



# Case Study: The nutritional management of a patient with acute myeloid leukaemia

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## Introduction

Acute promyelocytic leukaemia (APL) is a subtype of acute myeloid leukaemia (AML), categorised as AML subtype M3, and is characterised by translocation of the genes between the long (q) legs of chromosomes 15 and 17 [described as  $t(15;17)(q24;q21)$ ]. There are two different classification systems for AML, namely the World Health Organization (WHO) and the French-American-British (FAB) classifications. The FAB classification divides AML into eight subtypes based on morphology and the cytochemical staining of blasts.<sup>1</sup> The WHO classification is more complicated, since it requires evaluation of the blast cells by molecular analysis and flow cytometry.<sup>1</sup> Classification of the different types of AML is valuable to doctors when deciding on which chemotherapy regimen to use after remission has been achieved since each type may react differently to treatment owing to its different genetic make-up.<sup>2</sup> APL usually has a good prognosis.<sup>3,4</sup>

The aetiology of AML M3 or APL includes a genetic predisposition to instability in the genes located on the long legs of chromosomes 15 and 17.<sup>3</sup> The genes translocate due to DNA breakage, most likely caused by exposure to X-rays, smoking and chemicals, e.g. benzene and aromatic organic solvents.<sup>5</sup> Obese persons and children with Down's syndrome have an increased risk of developing leukaemia.<sup>5,6</sup>

The first symptoms of AML are very vague and generalised. These include fatigue, malaise, irritability, fever, pallor, weight loss, shortness of breath, loss of appetite, anaemia, easy bruising, petechiae, purpura, haemorrhage, palpitations, bone and joint pain, frequent infections, epistaxis, headaches, and nausea and vomiting, as well as mouth ulcers.<sup>5,7</sup>

Leukaemia is diagnosed via a bone marrow biopsy which is then sent for genetic testing (karyotyping) and viewing under a light microscope. The blood tests commonly show an elevated white blood cell count and reduced platelet count (leukopaenia). Elevated levels of lymphocytes (CD13, CD33 and CD117) are demonstrated using flow cytometry.<sup>3</sup>

The main goal of nutritional management in leukaemia patients is to maintain lean body mass and protein stores, and to support the immune system, which enables the patient to cope better with treatment and ensures the best outcome possible for the patient.<sup>7</sup>

## Case study

The patient, a 26-year old unmarried man, was admitted to Port Elizabeth Provincial Hospital, Port Elizabeth, on 29 April 2013 via transfer from the Nelson Mandela Academic Hospital with an unconfirmed diagnosis of APL, i.e. AML subtype M3.

## Medical history

The patient did not have any children and was a non-smoker, with a history of alcohol abuse (he had stopped drinking four years earlier). Two of his siblings could be tested in the event that a stem cell transplant was indicated, since they shared the same two parents as the patient. The patient had been unwell since March 2013 with fatigue, epistaxis and weight loss (~ 10% over the past six months). He also had a history of previous pulmonary tuberculosis six years prior, for which he had completed six months of treatment. The patient did not present with night sweats, but complained of loss of appetite, loss of weight and bleeding gums.

He had a subacute abdomen with abdominal pain and chronic diarrhoea, with no abdominal distension, but with suspicion of abdominal perforation, necessitating the initiation of total parenteral nutrition (TPN). An abdominal exploration revealed two perforations in the caecum secondary to ulceration and *Candida albicans* overgrowth. The terminal ileum was resected and a hemicolectomy with anastomoses was performed, necessitating continuation of the TPN postoperatively. The patient started passing stools on day 4 post surgery (day 9 post admission).

## Nutritional assessment

The usual markers were considered during nutritional assessment, i.e. anthropometry, biochemistry, clinical signs, diet history and medication.



**Table 1 a:** The patient's biochemistry and chemotherapy history for the first three weeks of treatment post admission (days 1-13)

Biochemical markers	Days Normal range	Baseline (day 0)	1	2	3	4	5	6	7	8	9	10	11	13
			TPN ATRA**	D		D	L							
Sodium	136-145 mmol/l	140		145	131	146	141	139	146	143	141	141	144	146
Potassium	3.5-5.1 mmol/l	3.8	3.9	3.4	5.9	3.5	3.5	3.4	3.8	3.9	3.9	2.4	2.5	2.6
Chloride	98-107 mmol/l	102		102	97	107	105	107	108	108	105	104	102	99
Urea	2.1-7.1 mmol/l	2.4		3.4	4.4	5.9	6.1	5.9	4.4	6.0	6.1	3.7	5.1	7.3
Creatinine	64-104 umol/l	39		34	56	38	26	15	30	25	29	31	34	38
Conjugated bilirubin	0-3 umol/l	1				3					4		3	
Total bilirubin	5-21 umol/l	10				9	16				9		10	9
Total protein	60-78 g/l	58				46	40				42		51	65
Albumin	35-52 g/l	18	17			14	19	16	12		13		16	28
ALP	40-120 U/l	125				150	119				147	211	212	361
GGT	0-60 U/l	86				62	54				96		71	212
ALT	5-40 U/l	34				10	26				13		31	14
AST	5-40 U/l	55				13	71				17		23	14
LDH	266-500 U/l													624
Corrected Ca	2.15-2.55 mmol/l	2.46	2.44	2.34	2.00	2.50	2.40	2.47	2.30		2.66			2.44
Magnesium	0.63-1.05 mmol/l	0.61	0.62	0.83	0.78		0.61	0.78	1.04		0.89			0.69
Phosphate	0.78-1.42 mmol/l	0.87	1.24	1.18	1.76	0.97	1.13	0.95	0.62		0.97			0.37
CRP	0-5 mg/l	37	104	207		121	135	134	185	123	76	100	196	301

ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, ATRA: all-trans retinoic acid, Ca: calcium, CRP: C-reactive protein, D: daunorubicin,

GGT: gamma-glutamyl transferase, L: laparotomy, LDH: lactate dehydrogenase, TPN: total parenteral nutrition

\* Total parenteral nutrition extends across days 1-13

\*\* All-trans retinoic acid extends across days 1-23

### Anthropometry

The patient weighed 35 kg on admission with a body mass index (BMI) of 13.4 kg/m<sup>2</sup>. The reported usual body weight for the patient was ~ 50 kg (BMI of 19.5 kg/m<sup>2</sup>).

### Biochemistry

On admission, the patient presented with a classic APL picture of elevated white cell counts and a reduced counts of red blood cells and platelets. He presented with an international normalised ratio (INR) of 14, and had thrombi in his right ileac vein.

The patient showed elevated CD13, CD33 and CD45 white blood cell counts, suggestive of APL. On stained slides, Auer rods were seen in some cells, i.e. another indication of APL. Fluorescent in situ hybridisation, a genetic test commonly referred to as FISH, confirmed the diagnosis as APL, due to the genetic translocation seen between the 15<sup>th</sup> and 17<sup>th</sup> chromosome, i.e. *t(15;17)(q24;q21)*.

As indicated in Table 1 a and b, the patient presented with refeeding syndrome (hypokalaemia and hypomagnesaemia) after the initiation of TPN. Thereafter, he presented with hyperkalaemia and hyperphosphatemia, possibly due to oversupplementation of intravenous potassium phosphate, indicating the need for electrolyte-free TPN. His potassium did normalise for a few days, but thereafter he consistently presented with hypokalaemia, even with daily intravenous (IV) supplementation with potassium chloride.

The patient's magnesium levels remained within an acceptable

range due to magnesium sulphate supplementation IV, since the TPN did not contain magnesium. His liver enzymes started to rise by day 13 of TPN, but he had started to pass stools and it was decided to gradually introduce nasogastric tube (NGT) feeding and wean him off TPN.

### Clinical signs

The patient presented with a right iliac deep vein thrombosis and a *Serratia* urinary tract infection. He also had bilateral pleural effusions. He was dehydrated and complained of backache and fatigue. Clubbing was not present. He had bleeding gums, secondary to a low platelet count and elevated INR, but no gingival hyperplasia, a distinguishing factor from acute lymphoblastic leukaemia. He also presented with anorexia and history of weight loss. The doctor classified him as "severely wasted". His bone marrow biopsy site on his right hip was septic with a *Serratia* infection, and he had bleeding around the anus.

After surgery, the patient developed abdominal fluid collection, wound dehiscence and neutropaenic sepsis with concomitant infections of vancomycin-resistant enterococci and *Klebsiella pneumoniae*. He was confined to an isolation room for the remainder of his stay. Reverse barrier nursing measures were put in place.

### Diet history

The patient was initially kept *nil per os* for the first two weeks because of a small bowel perforation and the resulting surgery. TPN



**Table 1 b:** The patient's biochemistry and chemotherapy history for the first three weeks of treatment post admission (days 14-23)

Biochemical markers	Days	Baseline (day 0)	14	15	16	17	18	19	21	22	23
	Normal range										
Sodium	136-145 mmol/l	140	151	149	150	149	143	147	147	145	150
Potassium	3.5-5.1 mmol/l	3.8	2.4	2.4	2.6	2.5	5.7	2.5	3.0	2.6	2.7
Chloride	98-107 mmol/l	102	109	110	113	113	109	107	113	111	114
Urea	2.1-7.1 mmol/l	2.4	16.8	7.2	7.2	6.5	3.7	5.6	5.9	6.6	6.8
Creatinine	64-104 umol/l	39	69	39	37	42	24	50	51	57	66
Conjugated bilirubin	0-3 umol/l	1		6	6		1		12	14	
Total bilirubin	5-21 umol/l	10		13	10		28	21	20	21	
Total protein	60-78 g/l	58		48	47		60	62	56	56	
Albumin	35-52 g/l	18	23	15	14		15	27	15	22	
ALP	40-120 U/l	125	358	305	252		424	352	281	293	
GGT	0-60 U/l	86	281	196	135		203	157	123	112	
ALT	5-40 U/l	34	12	10	9		10	12	7	9	
AST	5-40 U/l	55	12	11	8		53	17	10	11	
LDH	266-500 U/l										
Corrected Ca	2.15-2.55 mmol/l	2.46	2.25	2.16	2.28	2.40		2.25	2.36	2.17	2.12
Magnesium	0.63-1.05 mmol/l	0.61	1.12	0.71	0.74	0.90		0.90	0.77	0.79	0.78
Phosphate	0.78-1.42 mmol/l	0.87	0.57	1.54	1.51	1.50		1.00	0.86	1.01	1.07
CRP	0-5 mg/l	37	199	198	233	210	229	213	166	173.9	166

ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, ATRA: all-trans retinoic acid, Ca: calcium, CRP: C-reactive protein, D: daunorubicin, GGT: gamma-glutamyl transferase, L: laparotomy, LDH: lactate dehydrogenase, TPN: total parenteral nutrition

was indicated and initiated in consultation with the doctor. Only the first TPN bag contained electrolytes.

The patient was gradually weaned off TPN two weeks after admission while NGT feeds were introduced. He eventually progressed to a soft neutropaenic ward diet with oral supplementary sip feeds.

**Chemotherapy regimens**

The translocated gene in APL normally codes for the retinoic acid receptor  $\alpha$ . Treatment with all-trans retinoic acid (ATRA) induces differentiation in the majority of a patient's cells, which leads to a cure.<sup>2,8</sup>

The first goal in treating AML with chemotherapy is to achieve complete remission by reducing the number of leukemic cells to an undetectable level, i.e. < 5% blasts on bone marrow biopsy. There are three stages of chemotherapy, namely induction (one six-week cycle), consolidation (three cycles) and maintenance (two years). The average AML patient receives induction chemotherapy called 3+7, which consists of a cytosine arabinoside antimetabolite, e.g. etoposide or cytarabine; and an anthracycline, e.g. daunorubicin, idarubicin or doxorubicin.<sup>9</sup> The cytosine arabinoside antimetabolite is given for seven days and the anthracycline for three days, thus the name, 3+7. A patient with APL also receives an anthracycline, in addition to ATRA, for six weeks. APL is very sensitive to anthracycline. Excellent results have been obtained with this protocol.<sup>9</sup> The complete remission rate for APL is roughly 95% after induction.<sup>10</sup> It is important to note that all patients in remission will relapse if they default on their consolidation or maintenance chemotherapy regimens.

The post-remission or consolidation goal is to eliminate any residual undetectable disease and to achieve a cure. There are three cycles of consolidation chemotherapy. The first cycle thereof takes place at the same time as the induction. Two more consolidation chemotherapy cycles follow thereafter. The types of consolidation chemotherapy regimens differ between APL and other AML subtypes, and are also dependent on other factors, e.g. the patient's risk (high versus standard) and stock levels in the public sector. The patient's first cycle in the haematology unit consisted of adriamycin 25 mg/m<sup>2</sup> per day for four days. The second cycle was mitoxantrone 10 mg/m<sup>2</sup> per day for five days, and the third cycle consisted of adriamycin 60 mg/m<sup>2</sup> for one day.

If a patient is still in remission after completing the consolidation cycles, he or she receives two years of maintenance chemotherapy with methotrexate and 6-mercaptopurine.<sup>9,10</sup> Relapsed APL patients receive arsenic trioxide instead.<sup>4</sup> A prophylactic dose of 50 mg cytarabine, 15 mg methotrexate and 30 mg hydrocortisone is recommended via intrathecal administration in high-risk patients.<sup>11</sup>

If APL is suspected in a patient, it is recommended that ATRA should be started as soon as possible while waiting for diagnosis confirmation<sup>9</sup> since it rapidly ameliorates the coagulopathy typically seen in APL.<sup>4,9</sup> Because ATRA is so successful in inducing molecular remission, stem cell transplantation is not usually necessary in APL patients.<sup>4,10</sup>

The patient was placed on the modified *Programa para el Tratamiento de Hemopatías Malignas* (PEMETHA) chemotherapy induction protocol, one of the regimens for the treatment of APL, consisting



of an anthracycline, e.g. idarubicin, daunorubicin or doxorubicin, and ATRA (12 mg/m<sup>2</sup> daunorubicin IV bolus on days 2, 4, 6 and 8; and 45 mg/m<sup>2</sup> ATRA daily in two divided oral doses, starting on day 1).<sup>11</sup> The patient's dose was calculated according to his body surface area. The daunorubicin was stopped on day 5 post admission owing to surgery for the perforated caecum. Daunorubicin infusion was not reinitiated post surgery, but the patient continued on the ATRA daily doses until he finished the six-week cycle.

**Other medication**

The patient was on antiemetic medication to relieve the nausea and vomiting induced by chemotherapy. He also had diarrhoea (> 3 loose stools per day) due to antibiotics and IV magnesium

sulphate administration, and this was managed with paracetamol codeine phosphate, a side effect of which is constipation [500 mg paracetamol and 20 mg codeine phosphate (two tablets) taken six hourly, as needed].

**Nutritional requirements and care plan**

Setting nutrition-related goals in consultation with the patient empowered and enabled him to play an active role in his treatment and recovery.<sup>7</sup>

Many patients have nutritional deficiencies even before their diagnosis and subsequent treatment. The risk of malnutrition is compounded further when treatment is initiated. A micronutrient deficiency is possible in most cancer patients who consume < 60% of their daily energy requirements for > 10 days. Vomiting and diarrhoea further contribute to the loss of micronutrients. Adequate nutrition intervention and care can be beneficial to a patient's condition and disease progression.<sup>12</sup>

The patient's requirements were calculated according to the guidelines set out in Table II. The detailed nutrition care plan is set out in Tables III and IV a and b. Requirements were calculated on his actual body weight of 35 kg, which amounted to an energy range of 1 050-1 225 kcal total energy (30-35 kcal/kg) and 52.5-70.0 g protein (1.5-2.0 g/kg) which converted to 8.4-11.2 g nitrogen (N<sub>2</sub>) (~ 210-280 kcal), with a non-protein energy (NPE) to N<sub>2</sub> ratio of 75:1 to 100:1 (840-1 120 kcal: 8.4-11.2 g N<sub>2</sub>). Fluid requirements were estimated at between 1 050ml (1 ml/kcal or 30ml/kg) and 1 400 ml (40 ml/kg).

The patient was initially kept *nil per os* for two weeks because of a small bowel perforation and the resulting surgery. TPN was indicated and initiated on admission in consultation with the doctor. He was also at risk of developing refeeding syndrome. Therefore, TPN was initiated at 20 kcal/kg for the first 24 hours, as recommended by Webster-Gandy et al,<sup>14</sup> i.e. 700 kcal of total energy and 7 g N<sub>2</sub>.

Refeeding syndrome occurs from the introduction of carbohydrates into the gastrointestinal tract, which then stimulates insulin secretion.<sup>15</sup> Insulin then stimulates the sodium-potassium ATPase pump. This pump requires magnesium as a co-factor.<sup>15</sup> The pump drives potassium into the cells and sodium moves out. Insulin

**Table II:** Guidelines when assessing the nutritional needs of an adult cancer patient<sup>13</sup>

Nutritional needs estimation	Clinical situation
<b>Energy needs</b>	
25-30 kcal/kg	Maintenance
30-35 kcal/kg*	Malnourished and/or high-stress treatment, such as a bone marrow transplant*
35-45 kcal/kg	Severely depleted or hypermetabolic
<b>Protein needs</b>	
0.8-1.0 g/kg	Recommended dietary allowance for adults
1.0-1.5 g/kg	Most patients with cancer (adjust for visceral protein status and albumin levels)
1.5 g/kg	Bone marrow transplant recipients
1.5-2.0 g/kg*	Severely depleted patients with cancer*
<b>Fluid needs (choose from one of two of the following methods)</b>	
RDA or calorie based	1 ml/kcal
Age-based*	< 55 years of age = 30-40 ml/kg*
	55-65 years of age = 30 ml/kg
	> 65 years of age = 25 ml/kg

RDA: recommended dietary allowance  
\* Guidelines indicated were used in the case study patient

**Table III:** A history of total parenteral nutrition administration as per the calculated requirements (1 050 - 1 125 total kcal, 840-1 120 kcal non-protein energy and 8.4-11.2 g nitrogen)

Weight used = 35 kg	Day 1	TPN	Day 2	TPN	Day 4	TPN	Day 10	TPN
Energy (kcal/kg)	20	32 ml/hour	25	40 ml/hour	30	48 ml/hour	35	56 ml/hour
Total energy (kcal)	700	777	875	980	1 050	1 176	1 225	1 371
NPE (kcal)	640	640	800	800	960	960	1 120	1 120
N <sub>2</sub> (g)	6.4	4	8	8.2	9.6	9.8	11.2	11.4
Total protein (g)	40	25	50	51.25	60	61.25	70	71.25
Protein (g/kg)	1.14	0.71	1.43	1.46	1.71	1.75	2	2.0
Total glutamine (g) (0.35 g/kg IV)	12.25	3.6		7.3		8.8		10.2
Total fluid (ml) (30 ml/kg)	1 050	768		960		~ 1 150		1 345

IV: intravenous, N<sub>2</sub>: nitrogen, NPE: non-protein energy, TPN: total parenteral nutrition



**Table IV a:** A history of dietary progression from total parenteral nutrition to nasogastric tube feeds (days 13-15)

Nutritional requirements		Day 13			Day 14			Day 15
		TPN wean	NGT* feeds	Total	TPN wean	NGT feeds	Total	Full NGT feeds*
Administration rate	ml/hour	42	21	63	21	42	63	63
Total energy (kcal)	1 225	1 035	500	1 535	517.5	1 000	1 517.5	1 500
(35 kcal/kg)								
NPE (kcal)	1 120	845	487.2	1 332.2	422.5	974.4	1 396.9	1 461.6
N <sub>2</sub> (g)	11.2	8.6	3.2	11.8	4.3	6.4	10.7	9.6
Total protein (g)	70	53.75	20	73.75	26.875	40	66.875	60
Protein (g/kg)	2			2.12			1.9	
Fluid (ml) (30 ml/kg)	1050	~ 1 000	~ 500	~ 1 500	~500	~1 000	~1500	~1 500

N<sub>2</sub>: nitrogen, NGT: nasogastric tube, NPE: non-protein energy, TPN: total parenteral nutrition  
\* semi-elemental

**Table IV b:** A history of dietary progression from total parenteral nutrition to nasogastric tube feeds, and later, oral feeds (days 16-22)

Nutritional requirements NGT feeds*		Day 16			Day 18			Day 20			Day 22		
		NGT feeds*	Oral food	Total	NGT feeds*	Oral food	Total	NGT feeds**	Oral food	Total	Oral sip feeds	Oral food	Total
Administration rate	ml/hour	42			42			21					
Total energy (kcal)	1 225	1 000	900	1 900	1 000	900	1 900	500	1 350	1 850	800	900	1 700
(35 kcal/kg)													
NPE (kcal)	1 120	975.68	877.6	1 853.28	975.68	877.6	1 853.28	487.84	1 316.4	1 804.24	774.4	877.6	1 652
N <sub>2</sub> (g)	11.2	6.08	5.6	11.68	6.08	5.6	11.68	3.04	8.4	11.44	6.4	5.6	12
Total protein (g)	70	38	35	73	38	35	73	19	52.5	71.5	40	35	75
Protein g/kg	2			2.1			2.1			2.0			2.1
Fluid (ml) (30ml/kg)	1050	~ 1 000			~ 1 000			~ 500					

N<sub>2</sub>: nitrogen, NGT: nasogastric tube, NPE: non-protein energy, TPN: total parenteral nutrition  
\* standard  
\*\* standard with fibre

also stimulates phosphate shifts into the cell.<sup>15</sup> Therefore, this mechanism leads to low extracellular phosphate, magnesium and potassium. Thiamine is an essential co-enzyme for carbohydrate metabolism. Thiamine deficiency can develop in a depleted patient with refeeding syndrome.<sup>15</sup> Therefore, the administration of 250 mg of thiamine intravenously was suggested to the doctor according to the refeeding guidelines, and 100 mg thiamine weekly thereafter.<sup>15</sup> On Day 1, we could not use the most suitable all-in-one TPN bag which would have provided ~ 640 kcal NPE, 6.5 g N<sub>2</sub> and 5.8 g glutamine owing to stock challenges, but instead used a bag containing 640 kcal NPE, 4 g N<sub>2</sub> and 3.6 g glutamine. A bag with glutamine was chosen because of the patient's risk of chemotherapy-induced mucositis.<sup>12</sup> IV rehydration was also suggested to ensure that the fluid requirements were met; also necessary for medication administration. As a result of multiple electrolyte imbalances, including hyperkalaemia and hyperphosphataemia (Table I a), the TPN was changed to an electrolyte-free bag. The administration rate was increased to 25 kcal/kg per day on day 2, and 30 kcal/kg on day 4. The patient achieved the full rate of 35 kcal/kg by day 10.

He started passing stools on day 9 and was cautiously monitored for a few days. He was weaned off TPN on day 13, while a semi-elemental NGT feed containing 1 000 kcal and 40 g protein per litre (Table IV a) was concurrently introduced. He was off TPN on day 15

and on full NGT feeds. He started eating orally on day 16, and was completely weaned off NGT feeds by day 22 (Table IV b). He was then supplemented orally with high-energy, high-protein sip feeds to amend his oral intake of the full neutropaenic ward diet. Two sip feeds per day provided 800 kcal and 40 g protein.

A 1 mg vitamin B<sub>12</sub> injection was recommended at every follow-up via the outpatient clinic because of the patient's terminal ileum resection. The recommended maintenance dosage was 1 mg intramuscularly every month, but 6-8 injections a year would suffice.<sup>5</sup>

The patient was discharged after six weeks of induction and consolidation chemotherapy, and was provided with 24 x high-protein, high-energy sip feeds, providing 400 kcal and 20 g protein each; as well as 30 sachets of enriched peanut butter, providing 500 kcal and 12.3 g protein per sachet. The patient returned in two weeks for his second cycle of consolidation chemotherapy, and was in morphological remission on day 58. The complete history of outpatient supplementation and weight gain is set out in Table V.

#### Micronutrients

The mechanism of chemotherapy partly depends on the effect of reactive oxygen species. The supplementation of antioxidant micronutrients may influence this, possibly worsening the patient's



Table V: Weight history of the patient during the first 18 months of treatment

Day	Date	Weight	BMI (kg/m <sup>2</sup> )	Notes
-	26 April 2013	34.6 kg	13.4	Height of 160.7 cm
1	30 April 2013	35.0 kg	13.4	Started on induction chemotherapy for six weeks
42	10 June 2013	35.0 kg		Tolerating a full neutropaenic diet. Six weeks of chemotherapy completed. Discharged on INP of 24 x high-protein, high-energy sip feeds and 30 x enriched peanut butter sachets
58	26 June 2013	37.9 kg		Three quarters of the induction completed. Eating well. No diarrhoea. Morphological remission
	26 August 2013	45.2 kg		INP: 30 x enriched peanut butter sachets, and 30 x high-energy powder sachets (580 kcal, 12g protein). Underwent molecular remission
	9 September 2013	46.2 kg		Consolidation #3 INP of 42 x high-energy powder sachets. Doctor's notes report "eating well"
	9 October 2013	46.3 kg		Consolidation completed. Started two years of maintenance chemotherapy. Doctor's notes report "slowly gaining weight"
	3 December 2013	49.0 kg	18.6	Height of 162.5 cm (still in remission)
	7 January 2014 to 27 October 2014	49.5-50.6 kg		The patient's weight was maintained on supplements. He was handed over to Frere Hospital for further maintenance management on 27 October 2014

BMI: body mass index, INP: Integrated Nutrition Programme

prognosis.<sup>12</sup> The American Institute for Cancer Research evaluated available data on the effect of micronutrient supplementation on chemotherapy and radiotherapy. They concluded that taking dietary supplements during treatment is safe as long as the amount of micronutrients does not exceed the daily recommended dietary allowance.<sup>12</sup> The intake of antioxidants should not exceed the daily upper limits of safe intake, i.e. vitamin C ≤ 2 000 mg/day, vitamin E ≤ 250 mg alpha-tocopherol equivalent/day, selenium ≤ 400 µg/day. A daily intake of 500-2 000 mg vitamin C, 3 mg vitamin A, 10-15 mg vitamin B<sub>6</sub>, 0.4-1.0 mg folic acid, 4-10 mg zinc and 1-2 mg copper is recommended for wound healing post surgery. Tentative daily administration of 1.5-2.0 g long-chain omega-3 fatty acids is recommended for cancer cachexia and weight loss.<sup>12</sup> The patient received the following micronutrients daily: 5 mg folic acid, 50 mg zinc picolinate containing 9.5 mg elemental zinc, and a vitamin B complex twice daily (each tablet contained 5 mg vitamin B<sub>1</sub>, 2 mg vitamin B<sub>2</sub>, 20 mg vitamin B<sub>3</sub> and 2 mg vitamin B<sub>6</sub>.)

### Glutamine

Glutamine forms 25% of the free amino acid pool in the extracellular fluid and 60% in the skeletal muscle.<sup>16</sup> Skeletal muscle tissue is also the main site for L-glutamine synthesis and storage.<sup>17</sup> Glutamine is released with muscle protein metabolism during infection, inflammation or muscle trauma.<sup>17</sup> Approximately 30 g of lean tissue is broken down for each gram of nitrogen lost during stress, thereby releasing alanine and glutamine.<sup>18</sup> Glutamine is depleted during any damage to the enteric mucosa.<sup>19</sup> The pathogenesis of mucositis is complex. Both chemotherapy and radiotherapy damage the rapidly dividing normal cells, including the mucosal cells, which leads to the side-effects of mucositis and bone marrow suppression.<sup>20</sup>

Conflicting results have been reported in glutamine studies performed on oncology. Glutamine increased cell growth<sup>17,20</sup> in *in vitro* studies, but tumour growth was reduced in *in vivo* studies.<sup>17</sup> In one of these studies, glutamine caused tumour regression as a result of immune

clearance of the tumour because the glutamine was used as fuel by the natural killer cells.<sup>20,21</sup> Glutamine was also avidly consumed by the tumour cells, while natural killer cells' activity was depressed owing to a decrease in glutathione concentration.<sup>17</sup> Although glutamine could possibly "feed the tumour", it was suggested by Gaurav et al<sup>17</sup> that "because glutamine consumption by tumours is almost absolutely dissipative", increased tumour growth rate should be unexpected. Studies show that tumour growth diminishes during oral glutamine supplementation by restoring the function of the natural killer cells and improving protein metabolism.<sup>17</sup> It is also possible that oral glutamine supplementation may increase the selectivity of anti-tumour drugs owing to increased glutathione synthesis, thereby protecting the patient from oxidative stress.<sup>17</sup> Glutamine was also shown to protect against radiotherapy-induced oxidative stress.<sup>17</sup> The parenteral supplementation of glutamine was favoured in many studies in order to bypass erratic bioavailability and variable compliance with oral administration, especially in patients with feeding difficulties.<sup>16</sup>

IV glutamine protects the liver cells from oxidative injury by increasing intracellular glutathione during chemotherapy. It is also been suggested that oral glutamine supplementation enhances anti-tumour drug selectivity, protects the normal tissue and possibly sensitises the tumour cells to injury both via radiotherapy and chemotherapy.<sup>17</sup> There is a possible trend in the objective reduction of mucositis in non-bone marrow transplant patients receiving chemotherapy and/or radiotherapy.<sup>20</sup> A lower incidence of complications relating to infection resulted in acute nonlymphocytic leukaemia patients receiving supplemental glutamine.<sup>18</sup>

Mucosal breakdown in the gastrointestinal tract can be prevented by enteral or parenteral glutamine administration.<sup>19</sup> There is some evidence that IV glutamine has trophic effects in the ileum and proximal and distal colon, which becomes important with potential mucosal atrophy during TPN.<sup>17</sup> Twenty-five per cent of the control group experienced diarrhoea for >10 days, while none of the patients



receiving glutamine experienced diarrhoea in a study conducted on AML patients.<sup>18</sup>

IV glutamine supplementation reduced mucositis in the majority of cancer patients receiving chemotherapy.<sup>18</sup> Although other modalities for mucositis prevention are available, e.g. cryotherapy, granulocyte colony-stimulating factor, laser and granulocyte-macrophage colony-stimulating factor, efficacy is not uniform.<sup>17</sup>

High-dose doxorubicin (an anthracycline) causes acute, and sometimes chronic, cardiac toxicity.<sup>17</sup> Oxidative damage caused by doxorubicin decreases glutathione, and depletes superoxide dismutase in the cardiac muscle.<sup>17</sup> Glutamine plays a protective role by upregulating glutathione and inducing heat shock protein, which protects the myocardium against hypoxic or ischaemic injury.<sup>17</sup> Glutamine supplementation also maintains cardiac glutathione levels during the administration of methotrexate and cyclophosphamide.<sup>17</sup>

Significantly faster neutrophil recovery was reported in acute leukaemia patients on high-dose cytarabine who also received 20 g IV glutamine as part of parenteral nutrition, possibly as a result of the stimulation of lymphocyte proliferation.<sup>17</sup> Patients on IV glutamine supplementation in both of the studies by Piccirillo et al<sup>16</sup> achieved a lymphocyte count > 500  $\mu$ g significantly faster ( $p$ -values < 0.001 and 0.009) than patients receiving a placebo.

A reduction in the duration of neutropenia in AML patients was also shown with TPN supplemented with glutamine.<sup>18</sup> Patients receiving glutamine on days 1-5 in a study conducted by Sornsuvit et al<sup>18</sup> on AML patients receiving chemotherapy lost significantly less weight, and had a shorter length of stay and less severe oral mucositis than the controls. Webster-Gandy et al<sup>14</sup> also support parenteral glutamine supplementation because of its association with a shorter hospital stay. It is cost-effective, because it maintains the nutritional status and enhances neutrophil phagocytosis, was provided in the study by Sornsuvit et al.<sup>18</sup>

There are no known drug interactions with glutamine.<sup>17</sup> However, glutamine is antagonised physiologically by lactulose during the treatment of high ammonia levels during liver failure. Glutamate, a by-product of the glutamine metabolism, may cause brain excitation in patients. The drug may be less effective in patients with seizures.<sup>17</sup> It is contraindicated in cases of renal and hepatic insufficiency and metabolic acidosis.

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO)<sup>22</sup> has set out evidence-based clinical practice guidelines for mucositis. The guidelines, published by the European Society for Medical Oncology and the USA National Comprehensive Cancer Network, are both adaptations of the MASCC/ISOO guidelines. The latest guidelines update, based on systematic reviews of evidence for various interventions, was published in May 2014.<sup>22</sup> However, owing to inadequate or conflicting evidence, a guideline was not possible in relation to glutamine for all cancers, except in haematopoietic stem cell transplantation, where the recommendation was against the IV use of glutamine for the prevention of mucositis, based on level II evidence.<sup>22</sup>

### A neutropaenic diet

Neutropaenia in chemotherapy patients is a major risk factor for infection.<sup>23</sup> The rationale behind a neutropaenic diet is that bacterial translocation can take place from the gut to other body sites causing infection through the ingestion of organisms, such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus* and *Klebsiella* spp.<sup>23</sup> These organisms have been isolated from food, e.g. fresh vegetables, fresh salad, raw eggs and cold meat, as well as water and ice.<sup>23</sup> Some studies have been conducted on the benefit of the neutropaenic diet, but the sample sizes were very small.<sup>23</sup> Even though the literature is inconclusive as to the necessity of a neutropaenic diet in neutropaenic patients, and because it was stated following a Cochrane Collaboration review that recommendations could not be given since no evidence of effect was found, it was decided to err on the side of caution in the haematology unit, and place all of the oncology patients on a neutropaenic diet. It is prescribed that patients follow a neutropaenic diet at home for another six months after discharge, as recommended by Webster-Gandy et al.<sup>14</sup> There are no official published neutropaenic diet guidelines, but basic food safety principles are prudent in neutropaenic patients, such as avoiding uncooked meat, seafood, eggs, unwashed fruit and vegetables,<sup>23</sup> as well as hand washing and practising personal hygiene.<sup>24</sup> The dietary restriction also encompasses yoghurt and amasi (sour milk) because of their probiotic content. There is a need for larger randomised studies to be conducted on the effectiveness of the neutropaenic diet.

It should be kept in mind that diet alone does not play a role in the management of neutropaenia. Antimicrobial prophylaxis, colony-stimulating factors, a protective environment (i.e. isolation), oral care, central venous catheter care, hand washing and personal hygiene are recommended for cancer patients on chemotherapy in evidence-based guidelines developed by the Centers for Disease Control and Prevention for the management of neutropaenia and the prevention of opportunistic infections.<sup>24</sup>

### Conclusion

The weight trend shows that the patient managed to maintain his weight at 35 kg after six weeks of treatment and nutritional support. He was placed on the Integrated Nutrition Program on discharge, and managed to gain weight following frequent follow-ups and continuous supplementation. The patient was in clinical remission (normal neutrophil and platelet counts and < 5% blasts in the bone marrow) two-and-a-half months after the initiation of treatment. He remained in remission two months later. He received the three consolidation chemotherapy cycles. Six months after induction, he had completed his consolidation chemotherapy, remained in remission, and was placed on two years of maintenance chemotherapy of methotrexate and 6-mercaptopurine. He completed his maintenance chemotherapy in October 2015 and was deemed cured.

It is important to take note that weight loss in obese patients is just as detrimental as weight loss in patients with normal weight since even a small amount of weight loss can mask a higher loss of skeletal muscle mass.<sup>25</sup>



A long-term multidisciplinary approach to the management of oncology patients is recommended. By encouraging the patient, and frequently assessing and promptly intervening where nutritional-related barriers are noticed, the multi-disciplinary team will facilitate the patient in reaching his defined nutritional-related goals.<sup>7</sup> Improved physical exercise in haematological cancer patients can increase the efficacy of protein intake through stimulating protein anabolism after intensive chemotherapy.<sup>26</sup> Deterioration in dietary intake, sometimes observed in first-stage induction chemotherapy, may be attenuated in later chemotherapy cycles or after remission. This approach is in line with the recommendation of Malihi et al<sup>26</sup> that the “assessment of patients in further cycles seems of utmost importance”, including dietary counselling and supplementation, even for outpatients.

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