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Adjuvant chemotherapy represents a significant advance in the management of early-stage breast cancer and, as such, has saved many lives. Worldwide, adjuvant chemotherapy has benefitted all groups tested, including

The “Update on Adjuvant Chemotherapy for Early Breast Cancer,” by Drs. McCarthy and Swain, provides an excellent and concise overview of this complex and evolving subject. Nevertheless, additional data deserve mention, for example, from the overview analysis by the Early Breast Cancer Trialists’ Collaborative Group. In particular, studies of monotherapy with cytotoxic agents showed this approach to be inferior to combination chemotherapy.[1]

Role of Anthracycline Therapy
Most of the earlier chemotherapy trials included modifications of the CMF (cyclophosphamide, methotrexate, fluorouracil) combination. The addition of vincristine and prednisone (VP) failed to produce further gains, compared to the three-drug CMF combinations. However, the addition of an anthracycline as adjuvant therapy resulted in a further reduction in the risk of recurrence and had a favorable impact on survival.

In one Cancer and Leukemia Group B (CALGB) study, adjuvant therapy with CMFVP was followed by the administration of VATH (vinblastine, Adriamycin [doxorubicin], thiotepa, Halotestin [fluoxymesterone]), a regimen that is presumed to be non–cross-resistant with CMFVP.[2] This study demonstrated that the addition of a doxorubicin-containing combination to standard adjuvant chemotherapy resulted in a significant reduction in the risk of recurrence and death.

Although several individual studies and the collaborative group’s overview demonstrated the superiority of anthracycline-containing combinations (mostly FAC [fluorouracil, Adriamycin, cyclophosphamide] or FEC [fluorouracil, epirubicin, cyclophosphamide]) over CMF, four cycles of AC were reported to be equivalent to six cycles of CMF by the National Surgical Adjuvant Breast and Bowel Project. It is possible that deleting fluorouracil from the FAC combination reduced the antitumor activity of the combination. It is also possible that four cycles of AC represent suboptimal therapy.

In our own institutional experience,[3] the FAC combination provided results that, stage-by-stage and within every lymph node subgroup, produced antitumor activity superior to that of CMF or doxorubicin followed by CMF therapy, as reported by the Milan group.[4] Our experience with this regimen over the past 20 years also attests to the long-term safety of this combination.

Sequential Chemotherapy Regimens
The role of alternating non–cross-resistant therapy was also evaluated in several adjuvant studies from M. D. Anderson Cancer Center. Even modestly active drugs like methotrexate and vinblastine administered after FAC further reduced the risk of recurrence, compared to FAC alone. Since the encouraging results of our initial study, we reconfirmed these findings in a larger randomized study. With the more recent availability of the taxanes—arguably the most effective drugs against breast cancer—and with significant antitumor activity in anthracycline-exposed and/or refractory disease, we again tested the concept of sequential non–cross-resistant regimens. The single-agent antitumor activity of paclitaxel (Taxol) was prospectively compared to the FAC combination as preoperative therapy in patients with operable breast cancer. The early results of this trial demonstrated that paclitaxel and FAC had similar antitumor effects (as measured in response rates) in this setting.[5] Further data from this trial demonstrated that, compared to eight cycles of FAC, the addition of four cycles of paclitaxel to four cycles of FAC reduced the risk of recurrence by 26% at 4 years.[6] These results are consistent with those obtained in the larger intergroup (CALGB 93-44) study.[7] In our study,[6] the reduction in risk of recurrence was independent of the hormonal receptor status of the tumor, suggesting that the antitumor activity of paclitaxel is independent of hormonal receptor status. Drs. McCarthy and Swain appropriately note that additional follow-up of the intergroup study and the results of other recently completed trials will clarify the value of the taxanes in the
treatment of early breast cancer.

**Dose Intensity and Timing of Systemic Therapy**

The issue of dose intensity was clearly and appropriately addressed in this review. Currently, there is no evidence from controlled trials to support the use of dose-intensive therapies outside of an investigational study.

There is also no evidence to support the superiority of neoadjuvant therapy over postoperative adjuvant chemotherapy with the same regimen. However, neoadjuvant therapy provides early evidence of the efficacy of a systemic therapy. Patients with significant residual disease following neoadjuvant therapy have an unfavorable prognosis. This observation identifies a group of patients that could be offered alternative non-cross-resistant therapies. The ability to identify patients at higher risk of recurrence might also lend itself to an evaluation of the role of novel therapeutic approaches in this subset of patients.

Two such alternative therapies were evaluated in small randomized studies from our institution. In the first, high-dose chemotherapy with stem-cell support followed induction therapy with the FAC regimen[8]; and in the second, FAC was followed by a combination of methotrexate and vinblastine.[9] The results of the high-dose chemotherapy trial were disappointing, but the addition of the modestly active combination of methotrexate and vinblastine demonstrated the value of alternative non-cross-resistant therapies.

Several new cytotoxic, hormonal, and biological agents are currently available. The role of these new agents in favorably changing the natural history of breast cancer should be evaluated in well-designed studies. The results of such trials will bring us closer to the day when effective treatments will be available to every woman affected by this disease.

**References:**


