PALLIATIVE TREATMENT OF BONE METASTASES

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Bone metastases are frequently one of the first signs of disseminated disease in cancer patients and are especially seen in patients with breast, prostate and lung cancer. The prognosis of these patients is generally poor and the treatment is primarily palliative: the intention is to relieve pain, prevent fractures, maintain activity and, if possible, to prolong survival. Besides analgesics the therapeutic options include local treatment with radiotherapy and/or surgery, and systemic treatment using chemotherapy, endocrine therapy, radioisotopes as well as bisphosphonates. Social and psychological supportive care is also very important. Radiotherapy plays an important role, but the other modalities such as bisphosphonates may also offer the same level of palliation, but their definite role has not been as clearly defined. There have been few randomized trials comparing the therapeutic options, and the criteria for assessing response to therapy have, in general, been poorly defined. There is a need for rigorous clinical investigations which assess the efficacy of the various therapeutic possibilities by using well-defined and validated response criteria such as pain and quality of life.

Bone metastases are frequently one of the first signs of disseminated disease in cancer patients and are especially apparent in patients with breast, prostate and lung cancer (1). The prognosis of these patients is generally poor, but a certain proportion will survive for several years. More than 25% of the patients with bone metastases have no symptoms, whereas in the other 75% pain is the dominant symptom (1). Some patients develop pathological fractures, hypercalcemia and spinal cord compression, which will further reduce their quality of life. The treatment of bone metastases depends on the treatment aim. A treatment with curative intent is only possible in very few cases, and in most patients the treatment is palliative. Therefore, the aims of treatment will primarily be to relieve pain, prevent development of pathological fractures, improve mobility and function, and, if possible, to prolong survival. Treatment of bone metastases requires a broad approach (1, 2). Reduction of pain is one of the major goals, but besides analgesics more specific treatments are often needed, i.e. local treatment (radiotherapy and/or surgery) and systemic treatment (chemotherapy, endocrine therapy, radioisotopes and bisphosphonates). Both social and psychological supportive care may also be required. In the present paper the options for treatment of bone metastases will be reviewed briefly.

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Radiotherapy

Among the various treatment options palliative radiotherapy plays an important role. Local radiotherapy of painful bone metastases is very effective (1–4). Relief of pain is obtained in the majority of the patients with complete relief in more than half of them. The onset of pain relief occurs within a few days after treatment and reaches its maximum after 2–4 weeks. There does not seem to be a correlation between the primary site and the likelihood of pain relief (1). In a number of prospective studies the role of radiation therapy for relief of bone pain has been examined (1, 2), but various criticisms can be levelled at these studies, especially concerning the number of patients and response criteria. At doses of 8 Gy and higher there is no strong evidence for a dose-response relationship and no consistent advantage of multiple fractions over one or two large fractions (1, 5–7). In a

randomized study (5) a single treatment of 8 Gy was compared to 30 Gy in 10 fractions, and no difference in onset or duration of pain relief was found. However, in a randomized trial comparing 4 and 8 Gy as a single treatment the response rate obtained after 4 Gy seemed to be lower and the relapse rate higher than that of 8 Gy (7), which may suggest a dose-response relationship at lower doses.Thus, the present data indicate that in most patients local radiotherapy for painful localized bone metastases can be given as a single treatment of 8 Gy with the same efficacy and without increased toxicity. This would reduce the distress and inconvenience associated with radiotherapy. Responding patients with recurring pain can be effectively retreated with radiotherapy. In patients with expected long-term survival more data are needed to support the use of a single treatment.

Since most patients have multiple bone lesions some centers have used half body irradiation (HBI) instead of multiple separate radiation fields (1–3). Typically, HBI is given as a single fraction to the upper-half or lower-half of the body either alone or sequentially. The effect of HBI is similar to that obtained with local radiotherapy, and when using intensive antiemetics and radiation doses below 7 Gy the toxicity is acceptable (1, 3). The onset of pain relief occurs within 1–14 days of treatment, with half of the patients noting pain relief within 48 hours. In 60–80% of the responding patients the relief lasts until death. The administration of radioisotopes provides means of delivering radiation systemically for disseminated bone metastases: Iodine-131 for thyroid cancer and yttrium-90, phosphorous-32 and strontium-89 for breast and prostate cancer (1, 4). Strontium-89 in prostate cancer seem to give the same degree of pain relief as external irradiation (1, 4). Recent randomized studies have shown a reduction in consumption of analgesics and development of new pain sites as compared to both local or half body irradiation (8, 9). The toxicity of strontium-89 is acceptable (4, 8, 9) and in selected prostate cancer patients it could, despite being very expensive, be a useful palliative treatment modality. However, more well-designed prospective studies are required before strontium-89 can be used in the clinical routine. Phosphorous-32 has also been evaluated extensively for palliation of diffuse bone pain but due to severe haematological toxicity in 20–30% of the patients its use is very limited presently (4). Other isotopes are under investigations including rhenium-186 and samarium-153 (1, 4).

Surgery

Surgical treatment is used mainly for patients with pathological fractures or spinal cord compression. About 10–30% of patients with bone metastases will develop fractures of long bones that require surgical treatment (1, 2, 10). Regardless of the specific surgical procedure, the goal is to remove as much tumor tissue as possible without jeopardizing function and stability (1, 10). Fractures in weight-bearing bones are often treated surgically rather than conservatively. The indications for prophylactic fixation of impending fractures have not been defined clearly, but lytic lesions in weight-bearing bones with a diameter >2–3 cm or with cortical destruction $>50\%$ are reasonable indications for prophylactic surgery (1, 10). If there is still pain after the surgery, postoperative radiotherapy is likely to be beneficial (1).

Endocrine therapy

Endocrine therapy has few side effects, making it the preferable palliative treatment modality in hormone responsive tumors such as breast and prostate cancer (1, 2). In metastatic breast cancer about one-third of all patients can be expected to experience pain relief on endocrine therapies, and about 50% of estrogen receptor positive patients experience relief of pain (1, 11). The median duration of response is 9–12 months. Tamoxifen is generally the agent of choice for first-line endocrine treatment because of the almost complete absence of side effects, but there is no evidence that it is more effective than other forms of endocrine therapy (1, 2, 11). In patients who suffer relapse after responding to one type of endocrine therapy a similar proportion of the patients will benefit from one of the other types of endocrine therapy, but the duration of response is usually shorter (11).

In metastatic prostate cancer a wide range of response rates have been reported. Generally, 70–80% of previously untreated patients can be expected to obtain pain relief after hormonal treatment (1, 2, 12, 13). The pain relief from treatment may be quite dramatic and occur within 24 hours and, although variable and difficult to assess, the median duration of response is 12–18 months (1, 12, 13). Following failure of first-line endocrine treatment there is limited palliative benefit to second-line hormonal treatment, but some patients do experience transient relief of pain (12, 13).

Chemotherapy

The absence of assessment of the impact of chemotherapy on quality of life is particularly surprising given the toxicity often associated with chemotherapy. Nevertheless, chemotherapy is demonstrably effective in the treatment of bone metastases in malignancies such as breast cancer, small cell lung cancer, lymphomas, multiple myeloma and germinal cell tumors (1, 2). However, future randomized prospective trials can only extend the indications for chemotherapy for bone metastases if they include validated assessment of pain relief and quality of life.

In breast cancer a number of chemotherapeutic drugs effectively treat metastases (2, 11, 14). The data on pain relief are not very reliable. Nonetheless, a substantial

number of patients experience relief of pain (2, 11, 14). The bone pain in many patients responds promptly to chemotherapy (within 10–14 days). In the 20% of patients with breast cancer having only bone metastases the prognosis is more favorable (11), but the present data do not allow any final conclusion on management policies for this subgroup of patients.

Bisphosphonates

Bisphosphonates inhibit normal bone resorption (1). They are clinically useful for the treatment of hypercalcemia, but may also provide palliation of painful bone metastases from various tumors (15, 16). In patients with osteolytic metastases from breast cancer, they may reduce the frequency of pathological fractures, bone pain and hypercalcemia (15, 16), whereas their effect in metastatic prostate cancer seems more modest. Further investigations are needed to clarify the role of bisphosphonates as a palliative treatment for bone metastases.

Conclusion

Although in most patients with bone metastases the treatment is palliative, there is no reason to be nihilistic. In the majority of patients local and/or systemic treatment, and appropriate use of analgesics will relieve pain and maintain a reasonable functional level. The mechanisms by which pain is relieved are unclear but actions beyond a simple tumoricidal effect appear to be important. Whether the asymptomatic patient with bone metastases should receive immediate treatment remains a controversial point, and no trials have been performed to give a final answer to this important question. There is a need for rigorous clinical investigations which assess the efficacy of the various therapeutic possibilities by using well-defined and validated criteria of response.

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