

## Public health

## High-dose chemotherapy for high-risk primary breast cancer: an on-site review of the Bezwoda study

Raymond B Weiss, Robert M Rifkin, F Marc Stewart, Richard L Theriault, Lori A Williams, Allen A Herman, Roy A Beveridge

### Summary

**Background** The efficacy of high-dose chemotherapy with progenitor-cell rescue for women with breast cancer is a controversial issue. Although historically controlled trials have suggested a survival advantage for high-dose chemotherapy, several randomised studies have yet to confirm this advantage. Two studies, however, by Bezwoda, of patients with high-risk and metastatic disease, seemed to show a significant survival advantage for high-dose compared with conventional-dose chemotherapy for metastatic and high-risk primary breast cancer.

**Methods** To corroborate the study results before starting a large international confirmatory study, a US team did an on-site review of records for patients in the high-risk study. Limited numbers of records were made available for review, all of which were for patients who received the high-dose-chemotherapy regimen.

**Findings** There was much disparity between the reviewed records and the data presented at two international meetings. In addition, the reviewers saw no signed informed consent, and the institutional review committee had no record of approval for the investigational therapy. After the site visit, Bezwoda admitted scientific misconduct by using a different control chemotherapy regimen from that described in presented data.

**Interpretation** The Bezwoda study should not be used as the basis for further trials to test the efficacy of the cyclophosphamide, mitoxantrone, etoposide regimen for high-dose chemotherapy in women with high-risk primary breast cancer. This review validates the essential nature of on-site audits, especially in single-institution studies.

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Rockville, Washington, DC, USA (Prof R B Weiss MD); US Oncology Inc, 16825 Northchase Drive, Suite 1300, Houston, TX 77060 (R M Rifkin MD, L A Williams RN, R A Beveridge MD); Department of Medicine, University of Massachusetts Medical Center, Worcester, MA (Prof F M Stewart MD); Medical Breast Cancer Service, M D Anderson Cancer Center, Houston (Prof R L Theriault MD); and National School of Public Health, Medical University of Southern Africa, Pretoria, Republic of South Africa (Prof A A Herman MD)

**Correspondence to:** Dr Roy A Beveridge (e-mail: roy.beveridge@usoncology.com)

### Introduction

One of the most controversial issues in medical oncology has been the use of high-dose chemotherapy and autologous progenitor-cell transplantation for the treatment of breast cancer.<sup>1</sup> Phase II trials in patients with metastatic disease<sup>2</sup> or high-risk primary disease<sup>3,4</sup> have suggested significant disease-free and overall survival benefits from this therapeutic approach. As a result of such studies, breast cancer became the most common disease for which transplant therapy was given in the 1990s.<sup>5</sup> Thousands of women worldwide underwent transplant therapy, frequently as routine medical care. In December, 1990, randomised trials assessing the efficacy of high-dose chemotherapy in metastatic and high-risk primary breast cancer were begun at the University of Witwatersrand, Johannesburg, South Africa, by Werner Bezwoda. The protocols involved two cycles of high-dose chemotherapy (tandem transplants) with progenitor-cell support and no intervening standard-dose chemotherapy.<sup>6–9</sup> The high-dose chemotherapy regimen consisted of a combination of cyclophosphamide, mitoxantrone, and etoposide given in doses requiring progenitor-cell support. This upfront tandem-transplant programme was unique because other randomised trials involved induction chemotherapy followed by high-dose chemotherapy.<sup>10–13</sup> Patients with metastatic and high-risk, primary breast cancer were reported to have survival in the high-dose-chemotherapy groups superior to that in the standard-dose groups.<sup>6–9</sup>

The results of the trial in women with high-risk, primary breast cancer were presented at the plenary session of the 1999 meeting of the American Society of Clinical Oncology (ASCO) and at the 1999 European Cancer Conference ECCO-10<sup>8,9</sup> (slides available at [www.conference-cast.com/asco/lecture\\_frame.htm](http://www.conference-cast.com/asco/lecture_frame.htm) at time of publication, until April 3, 2000). This trial was the only randomised study at the ASCO meeting that showed an overall survival advantage for high-dose chemotherapy in women with breast cancer.

A meeting of leading oncologists involved in transplant and breast-cancer treatment was held under the auspices of the US National Cancer Institute in December, 1999, to discuss future studies of high-dose chemotherapy in breast cancer. A large randomised trial aimed at confirming Bezwoda's results was suggested, by comparison of Bezwoda's high-dose-chemotherapy regimen with the best contemporary conventional-dose regimen. Before any confirmatory trial was started, however, an on-site review of the Bezwoda data was believed to be essential. A team of US oncologists did the review in January, 2000. The results of the assessment are reported here.

### Review methods

Four physicians (RBW, RAB, FMS, and RLT) reviewed patients' records, and two other review-team members (RMR and LAW)

	Data source							
	ASCO abstract <sup>a</sup> (n=154)		ASCO slide presentation (n=154)		ECCO-10 abstract <sup>a</sup> (n=154)		On-site review (n=151 <sup>*</sup> )	
	Control	HDC	Control	HDC	Control	HDC	Control	HDC
Number of patients randomised	79	75	79	75	70 <sup>†</sup>	75	76	75
Records available for review	N/A	N/A	N/A	N/A	N/A	N/A	0	58

HDC=high-dose chemotherapy; N/A=not applicable.

<sup>\*</sup>Number of patients recorded on log. <sup>†</sup>Exactly as reported in abstract.<sup>9</sup>

**Table 1: Patients reported to be enrolled in trial and number reviewed**

did the on-site data entry and analysis. The members of the review team were selected to limit bias. They included three physicians who have experience as directors of progenitor-cell transplant programmes and who were currently participating actively in or designing future transplant studies for breast cancer. The nurse reviewer (LAW) has substantial experience in transplant research and quality assessment. Two physicians have varied and long-term experience in managing patients with breast cancer, and one has served as a chairperson and vice chairperson of institutional review boards. Two of the physicians also have long-term experience in doing on-site audits in the clinical trials programme funded by the National Cancer Institute.

Before the visit, RAB and LAW corresponded on many occasions with Bezwoda, the study's principal investigator, outlining the purposes and needs for the site visit. A full inspection of records for all 154 patients reported as being entered in the study presented at ASCO and ECCO-10 was requested. Bezwoda agreed to the review. The methods for the review were selected in accordance with established peer-review procedures.<sup>14</sup> A cut-off date of December, 1998, for data analysis was chosen by the team to be consistent with the data presented in the ASCO abstract and the slide presentation.

At the start of the on-site review, Bezwoda provided the team with a log of 90 patients' names reported to be those entered in the metastatic disease trial,<sup>6,7</sup> a log of 151 patients' names reported to have been entered in the high-risk study,<sup>8,9</sup> the outpatient records for 58 of the patients entered in the high-dose-chemotherapy group of the high-risk trial; and two memoranda from the Johannesburg Hospital Pharmacy and Therapeutics Committee giving approval for the two studies,

each dated Dec 10, 1990. No request was made to review any records for the metastatic-disease trial,<sup>6,7</sup> and no plans were made to do so.

During the on-site review, the team was repeatedly denied access to any records for patients in the control group of the high-risk study, and records for only 58 of 75 patients reported to have been in the high-dose-chemotherapy group were made available. Bezwoda allowed the reviewers only 2 days to complete the review.

After repeated requests, the team received a copy of the study protocol from Bezwoda, less than 1 week before the site visit. An audit worksheet was derived directly from this protocol, consisting of elements involving eligibility criteria, pretreatment assessment, chemotherapy delivery, and follow-up. A uniform system of coding was developed by the reviewers during an initial assessment of the available patients' records. Data from this assessment were immediately entered into a database. After the first data were entered, the four physicians reassessed each patient's record to clarify any uncertainties. A study data manager, designated by Bezwoda, was present during the review and assisted in the gathering of data. Final data entry was completed after resolution of the team's outstanding queries on day 2. Double-entry verification was done before the database was locked at the end of the visit.

An exit interview was held with Bezwoda, in accordance with standard procedures for site visits.<sup>14</sup> Discrepancies between the team's review and Bezwoda's public presentations were brought to his attention. A further request was made to assess at least one record for any patient reported to have been entered in the control group. This request was again denied. After completion of the exit interview, a preliminary report was provided to officials of the University of Witwatersrand. Prompt action was taken.

## Review findings

The study protocol provided to the review team had the short title "CNV vs HD-CNVp in high-risk breast cancer." This title did not reflect the study as described in the ASCO and ECCO-10 abstracts<sup>8,9</sup> or the ASCO slide presentation, in which the conventional-dose regimen was described as cyclophosphamide (C), doxorubicin (A), and fluorouracil (F), and not cyclophosphamide (C), mitoxantrone (N), and vincristine (V). The provided log of patients was

### Protocol eligibility criteria

#### Eligibility criteria from protocol supplied by Bezwoda

Female patients aged >18 years and <50 years

Patients must have had breast cancer with:

T1–T3a, node positive ( $\geq 7$  involved nodes), and/or

T3a, oestrogen-receptor negative, any node positive, or

T3a, any node status, with a strong family history (2 first-degree relatives) of primary breast cancer

Preserved end-organ function, no previous chemotherapy, no active infection, no radiographic study positive for metastases, and no other significant comorbid disease that would preclude safe administration of either chemotherapy regimen

#### Eligibility criteria for disease characteristics specified in ASCO abstract<sup>8</sup>

T1–T3a  $\geq 10$  involved nodes or

Tumour  $\geq 5$  cm with 7–9 involved nodes, plus at least one additional poor prognostic feature

#### Eligibility criteria for disease characteristics specified in ASCO slide presentation

Age  $\leq 55$  years

Female patients with surgically-excised, high-risk, primary breast cancer with:

T1–3a with  $\geq 10$  involved nodes, irrespective of oestrogen-receptor status, or

T3a ( $\geq 5$  cm) with  $\geq 7$  involved nodes and oestrogen-receptor negative, or

$\geq 7$  involved nodes with strong ( $\geq 2$  first-degree relatives) family history of breast cancer

Preserved end-organ function, no known HIV infection, and no radiographic study positive for metastases

No residual chest-wall tumour

No previous radiation therapy

#### Eligibility criteria for disease characteristics specified in ECCO-10 abstract<sup>9</sup>

Surgically treated high-risk breast cancer with:

T1–T3a  $\geq 10$  involved nodes or

Tumour  $\geq 5$  cm plus 7–9 nodes plus one additional poor risk factor (oestrogen-receptor negative, family history of breast cancer, or both)

	Data source				
	Study protocol	ASCO abstract <sup>§</sup>	ASCO slide presentation	ECCO-10 abstract <sup>§</sup>	On-site review
<b>Conventional-dose chemotherapy (mg/m<sup>2</sup>)</b>					
Cyclophosphamide	600	600	600	Not specified	Unavailable
Doxorubicin or epirubicin	60 or 75	50 or 70	50 or 70	Not specified	Unavailable
Fluorouracil	600	600	600	Not specified	Unavailable
<b>High-dose chemotherapy (mg/m<sup>2</sup>)</b>					
Cyclophosphamide	4400	4400	4400	4400	4400
Mitoxantrone*	35 or 45	45	45	45	35 or 45
Etoposide	1500	1500	1500	1500	1500
<b>Tamoxifen therapy</b>	Given to oestrogen-receptor-positive patients for 5 years	Not specified	Not specified	Not specified	Given to oestrogen-receptor-positive, negative and unknown patients
<b>Radiotherapy<sup>†</sup></b>	Not specified	Not specified	Previous radiotherapy was protocol exclusion	Not specified	Given before or after high-dose chemotherapy

\*Mitoxantrone at 35 mg/m<sup>2</sup> was administered to patients with previous adjuvant doxorubicin or left chest-wall irradiation as specified in protocol supplied by Bezwoda. †Chest-wall irradiation was given to patients receiving high-dose chemotherapy based on when they were first seen by Bezwoda (ie, before or after irradiation had been completed).

Table 2: Treatment regimens by data source

assumed to be accurate and to include all the patients entered in the study. Bezwoda confirmed this assumption. However, only 151 patients were listed on the enrolment log (table 1) compared with 154 in the abstracts and slide presentation.

Of the 58 records made available, the longest record was fewer than 20 pages, and the shortest had only one page. The entry criteria in the protocol were not consistent with those published (panel). Discrepancies in eligibility of patients included age, tumour category, and the number of involved axillary nodes. Furthermore, specifications of tamoxifen administration and mitoxantrone dose varied (table 2).

Table 3 shows patients' characteristics in the high-dose chemotherapy group compiled from four different sources. The proportion of white women receiving therapy differed greatly between the on-site information and the data presented at the ASCO slide presentation (7 vs 36%). Oestrogen-receptor status listed in the ASCO presentation and the on-site review were similar.

Only 20 of 58 patients were deemed by the reviewers to have fully documented eligibility for enrolment based on the protocol. Incorrect age and disease stage were taken to be serious eligibility deviations (table 4). 57% of the study cohort did not undergo the required assessment for occult metastases before entry or did not have adequate end-organ function documented. In addition, previous radiotherapy was specifically listed as a protocol exclusion criterion in the ASCO slide presentation but was not addressed in the ASCO abstract or the protocol document. However, the protocol provided for a dose adjustment of mitoxantrone if a

patient had received left chest-wall irradiation. Patients' records showed that 32 patients had received chest-wall irradiation, 22 before high-dose chemotherapy and ten after. Based on the ASCO slide presentation (panel), seven patients additional to those listed would be ineligible because of previous radiation therapy. Bezwoda stated that 74 (99%) of the 75 patients were eligible.

The protocol provided for variations in the mitoxantrone dose in the high-dose-chemotherapy regimen (table 2). A lower dose was to be used if radiation to the left chest wall had been administered or was anticipated (table 5). In accordance with the protocol, mitoxantrone 35 mg/m<sup>2</sup> should have been given to the six women with left-sided cancers who received radiotherapy before high-dose chemotherapy. The on-site review showed that mitoxantrone 35 mg/m<sup>2</sup> was given to all six women who received left-sided radiation before high-dose chemotherapy, and four of the six women who received left-sided radiation after high-dose chemotherapy. In addition, two women who received right-sided radiation therapy, one before and one after high-dose chemotherapy, received mitoxantrone 35 mg/m<sup>2</sup>. 13 patients, 12 with left-sided breast cancer and one with right-sided disease, who received no radiation therapy also received mitoxantrone 35 mg/m<sup>2</sup>

Reason for ineligibility*	Number of patients ineligible at on-site review (n=58)
Wrong age	1
Wrong tumour or node category <sup>†</sup>	8
Pretreatment eligibility unconfirmed <sup>‡</sup>	29

\*Patients could be deemed ineligible for more than one reason. †T4 tumour, six patients; nodes <7, two patients. ‡Results of protocol-specified pretreatment radiographic studies not available for review.

Table 4: Eligibility according to supplied protocol

	Data source			
	ASCO abstract <sup>§</sup> (n=75)	ASCO slide presentation (n=75)	ECCO-10 abstract <sup>§</sup> (n=75)	On-site review (n=58)
<b>Demography</b>				
Age (years)	Not specified	≤55	Not specified	24–53
Proportion of white patients (%)	Not specified	36	Not specified	7
<b>Menopausal status</b>				
Pre-menopausal (%)	Not specified	Not specified	Not specified	97
Post-menopausal (%)	Not specified	Not specified	Not specified	3
<b>Oestrogen-receptor status</b>				
Negative (%)	Not specified	47	Not specified	43
Positive (%)	Not specified	9	Not specified	9
Unknown (%)	Not specified	44	Not specified	48

Table 3: Patients' characteristics in high-dose-chemotherapy group by data source

Treatment	Number of patients eligible for treatment*	Number of patients treated*
<b>Mitoxantrone</b>		
35 mg/m <sup>2</sup>	6	25
45 mg/m <sup>2</sup>	51	32
<b>Tamoxifen</b>		
Oestrogen-receptor positive	5	4
Oestrogen-receptor negative	0	4
Oestrogen-receptor status unknown	0	21
<b>Radiotherapy</b>		
Before high-dose chemotherapy	0	22
After high-dose chemotherapy	0	10

\*Mitoxantrone dose unknown for one patient.

Table 5: Patients who received high-dose chemotherapy

Regimen	Data source			
	ASCO abstract <sup>a</sup> (n=154)	ASCO slide presentation (n=154)	ECCO-10 abstract <sup>a</sup> (n=154)	On-site review* (n=58)
Control group	52/79 (66%)	55/79 (70%)	52/70 (74%)	Unavailable
High-dose chemotherapy group	19/75 (25%)	21/75 (28%)	19/75 (25%)	19/58 (33%)

\*Only patients who had relapsed by December, 1998 (before ASCO presentation), are counted. Patients who relapsed after this date were coded for review as still in remission. Patients were not always followed up at intervals specified in provided protocol.

Table 6: Analysis for relapse

in the reviewed records. Of the 58 records reviewed, 25 showed use of the lower dose of mitoxantrone. By contrast, the two abstracts and the slide presentation suggested that the only mitoxantrone dose used in the high-dose-chemotherapy regimen was 45 mg/m<sup>2</sup> (table 3). In addition, 21 women with unknown oestrogen-receptor status and four with receptor-negative tumours received tamoxifen, even though it was not directed by the protocol.

Although the numbers of patients who relapsed seemed similar in all the data presentations (table 6), the exact numbers varied. Furthermore, four patients had a date of last contact more than 1 year before December, 1998, and 17 records were not available for review. Therefore, relapse information cannot be judged reliable.

In the ASCO abstract, the number of deaths in each treatment group was given, but no such information was included in the ASCO slide presentation (table 7). The on-site review noted eight deaths, the same as stated in the abstract, but records for the full study cohort were not available. Seven more patients were discovered who had relapsed more than 2 years before December, 1998, and were referred for terminal care with no additional follow-up. Because of the natural history of metastatic breast cancer, those women probably died. Therefore, the actual number of deaths in the high-dose-chemotherapy group was probably understated.

Although a brief consent form was attached to the protocol, no signed consent form appeared in any reviewed record. The chairperson of the Committee for Research on Human Subjects (Medical) at the University of Witwatersrand searched committee records back to 1975. No records were found that the protocol for this study, which was opened in December, 1990, had ever been submitted for review and approval as required by university policy (Peter Cleaton-Jones, personal communication).

## Comment

The study by Bezwoda was reported at two international meetings to be a randomised controlled trial that assessed the role of high-dose chemotherapy and

Regimen	Data source			
	ASCO abstract <sup>a</sup> (n=154)	ASCO slide presentation* (n=154)	ECCO-10 abstract** (n=154)	On-site review (n=58)
Control group	28/79 (35%)	Not specified	Not specified	Unavailable
High-dose chemotherapy group	8/75 (11%)	Not specified	Not specified	8/58 (14%) confirmed, 15/58 (26%) likely†

\*Only Kaplan-Meier survival plot presented in ASCO slides and at ECCO-10, and, therefore, no data are available for analysis. †Patients who relapsed >2 years before December, 1998, and whose records showed referral for terminal care with no further follow-up, are counted as death.

Table 7: Analysis of deaths

progenitor-cell transplant compared with standard cyclophosphamide, doxorubicin, and fluorouracil adjuvant treatment for high-risk primary breast cancer. The study had major importance because it showed, uniquely, a survival benefit for patients receiving high-dose chemotherapy in high-risk, primary breast cancer;<sup>11-13</sup> the experimental treatment group included novel, upfront, tandem progenitor-cell transplant; long follow-up was reported; and some oncologists had already adopted the Bezwoda transplant approach as standard therapy for high-risk, primary breast cancer. If the results of his study were verified, investigators worldwide proposed to confirm its benefit by testing it in a randomised trial with larger number of patients. The on-site review was aimed at validating the major conclusions of the study and providing greater understanding of the patients' characteristics and treatment technique.

After many communications with the principal investigator over 8 months, the site visit was made. No attempt was made to do a rigorous audit at a level required by the National Cancer Institute<sup>14</sup> or the pharmaceutical industry. Reasonable alternative information was accepted in lieu of a primary source to support inclusion of patients in the trial.

The protocol, which was purported to have been written in 1990, raised two issues of major concern: a reference to a 1997 paper in the bibliography, and procedures for use of filgrastim for mobilisation in the high-dose-chemotherapy group. The protocol cited the progenitor-cell mobilisation regimen as daily filgrastim 5 µg/kg. Filgrastim was not commercially available in South Africa until March, 1992. According to University officials, filgrastim was not approved for any investigational use for this trial. The review team asked Bezwoda if the protocol they were given was an updated version to which filgrastim had been added after it became commercially available. He said repeatedly that it had not been revised and that the document given to the review team was the original.

In the assessment of the study documents and 58 patients' records there were major discrepancies in the trial implementation and reporting of results. The number of discrepancies and protocol deviations in eligibility alone call into serious question the validity of the study. Key differences in eligibility criteria include discrepancies in age, nodal and tumour status, and radiotherapy as pretreatment exclusion criteria. The details of eligibility in the ASCO slide presentation was not reflected in the provided protocol (panel). Nine of the 58 patients reviewed did not meet major eligibility criteria (wrong age, T4 primary tumours, or <7 involved lymph nodes).

The study title on the protocol cover sheet and the document from the hospital pharmacy and therapeutics committee indicated that patients in the control group would be treated with cyclophosphamide, mitoxantrone, and vincristine, rather than cyclophosphamide, doxorubicin, and fluorouracil, as reported in the meeting presentations. Despite the treatment schema in the body of the protocol showing that controls would receive the latter chemotherapy combination, the discrepancy with the title raised the concern of review team members. Cyclophosphamide, mitoxantrone, and vincristine was the control treatment used in the similarly designed study of metastatic breast cancer done by Bezwoda,<sup>6,7</sup>

which was also opened in December, 1990. In the metastatic-disease study, Bezwoda was criticised for this control regimen because it was judged less acceptable than the cyclophosphamide, doxorubicin, and fluorouracil combination. The on-site team directly questioned Bezwoda about whether control patients of the high-risk study received cyclophosphamide, mitoxantrone, and vincristine chemotherapy, contrary to the presented data. He repeatedly denied that the control group received that regimen.

In addition to assessment of protocol adherence, the accuracy of data reported at the ASCO slide presentation was assessed. In the ASCO presentation, around 60% of patients were classified as black and 36% as white. Of the 58 patients reviewed, only 7% were white. The stated survival advantage could not be confirmed because not all records were provided and follow-up was not current. Mortality could, therefore, have been understated. There was also disparity between the protocol and the various data presentations for the doxorubicin and epirubicin doses (table 2).

After the site visit, a preliminary data analysis was sent to officials at the University of Witwatersrand. Bezwoda delivered a letter to the chairperson of the Committee for Research on Human Subjects acknowledging scientific misconduct and misrepresentation of the conventional-dose regimen as being cyclophosphamide, doxorubicin, and fluorouracil instead of cyclophosphamide, mitoxantrone, and vincristine.<sup>15</sup> In that letter, Bezwoda stated, "This was done out of a foolish desire to make the presentation more acceptable to an audience who I believed would have regarded CAF as a more familiar and more standard control arm."<sup>15</sup>

Scientific misconduct has seldom been reported compared with the number of published research reports.<sup>16</sup> The true frequency and magnitude remain unknown. In this case, the quality of research reporting and the reliability of the data presentations were reviewed. Such review of research results is not a current requirement for abstract presentations or scientific journals because of the honour system for submitting research studies for presentation or publication. The National Cancer Institute has developed requirements for auditing clinical trials when institutions receive US government funding,<sup>14,17</sup> and colleagues and collaborators commonly provide additional peer review by continuing involvement in a research study.

The review of the Bezwoda study did not confirm the validity of what was done and what was reported. The multiple discrepancies were of sufficient magnitude to invalidate the study results. Bezwoda's admission that he misrepresented the control group discredits his published findings. Therefore, the study results should not be used as the basis for future randomised trials. The review provides strong evidence that peer-review is an essential element in the conduct of a clinical trial.

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