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General Review

Current Impact of Adjuvant Chemotherapy in Resectable Cancer

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Cancer chemotherapy has developed rapidly over the last 20 years, and its wide application has substantially changed the management of an expanding range of tumors. Since the vast majority of cancer patients relapsing from optimal surgery and/or radiotherapy die of metastatic disease, the major therapeutic advance in cancer treatment is expected to result from a more effective systemic therapy, either in terms of new drugs and/or through a more strategic application of the available tools. Thanks to important results derived from experimental animal systems and to early favorable clinical reports, there have been changes in the therapeutic attitude and the achievements of past generations are being critically reviewed [7]. An increasing number of clinical oncologists are beginning to think in terms of minimal residual disease in given subsets treated with optimal local-regional therapy. Chemotherapy is now seriously considered as a potentially more effective treatment if applied in the presence of micrometastases, i.e., microfoci of less than 10^9 neoplastic cells. In contrast to what has been firmly established in animal tumor models [52], the therapeutic effect of growth-inhibiting compounds in combined-modality protocols has not yet been clearly proven to be strictly related to low tumor cell burden, high growth fraction, and short doubling time of micrometastases. Furthermore, it is only assumed that the activity of chemotherapy on micrometastases would be the same as that observed in advanced disease.

During the past decade a number of clinical studies were undertaken, and both promising and controversial results have been published [7, 57]. This paper will give a concise and critical review of the current status of adjuvant chemotherapy for various forms of resectable cancer. Some of the results summarized in the paper were recently reported in Paris during the Meeting on Adjuvant Therapies and Markers of Post-Surgical Minimal Residual Disease [6].

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Wilms' Tumor

The role and efficacy of multimodal therapy in Wilms' tumor is now established [26, 33]. At present, efforts are directed primarily at the refinement of treatment according to prognostic indicators such as histology, specimen weight, lymph-node status, and age [11]. Patients with anaplasia and/or sarcomatous stroma (unfavorable histology) were reported by Beckwith et al. [2] to have a 57% death rate, compared with 6.9% in patients with neither of these parameters (favorable histology). Children under 2 years of age have significantly higher 2-year relapse-free survival (RFS) and 5-year overall survival rates, while the smallest tumors (< 250 g) are associated with fewer abdominal relapses and deaths [33]. In children with stage I (tumor limited to the kidney, well encapsulated, and totally resected), postoperative irradiation (RT) seems to be unnecessary, since a 2-year survival rate of over 90% was reported both after multiple courses of dactinomycin over 15 months and after RT and dactinomycin [17]. Combined dactinomycin plus vincristine gave better survival results at 2 years at all stages than did single agents. However, there is a suggestion that fewer courses of dactinomycin and vincristine are probably required in stage-I patients, without jeopardizing the excellent survival rates [35]. In both stage-II (tumor extending locally beyond the kidney but totally resectable) and stage-III disease (cases with residual nonhematogenous tumor confined to the abdomen), the second National Wilms' Tumor Study suggested that the addition of adriamycin to dactinomycin and vincristine increased survival [41].

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Osteosarcoma

In osteogenic sarcoma, all problems dealing with contemporary cancer therapy, i.e., patient selection, importance of randomized trials, comparability of treatment regimens, early as against late reports, and cost-benefit ratio, are combined.

The rationale for the combined treatment modality was based on the following information: (1) The 5-year survival after amputation in patients selected many years ago was 19.7% (range: 16%–23%) in the review of Friedman and Carter [23]; (2) the radiologic evidence of pulmonary metastases was documented at a median of about 9 months after surgery; (3) tumor regression was observed in 40% of patients treated with high-dose methotrexate (HDMTX), with citrovorum factor (4 of 10) or with adriamycin (7 of 17) [42]. Early results, based on relatively small selected groups of patients evaluated for very short follow-up times and compared to historical controls, appeared exceptionally brilliant, either after HDMTX or adriamycin or after combination chemotherapy. Time has tempered the initial optimism, and in all published studies [6, 42] the percentage of patients with no metastases has been found to be more dependent on the length of follow-up than on the treatment schedule used. For instance, the study of Jaffé et al. [30], who originally reported a very favorable short-term RFS with HDMTX, now has only a 32% RFS at 5 years.

Parallel with less optimistic results, some doubts began to arise about the validity of the historical control group [12]. In fact, investigators at the Mayo Clinic have observed an RFS of about 35% [54] in their most recent group of patients treated with surgery only. Breur [12] noted similar results in the EORTC trial, in which about 30% of patients not receiving adjuvant therapy remained disease-free at 5 years. The improved survival after amputation alone could be due to unknown biological changes in the natural history of osteosarcoma or, more simply, to early diagnosis by more highly motivated physicians and more accurate staging procedures (e.g., lung tomography). Such favorable selection would affect the evaluation of combined-modality therapy if only historical controls were used for comparison.

Thus, although most published chemotherapy regimens have improved RFS and total survival rates, the difference is probably only small when results are compared with those obtained in more recent control series. It now seems appropriate for the real value of adjuvant therapy for operable osteogenic sarcoma to be demonstrated by new prospective randomized clinical trials, as in many other forms of neoplastic disease (e.g., amputation vs amputation plus HDMTX, as currently being studied at the Mayo Clinic). To insist only on sophisticated and expensive drug regimens and base the results on 'old' historical controls will probably delay understanding of the actual value of current therapeutic tools.

Soft-Tissue Sarcomas

In this rare group of tumors, an inadequate surgical approach is reflected in high local recurrence rates, i.e., 40%–80% in adult sarcomas and as much as 90% in childhood sarcomas. This is due to nonencapsulation of the tumor, which initially spreads along fascial planes and nerve trunks, and possibly also to a multifocal origin [10]. The prognosis is also affected by the size and site of the primary tumor and by histologic subgroup and grade. Adequate methods of improving local control and preventing hematogenous spread should also include adjuvant chemotherapy, since in general, metastatic soft-tissue sarcomas are sensitive to a number of drugs, and in particular to the association of adriamycin plus dacarbazine [44].

Rhabdomyosarcomas are the commonest soft-tissue sarcomas in the pediatric age group, and the embryonal variety is that most often recognized. Staging takes into account the resectability of the tumor and the presence of lymphatic spread from genitourinary and extremity sites. Bone marrow involvement should be excluded by means of marrow biopsies. Poor overall survival rates (10%–50%) have been reported after surgery or radiotherapy alone [10]. Embryonal rhabdomyosarcoma is highly responsive to various combination chemotherapy regimens, including cyclophosphamide, vincristine, and dactinomycin with or without adriamycin. Although the multiform disease presentations make the study of combined therapeutic programs extremely difficult, during the past decade several reports have indicated that an integrated multidisciplinary treatment has resulted in a substantial increase in the survival rate [7, 10, 25]. The value of adjuvant chemotherapy was first assessed through a randomized study. Heyn et al. [27] have in fact observed in a series of 32 children that the 2-year relapse rate after surgery alone was 55%, compared with 17% in those treated with surgery plus dactinomycin and vincristine. More recent controlled trials, such as that of the Intergroup Rhabdomyosarcoma Study [34, 36], have attempted to answer to some important clinical questions. In group-I disease (localized tumor, completely resected), RT did not seem to influence local tumor control when patients received VAC chemotherapy (vincristine, dactinomycin, and cyclophosphamide) for 2 years (RFS: no RT 87%; RT 78%; $P = 0.61$; 2-year survival: no RT 88%, RT 92%, $P = 0.33$). For group-II disease (gross excision with microscopic residual and/or extension into regional nodes or adjacent organs), VAC given for 2 years has not been found to be

significantly ($P = 0.17$) more effective (RFS 74%, 2-year survival 84%) than vincristine plus dactinomycin (RFS 68%, 2-year survival 76%), both groups also having received postoperative irradiation. In group-III disease (gross residual localized tumor), pulse VAC for 2 years was randomized versus VAC plus adriamycin. There are no significant differences in the rate and duration of response between the two treatment groups. Thus, available data indicate that a combined-modality approach can avoid mutilating surgical procedures, while in certain patient categories potential treatment sequelae from postoperative irradiation and intensive prolonged chemotherapy (as in group I) can be avoided without affecting RFS and total survival. Future studies should include site-specific treatment, which takes into account the prognostic and biological characteristics of the tumor [25, 34]. For instance, in some tumor sites, such as head and neck, where radical surgery is precluded, the optimal sequence of chemotherapy and radiotherapy remains to be defined. The same applies to tumors of the genitourinary organs, where intensive primary chemotherapy can reduce the extent of subsequent surgery and the amount of RT.

Compared with the situation in children, information on the usefulness of multimodal therapy for adult soft-tissue sarcomas is still limited. The place of RT as an adjuvant to surgery is disputed [10]. Postoperative RT following radical excision was recently reported to be as effective as radical amputation in achieving local control [48]. However, although local control can be achieved with high radiation doses ($\geqslant$ 6000 rads in 6 weeks), patients still succumb to metastatic disease [7]. Three studies carried out in Los Angeles and New York [7] have shown a decreased recurrence rate following the use of complex adjuvant chemotherapy protocols. However, the results are difficult to interpret, mainly because the studies were not randomized and the number of patients was relatively small. More valuable results were obtained in the NCI study conducted by Rosenberg et al. [48]. They randomly compared amputation with limb-sparing surgery plus postoperative RT, both groups having received adjuvant chemotherapy (escalating doses of adriamycin and cyclophosphamide plus six cycles of HDMTX) with or without immunotherapy with *C. parvum*. The 3-year actuarial analysis of 49 evaluable patients (head, neck, and trunk: 23; extremity: 26) compared with 66 historical controls revealed improvement in both RFS ($P < 0.001$) and overall survival ($P = 0.001$). Clearly, more well designed prospective randomized studies are required for proper assessment of (1) the value of postoperative RT in the control of local recurrence when radical vs nonradical excision is performed; (2) the effectiveness of adjuvant chemotherapy with regimens including methotrexate and/or adriamycin; (3) the role of chemoimmunotherapy; and (4) the prognostic significance of tumor histology, size, and site after the combined-modality approach.

Brain Tumors

Medulloblastoma

Maximal tumor resection followed by total neural axis radiation was reported 10 years ago [7] to yield a 5-year survival ranging from 25%—40%. To improve the cure rate, several combined programms have been undertaken in recent years. In 1970, the Royal Marsden Hospital in London started a prospective study with surgery plus RT to the cerebrospinal axis combined with lomustine (CCNU), vincristine, and intrathecal methotrexate [3]. Of 14 treated patients, 65% were alive at 2 years, compared with 48% of 88 children treated from 1950 to 1970 with only surgery plus irradiation. It should be noted, however, that the retrospective series was not entirely homogeneous in radiation dose and technique. In Milan, the Istituto Nazionale Tumori and the Istituto Neurologico have treated 27 children with a combined-treatment modality including surgery, RT to the cerebrospinal axis (3000 rads plus 2000 additional rads to the posterior fossa), and combination chemotherapy with intrathecal methotrexate, vincristine, and CCNU for 2 consecutive years. At January 1979, (F. Fossati-Bellani unpublished data), the 3-year RFS was 88.2% and the total survival was 92.4%. More recently, the Cooperative SIOP (International Society of Pediatric Oncology) Brain Tumor Trial [4] has reported the preliminary results of a study designed to determine the possible value of adjuvant chemotherapy in children with medulloblastoma and high-grade intracranial ependymomas. After maximal tumor excision, patients were randomized to receive either RT to the entire cerebrospinal axis or RT plus chemotherapy (vincristine plus CCNU) for approximately 48 weeks. In 214 evaluable medulloblastomas, the chemotherapy group showed a higher RFS (79.7%) compared to controls (66.9%), although the difference is not yet significant. The 2-year RFS in 30 patients with ependymomas was 84.6% for the controls and 88.2% for the chemotherapy group. The interim report of the Childrens Cancer Group Study [31] showed that at 18 months no difference was demonstrable in the survival status (about 70%) of patients (medulloblastoma 75, ependymoma 16) randomly treated with surgery plus RT or surgery plus RT and chemotherapy (vincristine, CCNU, prednisone). In conclusion, available results indicate that adjuvant-chemotherapy is improving the survival rates, at least in some studies. However, successful results were obtained only in nonrandomized studies and when treatment included intrathecal methotrexate. In contrast, randomized trials with no intrathecal methotrexate have so far failed to

definitely confirm the usefulness of systemic therapy. Most probably, in this disease also, contemporary patient selection and improved techniques of surgery and RT are partly responsible for the present improvement in survival over that in historical series, regardless of the use of adjuvant chemotherapy.

Malignant Gliomas

In glioblastoma multiforme (astrocytoma grades III and IV), the median survival after operation ranges from 4.5 to 6 months, while approximately 20% of patients are alive at 12 months and less than 10% at 24 months. Survival is also related to the extent of surgery, extensive resection being superior to partial resection, while external decompression gives very poor results [7, 24]. Postoperative RT was reported in the past by some investigators not to affect the overall survival consistently [24]. However, recent controlled studies [56] failed to support this concept fully. The availability of liposoluble nitrosourea compounds has recently stimulated interest in the pharmacological treatment of malignant gliomas. Their activity in inoperable or recurrent glioblastoma multiforme has been definitely established [20]. The first important controlled study with adjuvant chemotherapy was that of the Brain Tumor Study Group in the United States [56]. After surgical resection, 223 patients were randomized into four groups. The best median survival was that in the group treated with RT plus BCNU (40 weeks), followed by those given RT (37 weeks), BCNU (25 weeks), and no further therapy (17 weeks). The same group subsequently reported that BCNU was superior to MeCCNU. In a similar study carried out in Milan on 102 consecutive patients by Solero et al. [53], both RFS ($P = 0.05$) and total survival ($P = 0.03$) were significantly improved only in patients treated with RT plus CCNU, and not in those given RT plus BCNU, compared with patients treated with RT. In contrast, Reagan et al. and Band et al. [7] failed to demonstrate a significant superiority of RT plus CCNU over RT, while Robustelli [47] found a comparable median survival with RT plus BCNU (12 months) and with RT plus CCNU (11 months). Here again, patient selection (e.g., tumor grade, extent of surgical resection) and/or limited number of evaluable patients were probably the major cause of contradictory findings concerning the relative therapeutic merits of the nitrosourea derivatives, as observed in published controlled studies. Adjuvant chemotherapy for malignant gliomas can potentially be optimized by combination chemotherapy. However, the actual value of multiple-drug treatment must be demonstrated by means of properly randomized studies where patients are stratified by tumor grade (III vs IV) and extent of surgery (total vs subtotal resection).

Breast Cancer

Probably because of its frequency in Western countries and the lingering difficulties in crossing medical barriers, breast cancer now provides a classic example of the problems in the evolution of therapeutic research in cancer. When the results are carefully analyzed in series comprising consecutive patients staged, treated, and followed in a uniform fashion, the limits of treatment based only on anatomical principles such as radical mastectomy with or without RT appear evident [8]. Available findings indicate that the histologic status of axillary lymph nodes represents the single most useful prognostic factor in women with operable breast cancer (median RFS in breast cancer with positive nodes [N +] is about 3 years), and the pattern of relapse demonstrates a high frequency of distant metastases as first tumor recurrence. The status of current multimodality therapy for N+ breast cancer has recently been reviewed in detail [8, 15, 49]. So far, none of the numerous on-going trials has yet reached the point where a definitive conclusion, either positive or negative, can be drawn, since published results are still based on findings analyzed a maximum of 2 years after mastectomy. A longer follow-up has so far been achieved only by the Milan and NSABP groups, which can provide the 4-year results of their first trials on adequate numbers of patients at risk. After 12 cycles of CMF (cyclophosphamide, methotrexate, fluorouracil) the 4-year RFS (control 47.3% vs CMF 65.6%) and total survival (control 73.6% vs CMF 83.0%) confirm the initial findings, i.e., prolonged adjuvant combination chemotherapy can significantly (RFS: $P < 0.0001$; survival: $P = 0.05$) alter the early and intermediate course of N+ operable breast cancer [8, 49]. The total failure rate was significantly reduced by CMF even in the presence of a single histologically positive node, regardless of whether the adenopathy was clinically or only microscopically involved [8]. CMF also significantly reduced the incidence of local-regional recurrence, and the results (7.3%) appear competitive with those obtained with postoperative RT. With the dose schedule utilized, the beneficial effects of CMF appear to be limited to premenopausal women (RFS: control 40.8% vs CMF 75.0%; survival: control 70.6% vs CMF 89.6%). In this favorable group, preliminary results indicate that there is no significant difference in the 2-year RFS between 12 and 6 cycles of CMF [8]. In patients with treatment failure, 12 cycles of CMF delayed recurrence (i.e., increased the median time to relapse) also in postmenopausal women, especially those with more than three positive nodes, beyond that in controls. This indicates that CMF initially induced significant tumor cell kill, but the subsequent overgrowth of drug-resistant tumor cells was probably a major cause of chemotherapy failure in postmenopausal patients. In the NSABP

study [40], the 4-year RFS continues to indicate a significant difference in favor of patients receiving PAM chemotherapy (control 51% vs PAM 59%; $P = 0.03$). In this study too, the beneficial effect of single-agent chemotherapy seems to be restricted to women under 50, and especially to those with one to three positive axillary nodes (control 54% vs PAM 86%; $P = 0.006$). Available results from CMF and PAM studies suggest that adjuvant chemotherapy induced a direct cytotoxic effect as well as an indirect hormone effect in premenopausal women. However, the lack of significant correlation between incidence of relapse and drug-induced ovarian dysfunction in both CMF [5] and PAM [21] trials and the superiority of the 4-year CMF results over those obtained with adjuvant castration in N+ premenopausal women [5, 8] indicate that the benefit of adjuvant chemotherapy cannot be ascribed solely to medical ovariectomy.

As far as other on-going trials are concerned, all groups but the Swiss group have observed some beneficial effect on RFS in patients or subsets of patients subjected to various forms of adjuvant treatment. In four groups the initial results appear to be limited to premenopausal women, while in four other groups the opposite was observed [8, 49]. The differences are probably related to the number of patients at risk in each subset and also to limited follow-up.

In conclusion, current results appear promising as well as controversial. However, assuming that the intermediate analysis predicts for the long-term analysis to a certain extent, for the first time for about 40 years there are significant changes in both relapse and total survival rates after prolonged adjuvant chemotherapy, at least in premenopausal women. For the time being, CMF appears to be the treatment of choice for premenopausal women, since no other drug regimen has been shown so far to diminish recurrence rates and improve the overall survival over that achieved with surgery alone with a reasonable follow-up time. Should a young patient with involvement of one to three nodes refuse combination chemotherapy, then PAM could be substituted for CMF. Until more hard data become available, the use of adriamycin-containing regimens should be discouraged for routine use because of the potential delayed cardiac toxicity. For the time being, postmenopausal patients and node-negative women (N–) remain experimental groups. The role of adjuvant hormone therapy with or without chemotherapy and that of immunotherapy with or without chemotherapy remains to be defined.

Gastrointestinal Cancer

Gastric Carcinoma

No new findings have been recorded for this tumor since our last review [7]. Essentially, no significant difference in overall survival or recurrence rate was obtained in seven trials with thio-TEPA, mitomycin C, fluorodeoxyuridine, cyclophosphamide plus chromomycin A_3, and nitromin. The moderately favorable results claimed by two study groups in Soviet Union and in Japan [7] with adjuvant fluorouracil need to be confirmed. The results of ongoing studies with postoperative fluorouracil plus MeCCNU and with fluorouracil, adriamycin, and mitomycin C are not yet available.

Colorectal Carcinoma

Since the incidence of this disease is increasing in Western countries and since Dukes' B (muscularis involvement) and C (serosal and/or regional node involvement) lesions comprise 90% of all surgically treatable tumors, successful application of the multimodal primary treatment concept in this disease would have a marked effect in reducing overall cancer deaths [57]. As previously analyzed in detail [7], the only favorable reports on the usefulness of adjuvant fluorouracil, a drug which has only a limited activity in patients with advanced disease, have come from uncontrolled studies. Recently, the updated results of two controlled randomized studies have indicated some benefit from fluorouracil adjuvant therapy. Grage [6] showed that fluorouracil given for 1 year provided a small but significant RFS improvement in the group of patients with Dukes' C lesions and rectal carcinoma, the median follow-up being 28 months. The Veterans Administration Surgical Adjuvant Group (VASAG) [28] has reported a modest 8-year survival benefit (control 25.8%, fluorouracil 32.9%) in Dukes' C patients treated with fluorouracil over 18 months postoperatively. The advantage for the drug-treated group was not evident until the third year after surgery. The difference was not statistically significant. However, the authors claimed that the consistent slight benefit observed in all previous VASAG studies was not likely to be due to chance [28].

Bronchogenic Carcinoma

In non-small-cell carcinomas the prognosis remains catastrophic, despite innumerable efforts with various forms of combined treatment in all stages [7]. The recent prospective randomized trial conducted by the Veterans Administration Surgical Adjuvant Group after successful curative resection (controls vs cyclophosphamide vs cyclophosphamide plus methotrexate) also failed to show any benefit from adjuvant chemotherapy [51]. More recently, Karrer et al. [32] have reported some beneficial results from adjuvant chemotherapy selecting out certain subsets of the study population. Again, the multitude of variables involved in the trial prevents full acceptance of the favorable conclusions.

Malignant Melanoma

As previously reported [7], the prognostic variables in malignant melanoma are primarily related to the histopathologic degree of skin invasion (Clark's level) and/or the status of regional lymph nodes. In patients with Clark's level III–V and with regional nodes involved systemic therapy is clearly warranted, since treatment failure after surgery is usually caused by distant micrometastases. In recent years, adjuvant trials in melanoma have involved treatment with immunotherapy (BCG), chemotherapy, or a combination of the two. BCG immunotherapy was found effective in reducing the relapse rate in stage II-patients when results were compared with those obtained in historical controls [18]. However, in a prospective randomized trial, Pinsky et al. [45] failed to confirm the advantage of adjuvant BCG over surgery alone in either survival or relapse-free interval. As far as adjuvant chemotherapy and chemoimmunotherapy are concerned, Wood et al. [58] carried out a randomized study in 70 selected patients at high risk of recurrence. After resection of all clinically apparent tumor, including regional lymph node dissection, patients were assigned to receive dacarbazine (DTIC), BCG, or DTIC plus BCG. At 2 years, there have been no recurrences in 22 patients receiving combined chemoimmunotherapy, as against 6 in 20 patients (30%) receiving DTIC, and 5 in 28 (18%) receiving BCG. The authors concluded that in the prevention of early recurrence, the combined therapy arm was significantly superior to both the immunotherapy arm ($P < 0.05$) and the chemotherapy arm ($P < 0.01$). In terms of survival, DTIC plus BCG also was superior to DTIC alone ($P < 0.05$). The ongoing prospective randomized study of the World Health Organization is comparing DTIC therapy, BCG, DTIC plus BCG, and surgery alone (control) in patients with histologically involved regional nodes. The study, in which over 500 patients have been entered, is not sufficiently advanced for final results to be available. However, the actuarial analysis at 2 years (WHO, unpublished data) showed a significant increase in the RFS for all treatment groups against controls. The difference was more evident in the DTIC-treated arm ($P < 0.001$) and less consistent in the BCG arm ($P < 0.01$). Positive results in the RFS were not reflected in an improved survival rate at that stage. Positive results were also recently reported by Banzet et al. [1], who used a randomized study protocol in patients with Clark's level III-V. The results are somewhat difficult to interpret, mainly because of the complexity of the treatment protocol. Also in this study, the 2-year RFS was significantly improved by chemotherapy compared with surgery alone, but the overall survival was the same. The updated results of the Central Oncology Group [29], who have randomly treated 165 high-risk patients with surgery or surgery plus dacarbazine, revealed that after a median follow-up period of 2.5 years RFS was 45% for controls, as against 28% for chemotherapy-treated patients. At present, these conflicting results cannot be easily interpreted.

Testicular Cancer

The past decade has witnessed important changes in therapeutic concepts and results for nonseminomatous germ-cell tumors. The important question now is when and how best to integrate the three major therapeutic disciplines of oncology to improve the cure rate for each disease stage. It is well known that both surgery (orchiectomy plus retroperitoneal node dissection) and RT (irradiation of retroperitoneal node chains) may make a significant contribution to the management of early (clinical stage I) and intermediate (clinical stage II) disease. Besides removing the primary tumor for optimal histologic examination and playing a significant role in the staging of lymph-node disease, radical surgery provides the best possibility of long-term cure (about 80%) in patients with histologically negative retroperitoneal nodes (N–). A lower percentage cure rate (50%–60%) can be obtained in patients with histologically positive retroperitoneal nodes (N+). In carefully selected series (e.g., adenopathies < 2 cm, negative scalene node biopsy, and lung tomograms) RT can provide comparable results. The relative merits of surgery and RT were never tested in a prospective randomized trial in the past. Such a trial has recently been designed by the Northern California Oncology Group for clinical stage I disease. However, both surgical treatment and radiation have the same major limitation, namely, failures because of the development of distant metastases.

Recent developments in combination chemotherapy for advanced testicular tumors suggest possible increased cure rates in this disease with chemotherapy [16, 19, 50] and encourage evaluation of the role of adjuvant drug treatment in patients with operable N+ disease. In the past few years, the effectiveness of surgical adjuvant chemotherapy has been tested in a few selected series of patients [7]. Results appeared encouraging in terms of prolonged RFS. In a carefully staged series with retroperitoneal dissection, Vugrin et al. [55] have recently reported no relapse after 'mini VAB' (vinblastine, dactinomycin, bleomycin followed by dactinomycin plus chlorambucil for 2–3 years) in 25 patients with minimal retroperitoneal disease ($\leqslant 5$ nodes, < 2-cm, negative markers). In a group of 35 patients with more than five positive nodes and/or foci over 2 cm in size, ten relapsed within 8 months and one at 30 months. Median follow-up was 10 months (3–30) for the first

group and 17 months (4–56) for the second group. In a similar series of 14 patients treated in Milan (S. Monfardini, unpublished data) with adjuvant vinblastine plus bleomycin for about 3 months and followed a median of 17 months (8–30), relapse occurred in one of twelve cases with less than five positive nodes and in two of two with more than five. However, the limited number of treated patients and the lack of stratified and randomized studies prevent any critical evaluation of the actual impact of combined-modality treatment on total survival. In fact, the administration of toxic chemotherapy, including bleomycin and *cis*-platinum, must be weighed against the consideration that a significant percentage of all N+ patients may be cured with local therapy and patients who suffer recurrences after local therapy may have the possibility of being cured, even if they do have recurrent or metastatic disease, after intensive chemotherapy with or without reductive surgery [37]. A prospective randomized study comparing early chemotherapy of all patients with delayed chemotherapy of patients who, after radical surgery alone (control group), subsequently develop a recurrence has been recently designed by the Intergroup Cooperative of Testicular Cancer.

Gynecological Cancers

Carcinoma of the ovary is the most common cause of death in women suffering from gynecological malignancy. The disease is classified as advanced (FIGO stage III and IV) at presentation in nearly 70% of women, with a median survival ranging between 10 and 12 months after conventional palliative treatment. Furthermore, one-third of patients with localized disease (FIGO stage I and II) develop recurrent tumor following potentially curative procedures. The need for accurate initial staging techniques (i.e., lymphangiography and peritoneoscopy) [22], for careful assessment of residual disease after surgery [59] and of histologic grading [43] are recommended for the evaluation of therapeutic modalities. Combined-modality therapy, including surgery, radiotherapy, and single-agent chemotherapy (chlorambucil, melphalan), has not significantly improved the therapeutic results in localized disease [7, 13]. The results recently obtained in stage-III and -IV disease are encouraging. Four-drug combination chemotherapy (cyclophosphamide, methotrexate, fluorouracil, hexamethylmelamine) produced a 75% objective response rate, with a high incidence of complete remission (33%), and a 29-month median survival [59]. These results are significantly superior to those achieved with single-agent chemotherapy (melphalan). In view of the above-mentioned results, combination chemotherapy should also be randomly tested against melphalan in an adjuvant setting.

Interest in adjuvant therapy in resectable endometrial cancer was stimulated by the availability of a nontoxic systemic treatment, such as progestins, which are effective in disseminated disease. Current results are contradictory. In fact, in a prospective randomized study no improved 4-year RFS was observed after medroxyprogesterone acetate (MPA) given over 14 weeks postoperatively [7]. In contrast, in an uncontrolled study where MPA was given for 2 years, improved RFS ad overall survival were claimed [9]. As already stated, different methods of patient selection and treatment evaluation were probably responsible for the conflicting results.

At present, no clear data are available for multimodality therapy in cervical carcinoma of the uterus.

Other Tumors

Bladder cancer is potentially a fertile ground for future clinical trials [14]. In T_1 lesions intravesical chemotherapy has been suggested as adjuvant procedure to decrease the local recurrence rate. Although local instillation of Thiotepa has been used for more than 15 years, the results of recent controlled studies failed to demonstrate a significant impact on disease-free survival [6]. However, the number of recurrences in single patients was reported to be reduced. In more advanced stages (T_3, $N_{0\text{-}1\text{-}2}$), radical cystectomy plus irradiation in N+ patients should be tested against the same procedure followed by adjuvant chemotherapy with drugs found to be effective in disseminated disease (e.g., adriamycin, fluorouracil, *cis*-platinum).

Clear-cell carcinoma of the kidney is almost totally resistant to available drugs. Therefore, it seems that surgical adjuvant studies will be difficult unless new, specifically effective drugs appear on the horizon.

In epidermoid carcinomas of head and neck sites and, to a certain extent, also in carcinomas of the esophagus the pattern of presentation, treatment failure, and prognosis is specific to each of the primary sites. So far, most of the multimodality approaches have combined chemotherapy and radiotherapy in locally advanced tumors. The results are conflicting and often uninterpretable [39]. Once more, patient selection may have played an important role in either success or failure. Primary chemotherapy, particularly with vincristine, bleomycin, and methotrexate, has been utilized in attempts to make locally advanced tumors amenable to radical surgery. Appreciable results were obtained in selected series [38, 46], but the impact of this sequential approach on RFS and total survival is not yet clearly evaluable.

Conclusion

Research physicians of the present decade have had the unique opportunity of changing the role of medical treatment of cancer by integrating systemic therapy into early cancer management as a full partner [57]. The process of establishing the absolute clinical value of adjuvant therapy in various forms of cancer, and especially in some adult solid tumors, is expected to be rather slow and difficult. At present, multimodal primary therapy has been shown to be successful in some childhood and adult malignancies. However, published results in resectable cancer are not always clearly interpretable, either because the study was not randomized (e.g., osteosarcoma, adult soft-tissue sarcomas) or because the follow-up is still too short (e.g., breast cancer, melanoma).

Bias in patient selection, which classically occurs in historically controlled studies, must be avoided (Table 1). Investigators should recognize that, besides the multitude of variables acting on the natural history and requiring proper stratification, many patients today present with less advanced local disease, current methods of staging are more precise, and there have been important advances in radiation and surgical techniques. Moreover, supportive care is now more sophisticated and specific secondary treatments are available for many tumors in case of primary treatment failure. All these objective factors play an important role in affecting both relapse-free and total survival rates to different extents. Thus, for instance, osteosarcoma requires a prospective randomized trial primarily because of recently changed population selection for amputation; medulloblastoma primarily because of improved surgical and radiation techniques; and testicular cancer because of the improved efficacy of combination chemotherapy in patients relapsing after primary local-regional therapy. Resectable breast cancer will also require randomized trials to show a convincing improvement over current CMF results in premenopausal women, to allow better definition of the possible role of chemical castration and the prognostic importance of estrogen receptors, and to establish an effective treatment for postmenopausal subsets.

Since research should not grow and develop without the support of judicious skepticism toward premature findings, both clinicians and patients should be aware that time remains an essential ingredient in all clinical trials. Probably because multimodal therapy for human cancer is based on hard experimental findings [52], the new strategy is followed by medical and also public attention with considerable anxiety. Clinical investigators are always expected to produce successful results within a short period of time. This could lead to a dangerous game among research physicians, who could be tempted to overproject premature results. In our opinion, the credibility of a research physician should not depend upon the success for failure of a given treatment per se, but rather upon the correctness of the trial design and performance and on the caution exercised in interpretation of the results. As time goes on, initial findings also become progressively more valid in terms of risk benefit. The iatrogenic morbidity of multimodal therapy cannot yet be fully assessed. Since prolonged chemotherapy combined with radiotherapy [39] and/or surgery [7, 57] is expected to produce late complications, namely organ failure, enhanced immune suppression, and secondary neoplasms, whose incidence cannot yet be defined, continuous communication between clinicians and experimentalists should be improved, as should coordination among scattered clinical trials.

Table 1. Bias involved in historically controlled studies

1. Multitude of variables acting in the natural history
2. Changes in patient referral patterns and methods of staging
3. Advances in supportive care, surgical and radiation techniques
4. Investigator enthusiasm

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