Studies on Therapy of Osteosarcoma in Dogs Using BCG Vaccine

L. N. OWEN, D. E. BOSTOCK, and R. B. LAVELLE

INTRODUCTION

One of the most difficult tumors to treat both in canine and human medicine is the osteosarcoma. Attempts to avoid amputation and to cure the tumor by X-irradiation have been unsuccessful in both species. In 17 dogs doses of 4000–5000 R in fractionated doses of 1000 R over a 4 or 5 week period were given to the primary tumor from a 15 MeV linear accelerator giving 120–130 rads/minute with 100% penetration at 3 cm in tissue. Reduction in pain was remarkable but the mean pain-free survival time was only 4 months (1 month to 1 year) (5).

Five year survival figures in man following amputation or X-irradiation followed by amputation vary from zero to 20% (4). In the dog the prognosis is equally bad (1). At the time of amputation, performed only if thoracic radiography shows no evidence of lung metastases, micrometastases are almost invariably present and within a few weeks or months euthanasia becomes necessary. The problem of how to kill these relatively few malignant cells already present in the lungs at the time of amputation has been approached along three main lines.

Lung X-irradiation with a dose of 600 R on two occasions and a one-week interval has been found to be of no value in the dog (5). In man fractionated doses to the lungs of 150 R to approximately 2000 R produce improved results for 1–2 year survival but by 5 years the results were similar to historical controls (3).

Chemotherapy given prophylactically following amputation has produced initially good results in man (9) and trials are in progress in the USA, Great Britain, and elsewhere using particularly doxorubicin and methotrexate. Five-year survival figures are not yet available. No such trials in dogs have yet been reported.

Preliminary results using non-specific immunostimulation in dogs amputated for osteosarcoma have been reported (6–8). The rationale for this form of therapy has been described previously. The results for 20 such dogs given intravenous BCG on a number of occasions are now reported.

MATERIALS AND METHODS

Clinical cases

Dogs referred to the Department of Clinical Veterinary Medicine, University of Cambridge, were examined clinically and radiographically. In most instances the diagnosis of osteosarcoma was made on radiographic examination and confirmed histologically following amputation. Occasionally biopsy was necessary before amputation was performed. If there was no radiographic evidence of lung metastasis and no clinical evidence of metastasis elsewhere, permission was sought for amputation and therapy. Amputation in a large dog is always a difficult decision for the owner to make and we were able to influence their decision by (a) giving them the name and telephone number of owners who had dogs with limbs amputated, and (b) showing them a film of two Great Danes with a fore or hind limb amputation and a heavy Alsatian with a forelimb amputation.

There were 13 forelimb amputations, 6 in Great Danes, and 7 hind-limb amputations. Amputations were made at mid-shaft humerus or mid-shaft femur except where these bones were themselves the site of primary tumours. In these cases disarticulation at the shoulder or hip was performed.

Therapy

The details of therapy have been given previously (6). In brief, freeze-dried percutaneous BCG vaccine containing 50–250 × 10⁶ viable organisms was made up to 5 ml in normal saline and administered to dogs intravenously irrespective of size. The first injection was immediately before or soon after amputation and repeated injections were made at intervals of 1, 2, 4, 8, 8, 8 weeks. In 4 dogs autologous X-irradiated tumor cells (10,000 R) were administered on the first occasion mixed with the BCG vaccine.

As a safeguard against anaphylaxis an intramuscular

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1 This manuscript is based on a paper presented at the Fourth International Veterinary Radiological Conference in Cambridge, England, September 7–10, 1976.
2 From the Department of Veterinary Clinical Medicine, University of Cambridge, England where L. N. Owen is the Assistant Director of Research, D. E. Bostock is a Lecturer in Animal Pathology, and R. B. Lavelle is a University Assistant Surgeon to the Veterinary Hospital.
3 Glaxo Laboratories Ltd., Greenford, Middlesex, England.
injection of an antihistamine drug (mepyramine maleate\(^4\) or chlorpheniramine maleate\(^5\)) was made 20–30 minutes before the injection of BCG.

Results

(a) Amputation. In general both ourselves and the owners were pleased with the results of amputation. All owners had large gardens or easy access to fields where the dogs could run freely. In a Great Dane (Case 7) with a forelimb amputation the rather neurotic owner reported a reluctance to move and requested euthanasia. At necropsy there were very early arthritic changes present in the hip joint. Euthanasia was performed on two Alsatians (Cases 4 and 16) because of hip dysplasia. Case 16 was 10 years old and had already lived over a year post-amputation but Case 4 lived only 15 weeks. In neither dog were metastases found.

(b) Development of metastases. Details of the doses of BCG and survival times are given in the table. It will be seen that of the 20 dogs treated, 11 lived 6 months or more and 7 of these lived over a year. One dog is alive and clinically and radiographically free from metastases at 1 year 9 months. The time between the radiographic appearance of metastases and the ill-health of the dog necessitating euthanasia was very variable ranging from 2 weeks to 3 months. Euthanasia was performed in 5 dogs for reasons unrelated to osteosarcoma. In one of these dogs necropsy was not possible but at necropsy of the other four no metastases were found.

(c) Toxicity and Pathology. In spite of the previous administration of an antihistamine drug, one dog showed anaphylaxis following a second dose of BCG. The animal recovered following the immediate injection of soluble hydrocortisone.

The toxic effects and pathological effects (mainly granuloma formation in the lungs and liver and follicular lymphoid hyperplasia) have been described previously (6). Great care is required during the intravenous injection, as perivascular infiltration results in a granuloma which takes 6–8 weeks to heal.

It was common for anorexia to occur for a day or more after the injection of BCG and there was a mild pyrexia in many dogs. Glossitis occurred in one dog and a severe pharyngitis in another.

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DISCUSSION

We have not conducted a prospective randomized trial of amputation plus BCG against amputation alone. Consequently the results of this form of therapy are more difficult to interpret using historical controls. We have previously reported (6) median survival time, after amputation, of 14 weeks in 5 dogs receiving no other therapy and in 5 dogs receiving amputation plus unilateral lung X-irradiation. This compares with a median survival time in this treated group of 20 dogs of 25 weeks. Survival figures following amputation for osteosarcoma were reported in 1965 (1) and showed 17/29 dogs dead in 14 weeks or less. In our series of 20 dogs euthanasia was performed in only 3 dogs at 14 weeks or less—one of these having no metastases. The site or radiographical appearance or histological appearance of the tumors did not correlate with survival times. A Wolfhound bearing one of the largest and most malignant tumors (Case 20) where a pathological fracture of the tibia was present at the time of our first examination has been the longest survivor.

Considering the seriousness of the condition the toxic effects of therapy have been justifiable and acceptable to the owners. The results call for cautious optimism that a genuine delay in the development of metastases has occurred. The method of delay is currently under investigation in our laboratory. Probably one of the most important effects of BCG is to activate macrophages nonspecifically. There is now good evidence of recognition and destruction of malignant cells by activated macrophages (2). A recent paper has shown that in the mouse there is an induction of “natural killer” cells by BCG which may be partially responsible for the tumor regression associated with BCG therapy (10).

It is already clear, however, that the therapy at best is only one of delay and unlikely to lead to cures. It may be possible to develop some more specific type of immunotherapy. Alternatively, it may well be better to attempt chemotherapy following amputation to kill the majority of cells present and to attempt to kill the remaining cells using immunological methods.

As any one Veterinary School sees relatively few cases of canine osteosarcoma, collaboration on therapy between different schools is a worthwhile objective.

SUMMARY

BCG vaccine was injected intravenously at intervals of 1, 2, 4, 8, 8, 8 weeks to 20 dogs which had limbs amputated for osteosarcoma. The mean survival time was 25 weeks. “Historical” controls and U.S.A. figures showed survival times of about half this figure. In treated dogs 7/20 survived one year or more. Toxicity has not been severe.

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Department of Veterinary Clinical Medicine
University of Cambridge
Cambridge, England

REFERENCES


ZUSAMMENFASSUNG


RÉSUMÉ

On a injecté du vaccin BCG par voie intraveineuse à des fréquences de 1-2-4-8-8-8 semaines à des chiens auxquels on avait amputé des pattes en raison de cancer osseux. La durée moyenne de survie s'est établie à 25 semaines. Les contrôles "relatés dans des cas définis" et les chiffres trouvés aux Etats-Unis donnent des durées de survie d'environ la moitié de cela. 7 sur 20 des chiens soumis au traitement ont survécu un an ou plus. La toxicité n'a pas été sérieuse.