tween leucovorin and interferon occurs in the modulation of 5-FU effects on colon cancer. Both studies also suggest that prolonged treatment may lead to prolonged remission. Certainly the promise of a regimen with a 50% response rate and a response duration of over 1 year would considerably diminish doubts on the usefulness of chemotherapy in advanced colorectal cancer.

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Alternated Approach with Local Irradiation and Combination Chemotherapy Including Cisplatin or Carboplatin plus Epirubicin and Etoposide in Intermediate Stage Non-Small Cell Lung Cancer

Comella et al.[1] recently reported a randomized study to test the efficacy of two different protocols of alternated radiochemotherapy in Stage III nonsmall cell lung cancer (NSCLC). Fifty-eight patients were randomized to receive four cycles of cisplatin (60 mg/m^2 on day 1), etoposide (100 mg/m^2 on days 1–3), and epirubicin (50 mg/m^2 on day 1) alternated with three courses of thoracic radiotherapy of 15 Gy in five consecutive fractions (Arm A) or the same combined schedule but with carboplatin (300 mg/m^2) instead of cisplatin (Arm B). There was no significant difference between the two arms in terms of response, progression free interval, survival, or patterns of failure. Nevertheless, the administration of carboplatin was better tolerated.

Several remarks appear relevant:

1. Both chemotherapy and radiotherapy were delivered at suboptimal doses. This contradicts the rationale for an alternating regimen, which is to give both thoracic radiation and chemotherapy at full doses without compromising dose intensity. Positive randomized trials evaluating combined modality treatments in advanced NSCLC used a higher cisplatin dose intensity.[2,3] Radiotherapy delivered a total dose of 45 Gy only and in a split-course mode. As the authors state, a split-course irradiation may be less efficient than a continuous one in patients with NSCLC because of probable tumor cell repopulation during the rest period between treatment courses.[4]
2. The alternating approach may be inappropriate to treat NSCLC. This regimen was first evaluated in a series of laboratory studies using a rat hepatoma model, a very chemo- and radiosensitive tumor.[5] This strategy seemed to reduce the risk of the emergence of chemo- and radioresistant tumor cell populations if an interval of 7 days interval was respected between each treatment modality. The clinical investigation of alternating approaches has been thoroughly studied at the Institut Gustave-Roussy since the early 1980s.[6–8]

   Clinical trials have shown that alternating schedules were most beneficial in both chemosensitive and radiosensitive tumors such as small-cell lung cancer and non-Hodgkin's lymphoma. The advantage of combining both radiotherapy and chemotherapy relies on spatial cooperation, with radiotherapy focused on limited areas of bulky disease and chemotherapy eradicating smaller tumor deposits outside the radiation field. There are, however, theoretical and clinical reasons why we believe that these approaches may not be as effective in NSCLC. In contrast to small-cell lung cancer, there are few antineoplastic drugs with confirmed activity against NSCLC able to eradicate subclinical metastases. Failure to achieve local control with radiation therapy remains a major cause of death in many patients with locally advanced NSCLC. Even in Gandara et al.'s[9] study, which was an intensive, rapidly alternating regimen combining radiotherapy at a total dose of 60 Gy in three separate 10-day courses over 10 weeks and high dose cisplatin, the complete remission rate was only 18%, assessed 6 weeks after treatment. Six of 22 patients (27%) had local progression. Seagren et al.[10] explored a more intensive alternating regimen with radiotherapy three times daily for 3 days (16.2 Gy in 9 fractions) followed by chemotherapy (high dose cisplatin and vinblastine); three or four cycles were administered. This Phase I/II trial had to be discontinued because of severe myelosuppression.

   The most recent trials on advanced NSCLC are evaluating new combined modality treatments that integrate either surgery after radio-chemotherapy or hyperfractionated radiotherapy combined with chemotherapy. Attempts to increase the local control rate may result in a higher survival rate in patients with limited disease or when micrometastases can be controlled by chemotherapy.
3. Finally, this study could have led to interesting conclusions regarding the optimal chemotherapy regimen in an alternated schedule, as radiotherapy was similar in both arms. Unfortunately, the two arms cannot be really compared because the equitoxic dose ratio between carboplatin and cisplatin, which is considered to be 4:1, was not respected: the cisplatin dose was 20% lower.

In conclusion, this study supports the hypothesis that an alternated approach combining chemotherapy and thoracic radiotherapy may not be appropriate for treatment of advanced NSCLC. The treatment schedule did not improve survival but gave rise to substantial toxicity even though both chemotherapy and thoracic radiotherapy doses were suboptimal.

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Reproductive History and Prognosis in Patients with Operable Breast Cancer

Recently, Korzeniowski and Dyba[1] reported that pregnancy has an adverse effect on breast cancer prognosis. Further, pregnancy is associated with a poor prognosis in women with breast cancer, even years after the pregnancy has occurred.[2] In addition, we have reported that a history of pregnancy is independently associated with axillary lymph node involvement.[3] Our finding has recently been corroborated twice[4,5] and not confirmed once.[6] Moreover, others have found an increased incidence of lymph node involvement in pregnant women with breast cancer.[7]

A circulating tumor marker, lipid-associated sialic acid in plasma (LASA-P), is abnormally increased in plasma and serum of patients with gynecologic malignancies, including breast cancer.[8–10] LASA-P levels reflect alteration in the surface membrane of tumor cells. The LASA-P assay measures total gangliosides and glycoproteins.[9]

We measured LASA-P in a group of women with benign and malignant breast tumors. We now report that LASA-P is increased in the plasma of women with breast tumors who have been pregnant. Our finding confirms the findings of Korzeniowski and Dyba,[1] and suggests that pregnancy may alter the surface membranes of neoplastic cells, increasing their malignant potential.

We studied 207 women with benign and malignant breast tumors operated in Mount Sinai Medical Center between 1991 and 1994. Cases were selected for study if the number of pregnancies was known and LASA-P had been measured.

Plasma specimens to be assayed for LASA-P were collected in tubes containing ethylenediamine tetraacetic acid and frozen until tested. Lipid-associated sialic acid in plasma was determined by the procedure of Katopodis and Stock.[11] Dianon Systems (Stratford, Connecticut) performed all assays. Statistical analysis was done with the SPSS System.[12]

The average age of the 207 women studied was 48.5. The youngest woman was 16, and the oldest was 84. The average number of pregnancies was 2.4; the minimum number of pregnancies was 0 and the maximum was 10.

The concentration of LASA-P rose with the number of pregnancies in women with both benign and malignant tumors ($P = 0.0046$, one way ANOVA; Fig. 1). The mean age also varied in the patient groups. Women with benign breast tumors tended to be younger. Because LASA-P levels rise with age, we analyzed our data using multiple linear regression. Benign versus malignant, number of pregnancies, and age were the three independent variables (Table 1). Pregnancy had a significant effect on LASA-P levels ($P = 0.015$) that was independent of the effects of age ($P = 0.008$) and benign versus malignant ($P = 0.31$).

Pregnancy causes changes in the breast that might predispose to tumors of increased malignancy. At the beginning of pregnancy, there is heightened vascularity, as well as rapid growth and branching of mammary tissue.[13] Moreover, the mammary tissue is exposed to high levels of many hormones