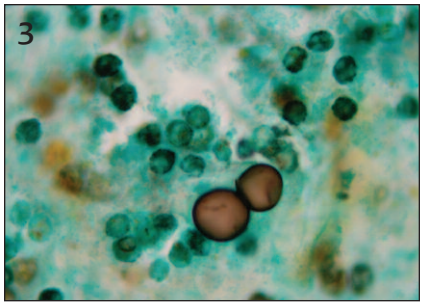


sites most commonly involve the skin, bone and genitourinary system[1] and occur most likely at the time of the primary infection, with potential for later relapse.

Patients with blastomycosis osteomyelitis most frequently present with pain and swelling of the affected area, often accompanied with an overlying skin abscess.[1] Most cases respond to treatment with antifungal drugs (amphotericin B and agents from the azole class), but some may also require surgical débridement.[3] Blastomycosis was suspected in our patient because of his history of residence in an area where the fungus is endemic, an unusual protracted course and an atypical location of the foot lesion. Furthermore, he did not have evidence of the more common causes of ulcers on the lower extremities, such as diabetic neuropathy (ulcer on weight-bearing surface, or areas of bony or shoe pressure), venous stasis disease (leg ulcer and venous stasis changes), gout (ulcer adjacent to joints and tophaceous debris) or lymphedema (ulcer with serous drainage and diffuse limb swelling).

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## IN THE LITERATURE

# Trastuzumab (Herceptin) and HER2-positive breast cancer

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-72.

**Background:** HER2 (human epidermal growth factor receptor 2) is present in 15%–25% of breast cancers. Women with HER2-positive breast cancer usually have more aggressive cancer, are at increased risk of recurrence and have a poorer survival than other women with breast cancer. Trastuzumab, a recombinant monoclonal antibody, acts against HER2 receptors.

**Design:** In this international randomized trial, women who had undergone surgical excision of a HER2-positive, early invasive breast cancer and who had completed 4 or more courses of chemotherapy were randomly assigned to receive trastuzumab every 3 weeks or observation alone (control group) for 1 or 2 years. Patients were included if they had adequate liver, kidney and bone marrow function and a normal left ventricular ejection fraction (LVEF). Women were excluded if they had metastases, prior invasive breast cancer, another neoplasm, or a cardiac condition such as angina pectoris requiring medication, uncontrolled hypertension or prior congestive heart failure or myocardial infarction. The primary outcome measure was disease-free survival; secondary end points were cardiac safety, overall survival, time to distant occurrence and site of first disease-free survival event.

**Table 1:** Outcomes of 4 trials of trastuzumab therapy for HER2-positive breast cancer

| Study | ARR, % | NNT | Absolute increased risk of CHF, % | No. needed to cause 1 case of CHF | Absolute increased survival |
|---|---|---|---|---|---|
| Piccart-Gebhart et al | 5.5* | 18 | 1.7 | 60 | No significant improval |
| Romond et al[1] | 11.8* | 8.5 | 3† | 30 | 2.5% at 3 yr |
| Marty et al[2] | 5‡ | 20 | 9§ | 11 | 4% at cut-off (about 3 yr) |
| Slamon et al[3] | 5¶ | 20 | 8 | 13 | 11% at 1 yr |

Note: HER2 = human epidermal growth factor receptor 2, ARR = absolute risk reduction, NNT = number needed to treat, CHF = congestive heart failure.
*Refers to disease-free survival, including no recurrence, death, new cancer [breast or other].
†New York Heart Association class III or IV CHF.
‡Refers to complete tumour response, assessed by radiologic and visual inspection.
§Asymptomatic decrease in left ventricular ejection fraction of ≥ 15%.
¶Refers to complete tumour response (no tumour seen), assessed by radiologic or clinical examination.

**Results:** The results presented were from an interim analysis of data for women who had been followed for 1 year (1694 in the trastuzumab group, 1693 in the control group). Events (recurrences, new cancer [breast or other], death) were half as common in the treatment group as in the control group (hazard ratio 0.54, 95% confidence interval 0.43–0.67), although there was no improve-

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ment in overall survival in the treatment group. The trastuzumab was stopped in 143 cases (8.5%) because of patient refusal or adverse events. The most common adverse events included congestive heart failure, infection and vascular disorders; serious adverse events occurred more frequently in the treatment group than in the control group (7.9% v. 4.4%).

**Commentary:** Women with HER2-positive breast cancer in this trial had reduced incidence of cancer recurrence after treatment with trastuzumab, although overall survival did not seem to improve. These findings are similar to postoperative outcomes reported by Romond and colleagues[1] and to earlier comparisons of first-line chemotherapy with and without trastuzumab in the treatment of HER2-positive cancers.[2,3]

Absolute risk reductions (ARRs) shown in Table 1 outline trastuzumab's additional contribution to disease-free survival in 4 published studies. ARRs incorporate information about how likely these events are in this population overall. In this study, 18 women would require treatment with trastuzumab for 1 year for 1 of them to benefit from its use in addition to standard chemotherapy. This number needed to treat is slightly more than that found by Romond and colleagues[1] but comparable to that reported in other studies.[2,3]

This benefit needs to be balanced against the adverse events reported. The treatment of 60 women with trastuzumab therapy plus standard chemotherapy in this study would result in 1 patient having symptomatic congestive heart failure. The treatment of only 21 patients (ARR 4.9%) would result in 1 patient having decreased LVEF. Congestive heart failure was even more common in the other studies shown in Table 1,[1–3] especially when trastuzumab was given at the same time rather than after standard chemotherapy was finished.[2,3]

Improved overall survival with the use of trastuzumab to treat HER2-positive breast cancer has also varied between trials (Table 1).

**Clinical implications:** Data support the use of trastuzumab in women with HER2-positive breast cancer, although unknown factors such as optimum dosing, timing and duration of therapy limit its use. Longer-term outcomes associated with trastuzumab therapy are unknown. Resistance to the drug is now developing as a problem.

The benefits of trastuzumab must be weighed against the drug's known cardiotoxic effects. Women with known cardiac disease were not included in the trials, and trastuzumab cannot be recommended for use in these patients. The risk of congestive heart failure or reduced LVEF in individual patients should be weighed against the likely benefit of treatment and risk of breast cancer recurrence. Future research is also needed to determine the long-term cardiac outcomes among women given trastuzumab.

HER2 testing is not widely available, and trastuzumab is not included on all provincial drug formularies. Women may, however, choose to get trastuzumab treatment in other locations if they have known HER2-positive cancer.

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