

RACHAEL'S HAD "REMARKABLE" RESULTS FROM LENALIDOMIDE

After four months on lenalidomide (Revlimid®), Rachael Symington's blood counts began to improve and she felt well enough to take her surf ski out for a paddle.

"I had a ball, but afterwards I was exhausted and very bruised from getting on and off the ski, but it was a bit of fun," said Rachael, who had taken nothing stronger than a painkiller before starting treatment on lenalidomide for her MDS, in October last year.

"It was an amazing experience. I had multiple side-effects and it took four months for my body to adjust to the drug. That's when my white and red blood counts started creeping up. I was elated," said Rachael, 39, of Adelaide.

During the two years before being diagnosed with MDS in October 2008 at the age of 36, Rachael had experienced intermittent health problems that began when she discovered a lump on her neck. The lump was removed along with her right thyroid in late-2006, and it was noted then that she was slightly anaemic.

Prescribed B12 injections every three months, she got on with life until a boating accident at the end of 2007. She didn't recover well and tests showed some of her blood counts were low.

Rachael's doctor decided to have her blood checked regularly and she continued to lead an active lifestyle, helping raise her son, Jaime, who is now 11, working as a quality and safety manager for an aged care organisation, swimming and being a volunteer lifeguard for her local Surf Life Saving club.

After having her appendix removed in 2008, the specialist commented about her abnormal blood results during recovery, and that's when Rachael was referred to a haematologist. A bone marrow biopsy showed she had MDS.

"I hadn't even heard of MDS, and it was during my second appointment that I was informed that this diagnosis had a possible poor prognosis.



Rachael Symington with her husband, David, and (below) out for a paddle

"My husband and I went straight to the Internet to find more information. In hindsight, this was a big mistake because there are so many types of MDS. The information on the Internet was misleading and I thought, after researching various sites, that I might only have three years to live," explained Rachael.

After a 90-minute consultation with a second haematologist, Rachael knew all about MDS and the treatment she could expect over the next 10 years. Further tests unequivocally showed she had Del (5q) MDS.

Rachael kept working, but in September 2009 she started feeling unwell, fatigued when exercising, and couldn't concentrate at work.

"I thought it was time to take a small break from work and my specialist wanted me to rest up. It wasn't an easy decision because I love my job," said Rachael, who still hadn't received any treatment at that stage.

Rachael needed to put her MDS "on the back burner" when her brother was diagnosed with bowel cancer. Sadly, he died in April last year, aged 50.

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NEW DRUGS COULD HALT EARLY MDS

Australian haematology registrar, Dr Andrew Guirguis, is investigating a new class of anti-cancer drugs to treat early-stage myelodysplasia.

Based at the Alfred Hospital / Monash University in Melbourne, Dr Guirguis was awarded a three-year Leukaemia Foundation clinical PhD scholarship [2011] to study myelodysplasia, apoptosis, and the potential role of BH3 mimetics.

The cells in our bodies have a limited lifespan. When they become old or damaged, they die. The process of cell death is known as apoptosis.

Cancer cells are characterised by their ability to avoid death. The rogue cells thrive because the apoptotic response has been shutdown. However, a new class of anti-cancer drugs called BH3 mimetics re-activate the apoptotic response, leaving cancer cells vulnerable to chemotherapy treatment. BH3 mimetics are man-made compounds that mimic the action of BH3 proteins – essential initiators of programmed cell death.

In contrast to other cancers, early-stage MDS is characterised by excessive apoptosis of the malignant stem cells. According to Dr Guirguis, using BH3 mimetics in this setting may be a new approach in cancer therapy.

“MDS patients become anaemic and require regular blood transfusions to overcome the decimation of their red blood cells,” he said.

“However, based on data in human MDS, we believe that the malignant MDS cells in the early phase of the disease may be susceptible to BH3 mimetics. With the drugs clearing malignant MDS stem cells more rapidly from the bone marrow.

“I’m hoping to demonstrate that these drugs do in fact increase the death of the progenitor MDS cells, and that this in turn enables healthy blood stem cells to repopulate the bone marrow. This would reduce the number of transfusions required by patients and potentially slow down the disease’s progression.”

RACHAEL’S HAD “REMARKABLE” RESULTS

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When Rachael’s blood counts dropped and her condition advanced “quite quickly” in February 2010, she considered her treatment options and was lucky to be able to access lenalidomide, as it wasn’t PBS-listed for MDS.

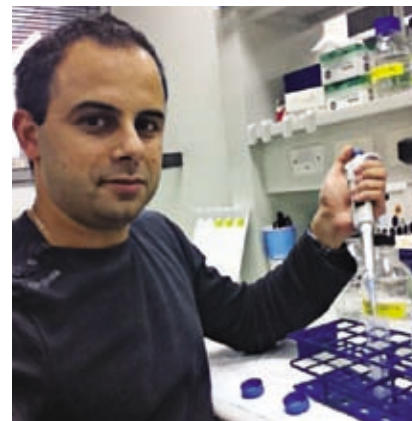
Rachael was also lucky that Medibank Private, which had a special fund, met the initial cost of the drug, and then the manufacturer, Celgene, has continued to provide the treatment on compassionate grounds. Each tablet costs \$300 for 10mg which Rachael takes for 21 days in a row followed by seven days off.

After six months on lenalidomide, Rachael described her results as “quite remarkable”. Her red cell, white cell and neutrophil counts were all up and the blast cells in her bone marrow had dropped from 6% to 1%.

After returning to work part-time in January this year, she started a second six-month treatment regimen in March.

Rachael hopes that after completing the next few months of treatment, she’ll be able to have a break from the drug. She explained that a bone marrow transplant is the only cure, but she hopes to avoid the need for one, as current advances in medicine give her real hope for the future.

Dr Guirguis is looking at the effect of BH3 mimetics using both a laboratory MDS model and human MDS cells. He is also looking at other cellular functions and different mechanisms to better understand the increased cell death of the malignant clone (or stem cells) in early-stage MDS.



Dr Andrew Guirguis

If successful, his work could lead to Phase I clinical trials of BH3 mimetics, either in isolation or in combination with other therapies, to treat transfusion-dependent MDS patients.

“I’ve been treating MDS patients since 2008, and I wanted to do something to slow down this disease and try and stop it progressing to leukaemia,” he said.

“My patients don’t have a good quality of life due to the number of blood transfusions they require. I’m very motivated to help them. BH3 mimetics could prove to be one possible major advancement for managing patients with low risk MDS.”

Dr Guirguis has largely focused on his PhD but continues to see patients once a week at the Alfred Hospital.

He thanked the Leukaemia Foundation for supporting his research.

“I like the balance of working in research as well as seeing patients. I get to take what I do at the bench into real life, which is very rewarding. However research funding is very difficult to obtain, and in reality it would have been difficult to go ahead with this project without the scholarship I received from the Leukaemia Foundation. I’m very grateful.”

Four out of her five siblings have been tested and her youngest brother and sister are both perfect matches as donors for a future bone marrow transplant.

Rachael says the Leukaemia Foundation’s *Talk Blood Cancer* website is “excellent”. Through it, she has linked up with three people, one of whom she communicates with regularly. She also finds the Foundation’s Telephone Forums very helpful and supportive by “hearing from others, making friends, sharing information and guest specialists come in and have a chat”.

Rachael has also taken part in the Foundation’s *Light the Night* events. “It’s really good to see the amount of support that’s out there and it makes you feel less alone,” she says.

In July 2011, the use of lenalidomide in the treatment of people with Del (5q) MDS will be considered for funding through the PBS system. The Leukaemia Foundation has provided a submission to the PBS to support this proposal and we will advise you of the outcome.

THE PROBLEM WITH IRON IN MDS

by Dr Anthony Mills, Clinical Haematologist, Princess Alexandra Hospital

Although iron is needed to make blood, you can get too much of a good thing.

The problem in MDS is one of disordered blood production. Extra iron won't improve the production of blood, as it is no use shovelling parts (iron) into the factory (the bone marrow) if the machinery is broken.

In fact, patients with MDS accumulate iron because the disordered blood production sends signals to the gut to absorb more iron.

Blood transfusions also cause iron-loading as each unit of blood contains 200-250mg of iron and the body has no mechanism for getting rid of this on its own.

Iron needs to be bound to special proteins in the body, as free iron can react with oxygen and produce potentially harmful free radicals. Excessive iron can overload the binding proteins and other storage mechanisms, leaving free, unbound iron in the body. The unbound iron is taken up by the cells, where free radicals attack the components of the cells and may lead to organ dysfunction.

The main organs that are susceptible to iron-induced damage are the liver, pancreas and the heart.

Liver iron is often markedly increased in MDS but cirrhosis (liver failure) is rare. Heart failure is more common in transfused MDS patients than the rest of the population, and diabetes from damage to the insulin-secreting cells in the pancreas is also more common.

Added problems of iron overload include increased susceptibility to infection and poorer outcomes from allogeneic stem cell transplants (transplants using stem cells from others). MDS patients with iron overload appear to have decreased likelihood of survival.

Iron chelation therapy entails taking medication which binds excess iron and helps the body excrete it in the urine or faeces.

Preliminary studies in patients with MDS appear to show an improved outcome in patients on such treatment¹⁻³ though definitive randomised trials are needed and are underway.

The most frequent iron-chelating agent used in MDS in Australia is deferasirox (Exjade®). These are dispersible tablets, usually taken once daily, and while they are usually well tolerated, the most common side-effect is diarrhoea.

MANAGING IRON OVERLOAD

What is the optimal management of iron overload in patients with MDS?

There is increasing evidence that excess iron is detrimental in patients with MDS, particularly in the lower risk group where iron overload can be seen over time. The National Comprehensive Cancer Network* guidelines recommend considering iron chelation therapy for lower risk patients with a serum ferritin level higher than of 2500 ng/mL^[1] and a cutoff of 1000 ng/mL is often used.

Iron chelation therapy can be administered by injection just under the skin using deferoxamine (Desferal®), or orally using deferasirox (Exjade®), which has been shown to be effective for MDS patients with iron overload^[2,3] as it is more convenient and results in greater compliance.

Several groups⁴⁻⁵ have produced recommendations for the use of iron chelation therapy, using the best of the early evidence that is available. Generally, they favour starting treatment if more than 20 blood transfusions have been given and serum ferritin (the protein that binds and stores iron) levels exceed 1000–2000 mcg/l.

There is also general agreement that the MDS patients most likely to benefit from chelation therapy are those who have a good survival expectancy, according to the International Prognostic Scoring System (IPSS), although patients considered for an allogeneic stem cell transplant may also benefit.

This is an active area of research and many new techniques for monitoring iron overload are being trialled, which will undoubtedly help to guide our choice for chelation therapy in the future.



Dr Anthony Mills

1. Leitch HA, Leger CS, Goodman TA, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. *Clinical Leukemia*. 2008;2:205-211.
2. Rose C, Brechignac S, Vassilief D, et al. Does iron chelation therapy improve survival in regularly transfused lower risk MDs patients? A multicenter study by the GFM. *Leukemia Research*. 2010 Jul;34(7):864-70.
3. Fox F, Kündgen A, Nachtkamp K, et al. Matchedpair analysis of 186 MDS patients receiving long-term iron chelation therapy or transfusion therapy only. *Blood*. 2009:ASH (Annual Meeting Abstracts), #1747.
4. Gattermann N, Porter JB, Lopes LF, Seymour J. Consensus statement on iron overload in myelodysplastic syndromes. *Hematology/Oncology Clinics of North America*. 2005;19 (suppl 1):18-25.
5. Alessandrino EP, Amadori S, Barosi G, et al. Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology. *Haematologia*.2002;87:1286-1306.

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Chelation is used with caution, especially in elderly patients and those with thrombocytopenia or renal impairment, and all patients should be closely monitored while receiving chelation therapy.

Occasionally, in patients with a good response to treatment, particularly those with deletion 5q who are receiving lenalidomide, phlebotomy (removing blood – similar to the process used in blood donation) is the optimal way to manage iron overload.^[4] The removed blood cannot be used as a blood donation.

If you are currently receiving blood transfusions for your MDS and not receiving iron chelation therapy, you may wish to speak to your doctor about whether this therapy is suitable for you.

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EDUCATION AND SUPPORT PROGRAMS

VICTORIA & TASMANIA		
5 Jul	11am-1pm	Hobart Taking Control Program, <i>Diet & Exercise</i> (also 20 Jul, <i>Role of the Social Worker</i> ; 2 Aug, <i>Emotional Support</i> ; 17 Aug, <i>Role of Natural Therapies</i>)
13 Jul	1.30-3pm	South Gippsland Blood Cancer Information & Support Forum
19 Jul	11am-1pm	Launceston Blood Cancer Information & Support Forum (also 16 Aug)
	1.30-3pm	Central Gippsland Blood Cancer Information & Support Forum (also 16 Aug)
21 Jul	1.30-3pm	West Gippsland Blood Cancer Information & Support Forum (also 18 Aug)
28 Jul	10-11.30am	Barwon Blood Cancer Information & Support Forum (also 25 Aug, 29 Sep)
	10am-12noon	Ballarat Blood Cancer Information & Support Forum South East Melbourne Blood Cancer Information & Support Forum
4 Aug	10-11.30am	Bone Marrow Transplant Information & Support Forum, Preston
11 Aug	10-11.30am	Mornington Blood Cancer Information & Support Forum
23 Aug	10.30am-12noon	Shepparton Blood Cancer Information & Support Forum
25 Aug	10am-12noon	Horsham Blood Cancer Information & Support Forum
22 Sep	6-8pm	South East Melbourne Blood Cancer Information and Support Forum
NORTHERN TERRITORY		
9 Jul		Patient Education Day, Darwin
2 Sep	10-11.30am	LMB Support Group, Coconut Grove

NEW SOUTH WALES / ACT		
15 Jul	10am – 12noon	Grief and Bereavement Support Group, Sydney (also 29 Jul, 12 Aug, 26 Aug, 9 Sep)
28 Jul	11am-1pm	Cancer Journey - <i>Managing Emotions</i> , Wollongong

WESTERN AUSTRALIA		
18 Jul	1.30-3pm	Patient Support Group, North Perth (also 25 Aug, 19 Sep)
29 Jul	10.30-11.30am	Bunbury Patient Cancer Support Group (also 26 Aug, 30 Sep)

QUEENSLAND		
16 Jul	9am-3pm	Taking Control program workshop
9 Aug	11am	<i>Getting Your Life In Order Following Diagnosis</i> , South Brisbane
18 Aug	10am-12noon	Caring for the Carer Program: <i>Role of the Carer</i>
25 Aug	10am-12noon	Caring for the Carer Program: <i>Carer Burnout</i>
31 Aug	11am	<i>Relaxation: Easier Said Than Done</i> , South Brisbane

TELEPHONE FORUMS		
MDS Phone Forum	Contact your local Support Services Co-ordinator Ph: 1800 620 420 Email: info@leukaemia.org.au	13 Jul (7pm AEST) 10 Aug; 14 Sep; 12 Oct; 9 Nov

For more information, visit: www.leukaemia.org.au (education & support programs section) or call: 1800 620 420

MANAGING IRON OVERLOAD

Should iron chelation be used in high-risk patients?

Generally iron chelation is not used in high-risk patients^[4] as they are at high risk of organ damage. Chelation should begin in sufficient time to avoid myocardial (heart) iron loading and to prevent iron toxicity.^[5] Therefore, the role of iron chelation is primarily established in lower-risk patients, given that the process of iron overload needs time to manifest.

However, there are exceptions, including high-risk patients who have achieved a very good response with azacitidine (Vidaza®), or high-risk patients who are scheduled to have an allogeneic (donor) stem cell transplant.^[6] The role of iron chelation with allogeneic transplantation is undergoing clinical investigation.

* The National Comprehensive Cancer Network is a not-for-profit alliance of 21 of the world's leading cancer centres and is dedicated to improving the quality and effectiveness of care provided to patients with cancer.

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1. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: myelodysplastic syndromes (V.2.2011). Available at: <http://www.nccn.org>. Accessed January 12, 2011.
2. List AF, Baer MR, Steensma D, et al. Deferasirox (ICL670; Exjade) reduces serum ferritin (SF) and labile plasma iron (LPI) in patients with myelodysplastic syndromes (MDS). Program and abstracts of the 50th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2008; San Francisco, California. Abstract 1470.
3. Gattermann N, Schmid M, Porta MD, et al. Efficacy and safety of deferasirox (Exjade) during 1 year of treatment in transfusion-dependent patients with myelodysplastic syndromes: results from EPIC trial. Program and abstracts of the 50th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2008; San Francisco, California. Abstract 633.
4. Gattermann N. Guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload. *Leukemia Res.* 2007;31(suppl 3):S10-S15.
5. List AF. Iron overload in myelodysplastic syndromes: diagnosis and management. *Cancer Control.* 2010;17(suppl):2-8.
6. Pullarkat V. Objectives of iron chelation therapy in myelodysplastic syndromes: more than meets the eye? *Blood.* 2009;114:5251-5255.

OUR VISION TO CURE AND MISSION TO CARE

The Leukaemia Foundation is the only national not-for-profit organisation dedicated to the care and cure of people affected by leukaemias, lymphomas, myeloma and related blood disorders.

The Foundation provides emotional support, accommodation, transportation and practical assistance for these people. It also funds research into cures and better treatments for leukaemias, lymphomas, myeloma and related blood disorders.

The Foundation receives no direct ongoing government funding and relies on the continuous support of individuals and corporate partners to provide its services and to fund its research programs.

To find out more about the work of the Leukaemia Foundation and how we can help, phone 1800 620 420 or visit www.leukaemia.org.au.

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Disclaimer: No person should rely on the contents of this publication without first obtaining advice from their treating specialist.