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MONDUZZI EDITORE
RECENT DIAGNOSTIC AND THERAPEUTICAL APPROACH ABOUT ON EARLY BREAST CANCER USING MONOCLONAL ANTIBODIES AND FLOW CYTOMETRIC ANALYSES

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Given the high incidence and persistent mortality of breast cancer, it is mandatory to establish reliable methods of diagnosis and fitted protocols of follow up so far the common effort to render a precise diagnosis of the disease in its early stages as undoubtedly produced positive results. A widely accepted approach, for instance, implies history, physical examination and mammography followed in cases considered suspicious by CT guided aspiration biopsy.

In our opinion this is the best approach to breast cancer especially for patients at risk (because of their family, history, age, nulliparity, history of severe menory dysplasia) so that it is recommended by the European Group for Breast Cancer Screening in order to carry out reliable protocols of screening, such a check up should be performed every 2-3 years. We are currently evaluating the accuracy of new diagnostic methodologies which do not require the use of radiations such as: ultrasound associated with fine needle aspiration biopsy and diaphanoscopy, however the results in terms of sensitivity and specificity are not comparable to the ones obtained by mammography. Despite the high specificity of the radiologic diagnosis, we noted as other authors reported previously that metastases from an occult breast carcinoma (meaning a carcinoma not detectable by X-rays ) are infrequent, however present in the 0.5 - 7% of the patients. More specifically the anatomic sites more often involved are respectively the lungs, above the diaphragm and the peritoneum beneath the diaphragm. Metastases from occult breast carcinoma are present in the axillary lymph nodes in the 0.3% of all cases and in the 0.5% of cases N+. We must also take into account, as stressed by Hystrom and others (1977) that often the dissemination to the metastatic sites of occult carcinomas differs from that observed in cases of clinically manifested tumors. As a matter of fact bony metastases are present in 50-80% of patients with
clinically evident breast cancer, whereas they occur only in the 33% of patients with occult disease.

It is mandatory that the primary tumor be found in order to avoid possible complications and to promptly establish a therapeutic regimen able to improve the patient's survival. Besides the above-mentioned tests, the use of ultrasound and CT scan is important in order to rule out the involvement of classical sites of metastases from breast carcinoma, such as liver, lung, pancreas, bones and brain. Lastly, the introduction of monoclonal antibodies capable of binding to specific antigens present in the neoplastic tissue as allowed to better detect both primary tumors and metastases by visualizing neoplastic foci otherwise not evident. Particularly, a recent breakthrough is represented by the following monoclonal antibodies (Mabs): anti-EMA, anti-CA 15-3 and anti-ER. All of these are antigens associated with breast carcinoma, more specifically the 5-6 is a protein linked to the estrogen receptor. As a consequence, the Mab ER-5 is specific only for the human tissues and is therefore a reliable marker for breast carcinoma. It is our belief that only by developing new diagnostic methodologies such as the one above mentioned, and combining TNM and Flow Cytometry, we can accomplish a better staging of cancer. We can then not only render a diagnosis of cancer disease at a cellular level, but also choose the adequate therapy (chemotherapy, monoclonal antibodies) to fight a disease that in our opinion should be considered as systemic from the beginning. In addition to the monoclonal antibodies, we think that it is necessary to develop other techniques such as:

A) scintigraphy both morphologic and circulating

B) proliferative kinetics

C) flow cytometry and plasmidy.

In order to define the relationship between the biologic aggressiveness and clinical behavior of neoplastic disease, the proliferative activity of the neoplastic cells determined on the basis of DNA synthesis, either by flow cytometry or by the incorporation of thymidine, can be studied in order to achieve a dynamic staging of the neoplasia and could therefore represent the elective approach to an early diagnosis of cancer in cases of severe histologic dysplasia. More specifically, the R.B.M. analysis by flow cytometry is of great relevance as to the clinical prognosis of the disease. As a matter of fact there is an undoubted correlation between plasmidy of neoplastic cells, size of the tumor and long term survival. The diploid cells, for instance, are associated with a smaller size of the primary tumor, as well as better grading and staging compared to what observed in carcinomas made up of aneuploid cells. There is also a correlation between plasmidy and hormonal status of the patient in particular because of the presence of estrogen receptors, assessed in the 64% of cases, it is been possible to start a more started hormone therapy. Lastly, we noted both prolonged disease-free interval and longer breast survival in patients with diploid breast carcinoma compared to those with aneuploid carcinomas. Once identify the patients at risk on the basis of their age, family history, hormonal status, parity, history of breast feeding,......, in the presence of suspicious mammographic findings, we consider useful to employ specific monoclonal antibodies in order detect primary breast carcinomas which could not be diagnosed otherwise. This methodology could also be applied to those patients carrying a diagnosis of severe multifocal dysplasia on the basis of mammographic evidence of chorionic disease with microcalcifications which might hide multiple foci of cancer. In cases with suspicious mammographic findings it is necessary to perform, whenever possible, an aspiration fine needle biopsy (FBNB) which can be either stereotactic or guided by ultrasound in order to obtain enough tissue for flow cytometry and eventually identify an incipient proliferation of neoplastic cells. It is also possible to apply modern techniques of

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immunohistochemistry to FNA to better evaluate these patients presenting, at
mammography, with nipple lesions or with severe dysplasia, as to their
prognosis. More specifically, the immunoperoxidase technique, by employing MAb
specific for the hormone receptors, allows us to detect their presence in the
neoplastic cells in order to:
1) classify the incipient neoplastic disease
2) determine the hormonal status of the patient
3) choose an adequate therapeutic protocol.

In addition all the test with MAbs, can be performed on patients with metastases from
unknown primary to rule out an occult breast carcinoma as well as on patients
with history of breast cancer surgically removed to eventually diagnose occult
micrometastases. Lastly specific monoclonal antibodies, can be used at the time of
surgery, to obtain a more precise staging as well as to carry out radioimmuno-
guided operations. As a matter of fact a recently introduced monoclonal antibody
( B 72.3 ), if used before surgery, allows to determine not only the size of the
tumor, but also the presence of distant metastases and to select, subsequently,
the most adequate treatment. More specifically, this new Mab ( B 72.3 ), of
murine origin, seems to be specific ( 85-92 % ) for the surface antigen TIG-72
present on the breast cancer cells. After marking it with I-125 , this Mab
works as a tracer and can therefore be injected 15-20 days before surgery so that
intraperatively, it is possible to detect through a neoprobe system 1000 the
gamma rays emitted by those neoplastic cells which are bound to the complex
Mabs – I-125.

In our opinion this new methodology not only contributes to better define
the extension of the primary tumor, but also allows to perform a new surgical pro-
cedure, the Radioimmuno-guided Surgery which is more reliable as far as the size of
the neoplasm as well as the occult micrometastases are concerned. Such a
procedure either by itself or in association with other therapeutic modalities
could become the elective treatment of mammary carcinoma as to removal of
the primary tumor, recurrence and micrometastases with subsequent improve of the
survival.

REFERENCES

Rolo delle testi associate alla chirurgia nel controllo della crescita
vol. I° pag. 13-38

2) Christov, K., Nivel, A., and Todaro, V.
DNA anaploidy and cell proliferation in breast tumors. Cancer 64: 673-679; 1999

3) Dodd, G.D.

4) Ellis G., Ferguson N., Yarwood, E., Livingston, R.B. and Cox, A.
Monoclonal antibodies for detection of occult carcinoma cells in bone marrow

DNA index and cell cycle analysis of primary breast cancer and synchronous


7) Goldberg, B.M.
Imaging and therapy of cancer with radiolabeled monoclonal antibodies. Immunity to cancer. II**: 413-427; 1999


10) Kline, T.S., Lundy, J., and Lozowski, H.
Monoclonal antibody B-72.3. Cancer 63: 2253-2256; 1999

11) Osborne, C.P., Ashina, S., Wong, G.Y., Old, L.J., and Cote, B.L.

12) Palmer, J.D., Jr; Bliditt, R.W., Stone, R.R., Rudolph, M.A., and Gonzalez, J.C.


14) Stern, E.E. and Cochran, A.J.