosphamide with or without radiation therapy. Ibid., p. 285-293.

32. Symposium on Ovarian Carcinoma. Nat'l Cancer Inst. Monogr. 42:1-191, 1975.

33. Young, R.C., Chabner, B.A., Hubbard, S.P., et al. Advanced ovarian carcinoma: a prospective clinical trial of melphalan (L-PAM) vs. combination chemotherpay (Hexa-CAF). N. Engl. J. Med. 299:1261-1266, 1978.

34. Dembo, A.J., Bush, R.S., Beale, F.A., et al. The Princess Margaret Hospital study of ovarian cancer: stages I, II, and asymptomatic III presentations. Cancer Treat. Rep. 63:249-254, 1979.

35. Ozols, R.F., Garvin, A.J., Costa, J., et al. Histologic grade in advanced ovarian cancer. Cancer Treat Rep. 63:255-263, 1979.

36. Hreshchyshyn, W.M., Norris, H.G., Park, R., et al. Postoperative treatment of resectable malignant and possibly malignant epithelial ovarian tumors with radiotherapy, melphalan, or no further treatment (Abstr. 9W57) Proc. of the 12th Int'l Cancer Congress, 1978, p. 157.

37. Griffiths, C.T., and Fuller, A.F. Intensive surgical and chemotherapeutic management of advanced ovarian cancer. Surg. Clin. North Am. 58:131-141, 1978.

38. Einhorn, L.H., and Donahue, J. Adjuvant chemotherapy for testicular cancer: is it necessary? In Adjuvant Therapy of Cancer II, S.E. Jones and S.E. Salmon, eds., Grune and Stratton, New York, 1979, p. 329-335.

39. Javadpour, N., and Muggia, F.M. The role of markers in the staging of testicular cancer and implications for the design of adjuvant trials. Ibid., p. 345-351.

40. Einhorn, L.H., and Donohue, J.P. Cisdiamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann. Int. Med. 87:293-298, 1977.

41. Allegra, J.C. Lippman, M.E., Simon, R., et al. Association between steroid hormone receptor status and disease-free interval in breast cancer, Cancer Treat. Rep. 63:1271-1277, 1979.

42. Freireich, E. Medical Grand Rounds, SWMS, February 28, 1980.

43. Rosenberg, S.A. Discussion at Adjuvant Therapy II, Tucson, April 1979.