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A review of the use of glutamine supplementation in the nutritional support of bone marrow transplant and cancer patients

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Abstract

The relationship between glutamine and malignancy can be traced back to the 1950s and the requirement for glutamine for malignant cell growth in culture. Later studies demonstrated a relationship between rate of proliferation of the malignant cells and glutamine usage. The excessive use of glutamine by malignant cells was seen as an opportunity for the development of a treatment using glutamine analogues but unfortunately excessive toxicity was seen during clinical trials. In animal models glutamine supplementation, initially thought to increase tumour growth, actually caused tumour regression due to improved immune clearance of the tumour and appeared to reduce the severity of the side-effects of chemo- and radiotherapy. This led to human studies in both traditional cancer therapy and bone marrow transplantation which we review here. Unfortunately the majority of the studies performed were small and had poor methodological reporting. There is clinical heterogeneity in terms of routes of administration, dosing schedules, chemotherapy regimens and diseases. Studies of glutamine studies in non-bone marrow transplantation chemo- and/or radiotherapy suggest a possible trend towards reductions in objective mucositis but no effect on subjective symptoms. There is no evidence for its effect on other clinical outcomes. For bone marrow transplantation there appears to be some benefit from oral glutamine in reducing mucositis and graft-versus-host-disease while intravenous glutamine may reduce infections but at the expense of an increased relapse rate. Good quality trials are required in this area.

Starting in the test tube…

The 1950's brought great advances in cell culture techniques such that mammalian cells could be continuously grown outside the body. The first immortal cell line used cervical cancer cells (HeLa cells) (Scherer *et al*, 1953). Much work was done in finding the best culture mediums that allowed maximal cell growth. One nutrient that was found to be important and used avidly by the tumour cells was glutamine (Eagle, 1976). Scientists, now aware of a relationship between cancer and glutamine, investigated matters further.

It became apparent that the more rapidly growing, hence more aggressive, the tumour the more glutamine it metabolised (Knox *et al*, 1969). Animal studies raised the possibility of a 'glutamine trap' where the tumour consumes glutamine at a higher rate than other tissues and deficiency occurs (Carrascosa *et al*, 1984). This deficiency, it was thought, may lead to the cahexia and weight loss of malignancy. However many of these studies used mouse and rat models of cancer where the tumour was between 10-20% of the body weight of the animal, a much greater proportion than in human malignancies.

Glutamine supplementation – good or bad?

In animal models with cancer many thought that glutamine supplementation would cause increased tumour growth as the amino acid appeared to be an important fuel for the tumour. Supplementation with glutamine actually caused tumour regression in some cases because of glutamine being the preferred fuel of the body's tumour killing cells the Natural Killer (NK) cells (Klimberg *et al*, 1996).

Glutamine was given to rats and mice after they had received chemo- and/or radiotherapy and it was found to reduce damage to the gut (Fox *et al*, 1988 and Klimberg *et al*, 1989) and

improve immune function hence reducing infections which are a major cause of morbidity and mortality in cancer patients.

Glutamine analogues were then investigated with the hypothesis that as tumour cells utilise glutamine at a higher rate than normal tissues then toxic glutamine analogues would be preferentially taken up by the cancer (Souba, 1993).

Human studies

With the encouraging evidence from animal studies of decreased side-effects of chemo- and radiotherapy and the suggestion that glutamine does not increase tumour size several studies of glutamine supplementation in humans were conducted.

The studies either gave oral or intravenous glutamine and the intravenous glutamine was either given with total parenteral nutrition or alone. The studies can be further divided into those patients receiving bone marrow transplantation and those receiving traditional chemotherapy.

Chemotherapy and radiotherapy

Traditional chemotherapy involves the administration of cytotoxic drugs which kill rapidly dividing cells, which include malignant cells. After administration there is a rest period where the body recovers from the chemotherapy before more is given. Chemotherapy also damages rapidly dividing normal cells e.g. cells lining the gut, hair follicles and the bone marrow. It is the damage to the normal cells which lead to the side-effects (mucositis from gut damage and increased infections from bone marrow damage). Radiotherapy is the administration of radiation, usually in the form of ionising radiation which as in chemotherapy damages rapidly dividing cells.

A brief search of PubMed revealed nine randomised controlled trials which administer glutamine to patients receiving chemotherapy and/or radiotherapy (Anderson, 1998; Cerchietti, 2006; Daniele, 2001; Decker-Baumann, 1999; Huang, 2000; Okuno, 1999; Peterson, 2006; van Zaanen, 1994) . These trials are summarised in table 1.

The three

Bone marrow transplantation

The dose limiting factor in giving chemotherapy is bone marrow toxicity. The harvesting of a patient's bone marrow, storing it while chemotherapy is administered and then re-infusing the marrow after the chemotherapy allows higher doses of chemotherapy to be given (autologous transplantation) as the bone marrow is spared from the effects of the chemotherapy. Using a donor's marrow (allogeneic transplantation) has the added advantage that the transplanted cells attack malignant cells (graft versus leukaemia effect) but this can also be detrimental if the graft attacks normal tissues (graft versus host disease). Bone marrow transplantation results in prolonged hospitalisation, infections and mucositis, to a greater extent than traditional chemotherapy regimens.

A detailed search for articles on glutamine and bone marrow transplantation was performed as part of a systematic review (submitted to *Bone Marrow Transplantation* for consideration of publication) a summary of which is detailed here.

Conclusions

Acknowledgements and conflict of interest

No conflicts of interest to declare.

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Figures and Tables

Table 1 – Summary of randomised controlled trials of the administration of glutamine to patients receiving chemo- and/or radio-therapy.

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200 **Table 1**

Trial	Glutamine	Disease	Chemotherapy	Outcomes
Anderson 1998	Oral	Soft tissue tumours	Various	Mucositis
Cerchietta 2006	Intravenous	Head/Neck	Chemoradiotherapy	Mucositis and infections
Danielle 2001	Oral	Bowel	5-FU	Mucositis
Decker-Bauman 1999	Intravenous	Bowel	5-FU	Mucositis
Huang 2000	Oral	Head/Neck	Radiotherapy	Mucositis
Jebb 1994	Oral	Bowel	5-FU	Mucositis
Onkuno 1999	Oral	Bowel	5-FU	Mucositis
Peterson 2006	Oral	Breast	Anthracyclines	Mucositis
van Zaanen 1994	Intravenous	Haematological	Various	Infections and Toxicities

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