

# Study Backs Radiation After Lymphadenectomy

VITALS

**Major Finding:** Radiation therapy after lymphadenectomy reduces melanoma recurrence in patients at high risk.

**Source of Data:** Phase III intergroup trial of 217 fully evaluable patients.

**Disclosures:** The study was supported by the Australia and New Zealand Melanoma Trial Group, National Health and Medical Research Council of Australia, and Cancer Council Victoria. Dr. Burmeister and Dr. Ballo reported no conflicts of interest.

BY PATRICE WENDLING

CHICAGO — Radiation therapy significantly reduced the risk of recurrence in melanoma patients at high risk of relapse after lymphadenectomy, according to a phase III intergroup trial.

Among 217 fully evaluable patients, 68% of patients treated with external beam radiation

after surgery had lymph node field recurrence at 2 years, compared with 80% of those observed after surgery. In an intent-to-treat analysis in 248 patients, recurrence rates were 65% vs. 82%, respectively. Median follow-up was 39 months.

Early radiotherapy toxicity appears minimal, Dr. Bryan Burmeister reported on behalf

of the Trans Tasman Radiation Oncology Group 02.01/Australia and New Zealand Melanoma Trial Group 01.02 at the annual meeting of the American Society for Radiation Oncology (ASTRO).

"I believe this is the only real advance in the management of melanoma to happen in the last 15 years, since the interferon data came out," Dr. Burmeister said in a press briefing. He urged physicians to discuss radiation therapy as an option with their melanoma patients.

Dr. Matthew Ballo, who was invited to discuss the results during the plenary presentation, said that the value of adjuvant radiotherapy in melanoma has been debated for years, and that as recently as 2004 it was viewed as a management approach of undetermined potential that should not be considered in routine practice.

"We now have high-level evidence supporting radiation therapy in selected patients with lymph node disease from

## BRIEF SUMMARY

**ALTABAX™ (retapamulin ointment), 1%**

The following is a brief summary only; see full prescribing information for complete product information.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS****5.1 Local Irritation**

In the event of sensitization or severe local irritation from ALTABAX, usage should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted [See Patient Counseling Information (17)].

**5.2 Not for Systemic or Mucosal Use**

ALTABAX is not intended for ingestion or for oral, intranasal, ophthalmic, or intravaginal use. ALTABAX has not been evaluated for use on mucosal surfaces [See Patient Counseling Information (17)].

**5.3 Potential for Microbial Overgrowth**

The use of antibiotics may promote the selection of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing ALTABAX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**6 ADVERSE REACTIONS****6.1 Clinical Studies Experience**

The safety profile of ALTABAX was assessed in 2,115 adult and pediatric patients ≥9 months who used at least one dose from a 5-day, twice a day regimen of retapamulin ointment. Control groups included 819 adult and pediatric patients who used at least one dose of the active control (oral cephalexin), 172 patients who used an active topical comparator (not available in the US), and 71 patients who used placebo.

Adverse events rated by investigators as drug-related occurred in 5.5% (116/2,115) of patients treated with retapamulin ointment, 6.6% (54/819) of patients receiving cephalexin, and 2.8% (2/71) of patients receiving placebo. The most common drug-related adverse events (≥1% of patients) were application site irritation (1.4%) in the retapamulin group, diarrhea (1.7%) in the cephalexin group, and application site pruritus (1.4%) and application site paresthesia (1.4%) in the placebo group.

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

**Adults:** The adverse events, regardless of attribution, reported in at least 1% of adults (18 years of age and older) who received

ALTABAX are listed in Table 1.

**Table 1. Adverse Events Reported by ≥1% of Adult Patients Treated With ALTABAX in Phase 3 Clinical Studies**

Adverse Event	ALTABAX N=1527 %	Cephalexin N=698 %
Headache	2.0	2.0
Application site irritation	1.6	<1.0
Diarrhea	1.4	2.3
Nausea	1.2	1.9
Nasopharyngitis	1.2	<1.0
Creatinine phosphokinase increased	<1.0	1.0

**Pediatrics:** The adverse events, regardless of attribution, reported in at least 1% of pediatric patients aged 9 months to 17 years who received ALTABAX are listed in Table 2.

**Table 2. Adverse Events Reported by ≥1% in Pediatric Patients Aged 9 Months to 17 Years Treated With ALTABAX in Phase 3 Clinical Studies**

Adverse Event	ALTABAX N=588 %	Cephalexin N=121 %	Placebo N=64 %
Application site pruritus	1.9	0	0
Diarrhea	1.7	5.0	0
Nasopharyngitis	1.5	1.7	0
Pruritus	1.5	1.0	1.6
Eczeema	1.0	0	0
Headache	1.2	1.7	0
Pyrexia	1.2	<1.0	1.6

**Other Adverse Events:** Application site pain, erythema, and contact dermatitis were reported in less than 1% of patients in clinical studies.

**7 DRUG INTERACTIONS**

Co-administration of oral ketoconazole 200 mg twice daily increased retapamulin geometric mean AUC<sub>0-24</sub> and C<sub>max</sub> by 81% after topical application of retapamulin ointment, 1% on the abraded skin of healthy adult males. Due to low systemic exposure to retapamulin following topical application in patients, dosage adjustments for retapamulin are unnecessary when co-administered with CYP3A4 inhibitors, such as ketoconazole. Based on in vitro P450 inhibition studies and the low systemic exposure observed following topical application of ALTABAX, retapamulin is unlikely to affect the metabolism of other P450 substrates.

The effect of concurrent application of ALTABAX and other topical products to the same area of skin has not been studied.

**8 USE IN SPECIFIC POPULATIONS****8.1 Pregnancy**

**Pregnancy Category B.** Effects on embryo-fetal development were assessed in

pregnant rats given 50, 150, or 450 mg/kg/day by oral gavage on days 6 to 17 postcoitus.

Maternal toxicity (decreased body weight gain and food consumption) and developmental toxicity (decreased fetal body weight and delayed skeletal ossification) were evident at doses ≥150 mg/kg/day. There were no treatment-related malformations observed in fetal rats.

Retapamulin was given as a continuous intravenous infusion to pregnant rabbits at dosages of 2.4, 7.2, or 24 mg/kg/day from day 7 to 19 of gestation. Maternal toxicity (decreased body weight gain, food consumption, and abortions) was demonstrated at dosages ≥7.2 mg/kg/day (8-fold the estimated maximum achievable human exposure, based on AUC, at 7.2 mg/kg/day). There was no treatment-related effect on embryo-fetal development.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALTABAX should be used in pregnancy only when the potential benefits outweigh the potential risk.

**8.3 Nursing Mothers**

It is not known whether retapamulin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALTABAX is administered to a nursing woman. The safe use of retapamulin during breast-feeding has not been established.

**8.4 Pediatric Use**

The safety and effectiveness of ALTABAX in the treatment of impetigo have been established in pediatric patients 9 months to 17 years of age. Use of ALTABAX in pediatric patients is supported by evidence from adequate and well-controlled studies of ALTABAX in which 588 pediatric patients received at least one dose of retapamulin ointment, 1% [see Adverse Reactions (6), Clinical Studies (14)]. The magnitude of efficacy and the safety profile of ALTABAX in pediatric patients 9 months and older were similar to those in adults.

The safety and effectiveness of ALTABAX in pediatric patients younger than 9 months of age have not been established.

**8.5 Geriatric Use**

Of the total number of patients in the adequate and well-controlled studies of ALTABAX, 234 patients were 65 years of age and older, of whom 114 patients were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients.

**10 OVERDOSAGE**

Overdosage with ALTABAX has not been reported. Any signs or symptoms of overdose, either topically or by accidental ingestion, should be treated symptomatically consistent with good clinical practice.

There is no known antidote for overdoses of ALTABAX.

**13 NONCLINICAL TOXICOLOGY****13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with retapamulin.

Retapamulin showed no genotoxicity when evaluated in vitro for gene mutation and/or chromosomal effects in the mouse lymphoma cell assay, in cultured human peripheral blood lymphocytes, or when evaluated in vivo in a rat micronucleus test.

No evidence of impaired fertility was found in male or female rats given retapamulin 50, 150, or 450 mg/kg/day orally.

**17 PATIENT COUNSELING INFORMATION**

Patients using ALTABAX and/or their guardians should receive the following information and instructions:

- Use ALTABAX as directed by the healthcare practitioner. As with any topical medication, patients and caregivers should wash their hands after application if the hands are not the area for treatment.

- ALTABAX is for external use only. Do not swallow ALTABAX or use it in the eyes, on the mouth or lips, inside the nose, or inside the female genital area.

- The treated area may be covered by a sterile bandage or gauze dressing, if desired. This may also be helpful for infants and young children who accidentally touch or lick the lesion site. A bandage will protect the treated area and avoid accidental transfer of ointment to the eyes or other areas.

- Use the medication for the full time recommended by the healthcare practitioner, even though symptoms may have improved.

- Notify the healthcare practitioner if there is no improvement in symptoms within 3 to 4 days after starting use of ALTABAX.

- ALTABAX may cause reactions at the site of application of the ointment. Inform the healthcare practitioner if the area of application worsens in irritation, redness, itching, burning, swelling, blistering, or oozing.

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DR. BURMEISTER

malignant melanoma," he said.

He cautioned that the lack of overall survival benefit observed in the trial may impede rapid acceptance of the data. Median survival times were 31 months with radiotherapy and 34 months with observation ( $P = .14$ ). There were 120 deaths, 2 of which were not melanoma related.

Dr. Ballo suggested that radiologists in the clinical arena stress the importance of regional control, and remind colleagues in the academic arena that improvements in outcome occur in small steps. Relapse rates in patients with high-risk features, such as those in the study, are 30%-50%, he noted.

Patients were eligible if they had involvement of at least one parotid, at least two cervical or axillary, or at least three groin nodes; or extranodal spread; or a minimum metastatic node diameter of 3 cm in the neck or axilla or 4 cm in the groin. Patients randomized to radiation received 48 Gy in 20 fractions. Radiotherapy compliance was 79%.

Grade 3 toxicities 2 weeks post radiation included 18 cases of dermatitis and 2 of pain. At 6 weeks, there were five cases of dermatitis, two of pain, and one of fatigue, said Dr. Burmeister, director of radiation oncology at Princess Alexandra Hospital in Brisbane, Australia. No grade 4 early toxicities were reported.

Longer-term results are needed to assess fibrosis, lymphedema, and brachial plexopathy, as well as recurrence-related morbidity in the control arm, said Dr. Ballo, head of radiation oncology at the M.D. Anderson Clinical Care Center in Nassau Bay, Tex. ■