As single agents, the taxanes were associated with improved overall survival compared to historically accepted standard regimens. In some cases, combinations of chemotherapy agents have also been associated with improved survival although this is a complex body of data. In many cases, a combination of drugs compared to the same agents given in sequence yields less "activity" but the same overall survival. On the other hand, the fact that, for example, a combination of docetaxel and capecitabine, or a combination of gemcitabine and paditaxel can improve overall survival compared to the taxane alone, supports the hypothesis that overall survival is in fact changeable. The active biological agents now available (trastuzumab and bevacizumab) also appear capable of improving overall survival.

For breast cancer the overall death rate appears to be declining and this is certainly multifactorial in origin. However, it is increasingly likely that some of the fall in mortality rates may be attributable to improved systemic therapy for metastatic disease even if these treatments are not "curative". This lecture will review this data in detail and suggest optimal strategies for the use of available agents as well as possible studies for the near future.

5 Invited

Efficient use of bisphosphonates in metastatic bone disease

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In recent years the treatment of bone metastases by radiotherapy and systemic endocrine and cytotoxic drugs has been supplemented by the co-administration of BP. These drugs are potent inhibitors of tumour-induced bone resorption that can relieve metastatic bone pain and improve the structural integrity of bone. Zoledronic acid and ibandronate are the most potent agents available and prevent 40–50% of the expected skeletal morbidity from advanced breast cancer [1]. Zoledronic acid also significantly reduces the risk of a skeletal complication in endocrine resistant prostate cancer (hazard ratio [HR] 0.64) and in a broad range of solid tumours other than breast and prostate cancers (HR 0.69). Thus BP should now be considered for any patient with symptomatic bone metastases, especially when bone is the dominant site of metastasis. However, for economic reasons selection or prioritisation of patients for BP may in some situations be necessary and more cost effective use of BP is desired in view of the long term nature of treatment.

It is now clear that the risk of a skeletal complication is related to the rate of bone resorption. Patients with rapid bone resorption, as measured by type I collagen fragments, are at significantly greater risk of an event and thus have potentially more to gain from the administration of a BP. Additionally, suppression of bone resorption should be the aim of treatment. Patients failing to normalise bone resorption are at much higher risk of future skeletal complications, progression of disease and death [2]. Attention is now turning to the development of more rational treatment schedules using biochemical markers of bone metabolism to guide treatment in individual patients. BISMARK, a large phase III trial comparing a standard schedule of zoledronic acid to marker directed therapy has recently commenced in the UK and is expected to become an international study during 2006.

References

[1] Coleman RE. Ann Oncol 16: 687–695, 2005.
[2] Coleman RE, Major P, Lipton A, et al. J Clin Oncol 23: 4925–35, 2005.

6 Invited

Need for new drugs in metastatic breast cancer (MBC)

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Patients who present with metastatic disease, either de novo or following surgery, are treated in the vast majority of cases with palliative intent, since progression and ultimately death from breast cancer, are almost inevitable. Most patients can be shown to have objective responses, many times associated with palliation of symptoms, but complete response (CR) are uncommon and responses are short-lived. The median survival for patients with metastases at diagnosis is around 2–3 year with less than 20% still alive at years. Although the treatment of MBC is usually palliative in intent, this malignancy readily responds to systemic agents, and prolongation of survival and symptom palliation are now possible with modern medical management. Systemic treatments are in continual evolution as more active chemotherapeutic agents become available and biological factors have been incorporated into treatment.

Hormonal treatment is the treatment of choice for hormone-sensitive, non life threatening MBC. It has the advantage of being efficacious, easy to administer and well tolerated. For women who are not candidates for hormonal therapy, cytotoxic chemotherapy is currently the treatment of choice. There are many agents that are available for the treatment of MBC which are used alone or in combination according to the clinical situation. The most active drugs are the anthracyclines, tubulin-interacting agents, alkylating agents and antimetabolites. Used as single agents they produce response rates of 20–70%. The now common use of anthracyclines in the adjuvant/neoadjuvant of early breast cancer has both increased the incidence of anthracycline resistant MBC, and restricted the use of the anthracyclines in later stages of the disease in order to avoid the cardiac cumulative dose-limiting toxicity. The introduction of taxanes in the 1990s has led to additional improvement in the management of MBC and there is an increasing trend towards using taxanes earlier in the management of breast cancer. With the growing understanding of the biology of breast cancer, multiple new targets for anti-cancer therapies are being identified. Trastuzumab which targets the HER2 receptor is approved for use, either in monotherapy or in combination with chemotherapy in HER2 positive MBC following the publication of positive survival data. Its approval has allowed clinicians to tailor treatment according to HER2 status and has highlighted the different prognoses of the HER2 positive and negative population.

Improvement in survival is an important treatment goal. Developing, for the control of advanced, relapsed or refractory breast cancer, new well-tolerated agents with novel mechanisms of action, and non-overlapping toxicity, that could be combined with established treatment, is a justified endeavour and a continuous challenge.

1. New cytotoxic agents: The new drug development is mainly focused towards tubulin inhibitors. Microtubular structures are required for cell division and vital interphase processes, and their disruption causes cell death. Tubulin, a structural subunit of microtubules, is a clinically validated target for anti-cancer therapy. Two classes of tubulin-interacting agents, taxanes (paclitaxel and docetaxel, microtubule stabilizers) and vinca alkaloids (vinorelbine, tubulin polymerization inhibitor) are on the market.

Several new taxanes derivatives including paclitaxel conjugates, new formulations and 2nd generation taxanes (XRP 9881, XRP 6258) are under clinical development (phase II and phase III trials). These 2nd generation taxanes are active in preclinical models of paclitaxel/docetaxel resistance and further potential benefits include activity against MDR-1 expressing tumors and the ability to cross the blood-brain barrier. Epothilones, (ixabepilone, epothilone D) a new class of microtubule stabilizers, have very promising efficacy in heavily and taxanes-naive treated patients. E7389, a structurally simplified analog of Halichondrin B with a novel anti-tubulin activity, characterized by sequestration of tubulin into nonfunctional aggregates and prevention of microtubule growth seems safe and effective in patients with refractory breast cancer.

Vinflunine (Javlor) is a novel tubulin polymerization inhibitor obtained by semi-synthetic process from vinca alkaloid base showing higher antitumour activity compared with parent compounds. Vinflunine showed definite (high or moderate) antitumour activity in 64% of xenografts tested, versus moderate activity only with vinorelbine in 27%. Against the human MX-1 breast xenografts, vinflunine produced an overall growth inhibition of 61% whereas vinorelbine did not result in any significant inhibition under the same experimental conditions. The results of a recent phase II trial demonstrated that vinflunine is an active, well tolerated drug in the treatment of metastatic breast cancer patients previously treated with anthracycline and taxane-based regimens. Other polymerization inhibitors as new dolastatin are currently being investigated.

2. Targeted therapies: Bevacizumab is a promising new therapy with a novel mechanism of action that targets angiogenesis. Bevacizumab improved response rate, PFS in patients with chemotherapy naive MBC when added to paditaxel in a large phase III trial. SU11248 is an oral multitargeted tyrosine kinase receptor inhibitor (TKI) with antitumor and antiangiogenic activity, inhibiting VEGFR, PDGFR, KIT and FLT3 TKs. Results of a recent a phase II study reported that SU11248 has significant single-agent activity in patients with refractory MBC. Lapatinib is a selective, reversible, oral small molecule inhibitor of both ErbB1 (EGFR) and ErbB2 (HER-2/neu) kinase activity. From phase II studies, lapatinib appeared well tolerated and showed evidence of activity as first-line and after trastuzumab failure for women with HER-2-amplified advanced breast cancer. In addition, lapatinib has the ability to cross the blood-brain barrier.

Other targeted therapies as farnesyl transferase inhibitors, mTOR inhibitors are currently being investigated.

New cytotoxic agents and new targeted therapies are currently developed. Some demonstrated promising activity in MBC and can be combined with established treatments for breast cancer.