Acta Oncologica Vol. 31, No. 2, pp. 215–218, 1992

INDICATIONS FOR CYTOSTATIC THERAPY IN METASTATIC BREAST CANCER

STENER KVINNSLAND

Generalized breast cancer is always incurable. The heterogeneity of this disease is reflected by wide variation in treatment response and survival duration. No well-defined factors have been found which can distinguish the patients most likely to benefit from chemotherapy. No superior drug combination or schedule has been convincingly established, and basic facts on quality of life issues are still lacking. The most important treatment goal is to provide meaningful palliation for the individual patient. Indications for chemotherapy are life-threatening disease, distant metastases in receptor-negative disease, and clinically hormone resistant disease. In future trials the importance of potentially relevant biological factors for treatment should be evaluated, and such analyses should, at least partly, replace the presently conducted phase II and phase III studies.

Key words: Breast cancer, metastatic disease, chemotherapy, indications.

Acta Oncol., Vol. 31, No. 2, pp. 215–218, 1992.

Once distant metastases become apparant, breast cancer is an invariably incurable disease. In spite of this fact, responses to therapy and survival duration after the first recurrence is most variable (1–3), demonstrating the biological heterogeneity of the disease. Sometimes responses lasting for years can be seen (4). During the last two decades a very large number of chemotherapy trials has been carried out to find drug combinations or new schedules with higher efficacy, i.e. higher response rates, prolonged duration of effect, survival benefit and even cure (for reviews, see (5–7)). It is probably correct to say, although survival differences are reported from time to time, that real differences between the vast array of combinations and schedules used remain marginal, if present at all.

Paper presented at the 4th Scandinavian Breast Cancer Symposium, June 3–5, 1991, at Haikko Manor, Porvoo, Finland.
Submitted 5 June 1991.
Accepted 26 August 1991.
Correspondence to: Prof. Stener Kvinnsland, The Norwegian Radium Hospital, Montebello, N-0310 Oslo 3, Norway.

In this context it cannot be stated that the issue of dose/response or dose intensity/response has been solved with regard to survival and possibility of cure in advanced breast cancer (8). The optimal use of autologous bone marrow transplantation, such as the use of highly cleaned stem cell preparations clonally expanded by relevant growth factors and bone marrow supportive treatments may hopefully change this.

What then is the basis for our treatment? What are the goals of the treatment and what are the indications for starting chemotherapy in metastatic breast cancer?

Predictive factors

In contrast to the situation in endocrine therapy, no well-defined factors exist to distinguish patients likely to benefit from chemotherapy. Some factors of possible importance are shown in Table 1; most of them relate to tumor burden and the time course of the disease (9, 10). In Table 2 a summary is given of some basic aspects of metastatic breast cancer, not necessarily generally agreed upon in all details, of relevance to the discussion of indications for chemotherapy.

Table 1

Factors of possible importance for predicting response to chemotherapy

1. Factors related to tumor load
   - Performance status
   - Number of metastatic sites
   - Specific organ sites involved
   - Abnormal hematological and biochemical values
   - Disease-free interval
2. Other potential factors
   - Age
   - Menopausal status
   - Prior adjuvant chemotherapy
   - Psychosocial factors

Table 2

Some fundamental facts concerning chemotherapy of metastatic breast cancer

1. Metastatic breast cancer (distant metastases) is an incurable disease.
2. Predictive factors for the outcome of chemotherapy have not been established in prospectively designed clinical trials.
3. The influence of biologically relevant factors has still not been analysed in clinical trials on chemotherapy of metastatic breast cancer.
4. A superior drug combination or schedule has never been convincingly established.
5. Basic facts on life quality issues are still lacking, and well validated and generally accepted questionnaires have not been fully developed.

Treatment goals

Indications, in clinical practice in general but also within the context of clinical trials, have to be discussed within the framework of realistic expectations. Some possible treatment goals are suggested in Table 3. The main goal is to provide good palliation for as many patients as possible. Increasing attention has lately been paid to the importance of quality of life issues in palliative breast cancer treatment (11, 12). Trying not to ignore the complexity of the term quality of life, two of the more important measures in relation to chemotherapy for the individual patient are: 1) The ratio (therapeutic ratio) between palliation (effect) and side-effects. 2) The time spent without symptoms and treatment.

Table 3

Treatment goals in metastatic breast cancer: some suggestions

1. To provide meaningful palliation for the individual patient.
2. To provide new knowledge on the use of chemotherapy in metastatic breast cancer.
   - A. Analyse role of biologic parameters for the guidance of therapy.
   - B. Establish relevant efficacy measures (endpoints), as response rate, (median) time to treatment failure, survival from first recurrence (not only from start of trial).
   - C. Analyse efficacy measures in relation to other (new) endpoints, as quality of life parameters.
3. To provide suggestions for alternative combinations of drugs or schedules for adjuvant and neoadjuvant treatment situations.

Further, more work should be invested in the analysis of the relevance of different end points (13). It is also of importance to develop and apply good biostatistical methodology (14), in order to improve the power of individual studies, and perhaps even to lessen the number of patients needed for the conclusions.

A third goal is to provide data from the treatment of metastatic breast cancer of possible relevance for the treatment of primary breast cancer in adjuvant or neoadjuvant clinical settings. Referring to experience from both adjuvant chemo- and endocrine therapy in breast cancer, it is probably correct to say that the relevance of experience from the metastatic situation with regard to drugs and schedules used, is at best limited. Much remains to be learned on differences in biologically relevant parameters between primary tumors and metastatic deposits.

Some of the presently known factors which could be of relevance for selecting patients for chemotherapy and reaching the treatment goals are proliferation parameters (15–17), tumor differentiation markers (18, 19), growth factors (20, 21), hormone and growth factor receptors (22, 23), proto-oncogenes and proto-oncogene products (24, 25), parameters of chemotherapy resistance (26, 27) (Table 4).

Indications for chemotherapy

Some guidelines for the indication of chemotherapy in metastatic breast cancer are given in Table 5. These guidelines could of course be modified according to the motivation of the patient and her age and general condition. The main challenge is to predict a hormone-resistant situation, either from the time of diagnosis of first recurrence, or after previous trials with endocrine therapy. An adequate

Table 4

Biological parameters, preferably obtainable in fine-needle aspirates: candidates of possible importance

1. Proliferation parameters (Ki 67)
2. Hormone receptors (ER, PgR)
3. Growth factors/growth factor receptors (cathepsin D, EGFR, etc.)
4. Proto-oncogene/anti-oncogene products (ERB2/neu, INT 2, p53, etc.)
5. Markers of differentiation (cytokeratins, milk proteins, gross cystic disease fluid proteins, etc.)
6. Markers of drug resistance (P-glycoprotein)

Table 5

Indications for chemotherapy in patients with metastatic breast cancer (symptomatic disease?)

1. Life-threatening disease (extensive vital organ involvement and/or large total tumor burden; rapid progression)
2. Distant metastases in patients with steroid hormone receptor negative tumors
3. In patients with progressive and hormone resistant disease (not controlled by local treatment)

use of endocrine therapy is one of the most important prerequisites for a reasonable start of chemotherapy.

Important for all 3 situations is the question of when to start chemotherapy, after having established metastatic breast cancer in progression. Should palliative chemotherapy be started in an asymptomatic patient? Although some information has been provided (7), this problem has not so far been adequately addressed in trials with the relevant end-points.

What can be expected with regard to improvements in the future?

With the possible exception of the influence of dose, not yet fully evaluated, dramatic improvements with regard to efficacy (response rate and duration of response) cannot be expected within a short time with the presently used drugs and treatment principles. Only minor developments are to be expected from changes in way of administration and new schedules, based on more information on pharmacokinetics of individual drugs. It might be possible, preferably by needle biopsies, to obtain valuable information on tumor cell or other biological characteristics, which may be of particular value for choice of therapy in the metastatic situation. The methods needed will hopefully be developed and tested in the near future.

The large numbers of phase II and III chemotherapy studies in metastatic breast cancer should therefore, at least partly, be replaced by studies aiming at providing data on the role of different biological parameters in relation to treatment effects.

REFERENCES

1. Paterson, AHG, Szafran O, Hanson J, et al. Responses to treatment and its influence on survival in metastatic breast cancer. Am J Clin Oncol 1985; 8: 283–92.
2. Ahmann D, Schaid DJ, Bisel HF, et al. The effect on survival of initiating chemotherapy in advanced breast cancer: polychemotherapy versus single drug. J Clin Oncol 1987; 5: 1928–32.
3. Petru E, Schmal D. No relevant influence on overall survival time in patients with metastatic breast cancer undergoing combination chemotherapy. J Cancer Res Clin Oncol 1988; 114: 183–5.
4. McGuire WL. Prognostic factors for recurrence and survival in human breast cancer. Breast Cancer Res Treat 1987; 10: 5–9.
5. Gundersen S, Kvinnsland S. Chemotherapy in advanced breast cancer. A review. Acta Oncol 1987; 26: 81–7.
6. Davidson NE, Lippman ME. Treatment of metastatic breast cancer. In: Lippman ME, Lichter AS, Danforth DN, eds. Diagnosis and management of breast cancer. Philadelphia: Saunders, 1988: pp 375–406.
7. Garber JE, Henderson IC. The use of chemotherapy in metastatic breast cancer. In: Henderson IC, ed. Diagnosis and therapy of breast cancer. Hematol Oncol Clin North Am 1989; 3: 807–21.
8. Henderson IC, Hayes DF, Gelman R. Dose response in the treatment of breast cancer: a critical review. J Clin Oncol 1988; 6: 1501–15.
9. Swenerton KD, Legha SS, Smith T, et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. Cancer Res 1979; 39: 1552–62.
10. Henderson IC. Chemotherapy for advanced disease. In: Bonadonna G, ed. Breast cancer: diagnosis and management. Chichester: John Wiley & Sons, 1984: pp. 247–80.
11. Coates A, Gebski V, Bishop JF, et al. Improving the quality of life during chemotherapy for advanced breast cancer: a comparison of intermittent and continuous treatment strategies. N Eng J Med 1987; 317: 1490–5.
12. Tannock IF, Boyd NF, DeBoer G, et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. J Clin Oncol 1988; 6: 1377–87.
13. Brincker H. Distant recurrence in breast cancer. Survival expectations and first choice of chemotherapy regimen. Acta Oncol 1988; 27: 729–32.
14. Skovlund E. Sequential two-sample methods in controlled clinical trials (dissertation). Oslo: Universitas Osloensis, 1990.
15. Tubiana M, Pejovic MH, Koscielny S, Chavaudra N, Gioanni J, Malaise EP. Growth rate, kinetics of tumor cell proliferation and long term outcome in human breast cancer. Int J Cancer 1989; 44: 17–22.
16. Sigurdsson H, Baldetorp B, Borg Å, et al. Indicators of prognosis in node-negative breast cancer. N Engl J Med 1990; 322: 1045–53.
17. Dawson AE, Norton JA, Weinberg DS. Comparative assessment of proliferation and DNA content in breast carcinoma by image analysis and flow cytometry. Am J Pathol 1990; 136: 1115–24.
18. Russo J, Russo IH. Immunocytochemical markers in breast cancer. In: DeLellis RA, ed. Advances in immunohistochemistry. Raven Press, New York: 1988: pp. 431–75.
19. Søreide JA, Lea OA, Anda O, Skarstein A, Varhaug JE, Kvinnsland S. Progesterone-binding cyst protein (PBCP) in operable breast cancer. Correlations to prognostic factors and predictive value for effect of adjuvant tamoxifen treatment. Anticancer Res 1991; 11: 1323–6.
20. Thorpe SM, Rochefort H, Garcia M, et al. Association between high concentration of Mw 52000 cathepsin D and poor prognosis in primary human breast cancer. Cancer Res 1989; 49: 6008–14.
21. Huff KK, Kaufman D, Gabbay KH, Spencer EM, Lippman ME, Dickson RB. Human breast cancer cells secrete an insulin-like growth factor-I-related polypeptide. Cancer Res 1986; 46: 4613–9.
22. Clark GM, Sledge GW, Osborne CK, McGuire WL. Survival from first recurrence: relative importance of prognostic factors in 1015 breast cancer patients. J Clin Oncol 1987; 5: 55–61.
23. Harris, AL. Epidermal growth factor receptor in human breast cancer. Recent Results Cancer Res 1989; 113: 70–7.

24. Perren TJ. c-erbB-2 oncogene as a prognostic marker in breast cancer. Br J Cancer 1991; 63: 328–32.
25. Borg Å, Sigurdsson H, Clark GM, et al. Association of INT2/HST1 co-amplification in primary breast cancer with hormone-dependent phenotype and poor prognosis. Br J Cancer 1991; 63: 136–42.
26. Merkel DE, Fuqua SAW, Tandon AK, Hill SM, Buzdar AU, McGuire WL. Electrophoretic analysis of 248 clinical breast cancer specimens for P-glycoprotein overexpression or gene amplification. J Clin Oncol 1989; 7: 1129–36.
27. Sanfilippo O, Ronchi E, De Marco C, Di Fronzo G, Silvestrini R. Expression of P-glycoprotein in breast cancer tissue and in vitro resistance to doxorubicin and vincristine. Eur J Cancer 1991; 27: 155–8.