Medicines Adverse Reactions Committee

Meeting date	7/12/2023	Agenda item	3.2.4
Title	**Tumour lysis syndrome with tyrosine kinase inhibitors and monoclonal antibodies when used in cancer treatment**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Products Tyrosine kinase inhibitors used in cancer treatment Monoclonal antibodies used in cancer treatment			
PHARMAC funding	Please refer to the PHARMAC pharmaceutical schedule and hospital medicines list		
Previous MARC meetings	This topic has not been previously reviewed by the MARC		
Prescriber Update	None		
Classification	Prescription medicine		
Advice sought	**The Committee is asked to advise on the following:** • Whether information on tumour lysis syndrome should be included in data sheets for all tyrosine kinase inhibitors and monoclonal antibodies used in cancer treatment. Note that the actions for monitoring for tumour lysis syndrome qualifies for addition to section 4.4 (warnings and precautions) as well as section 4.8 (undesirable effects). However, addition to section 5 (pharmacological properties) is not considered acceptable.		

Table of Contents

1 PURPOSE ... 3
2 BACKGROUND ... 3
2.1 Tyrosine kinase inhibitors (TKIs) [1] ... 3
2.2 Monoclonal antibodies (mAbs) [2] ... 5
2.2.1 Immune checkpoint inhibitors (ICIs) [3] ... 6
2.3 Tumour lysis syndrome [4-6] ... 7
2.3.1 Incidence [7] ... 8
2.3.2 Risk factors [5, 7] ... 8
2.3.3 Monitoring and prophylaxis [5, 6] ... 10
2.4 Other reference texts ... 10
2.4.1 New Zealand Formulary (NZF) ... 10
2.4.2 Best Practice Advocacy Centre (BPAC) ... 10
2.5 Data sheets ... 11
2.5.1 New Zealand ... 11
3 SCIENTIFIC INFORMATION ... 20
3.1 Published literature ... 20
3.1.1 Tyrosine kinase inhibitors ... 20
3.1.2 Monoclonal antibodies ... 22
3.2 CARM data ... 26
4 DISCUSSION AND CONCLUSIONS ... 26
5 ADVICE SOUGHT ... 27
6 REFERENCES ... 27

1 PURPOSE

Tumour lysis syndrome (TLS) is an oncologic emergency that is the result of massive tumour cell lysis releasing potassium, phosphate and nucleic acids into the systemic circulation. This could lead to potentially life-threatening acute kidney injury (AKI) and cardiac arrhythmias. TLS most commonly occurs after the initiation of cytotoxic therapy in patients with high-grade haematological malignancies, but it can also occur with other tumour types.

Tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) are commonly indicated to treat various types of cancer, including haematological cancers and solid tumours. Because TLS commonly occurs soon after initiation of cytotoxic treatment, TKIs and mAbs have been discussed as possible causes of TLS (ie, a class effect) in patients with cancer. This report presents the available information and the committee is asked to advise on information on TLS that should be included in the data sheets for these medicines.

2 BACKGROUND

The tyrosine kinase inhibitors and monoclonal antibodies described in this section are those used in cancer.

2.1 Tyrosine kinase inhibitors (TKIs) [1]

Tyrosine kinase inhibitors (TKIs) are a broad group of pharmacological agents that disrupt signal transduction pathway protein kinases. TKIs target the site of a kinase protein, preventing phosphorylation of intracellular targets, resulting in disruption of cell proliferation.

Tyrosine kinase enzymes are categorised as receptor tyrosine kinases (RTKs), nonreceptor tyrosine kinases (NRTKs) and dual specificity kinases (DSKs), which phosphorylate serine, threonine and tyrosine residues. RTKs are transmembrane receptors that include numerous receptors such as vascular endothelial growth factor receptors, platelet-derived growth factor receptors, insulin receptor family, and the ErbB (including HER and EGFR) receptor family. NRTKs are cytoplasmic proteins that consist of 13 families. There are over 50 FDA-approved TKIs that have been used as therapeutic options for solid and haematologic malignancies. Those that are approved in NZ are shown in Table 1.

Table 1: Tyrosine kinase inhibitors approved in NZ, their targets and indications

Substance	Target	Indications [a]
acalabrutinib	Bruton's tyrosine kinase	Mantle cell lymphoma (MCL) Chronic lymphocytic leukaemia (CLL)
afatinib	ErbB family	Non-squamous non-small cell carcinoma of the lung Non-small cell carcinoma of the lung
alectinib	Anaplastic lymphoma kinase (ALK)	Non-small cell lung cancer (NSCLC)
axitinib	Vascular endothelial growth factor (VEGF) receptors	Renal cell carcinoma (RCC)
bortezomib	Proteasome	Multiple myeloma
carfilzomib	Proteasome	Multiple myeloma
cobimetinib	MEK1 and MEK2 (mitogen-activated)	Melanoma
crizotinib	Anaplastic lymphoma kinase (ALK)	Non-small cell lung cancer (NSCLC)
dabrafenib	RAF kinases	Melanoma Anaplastic thyroid cancer Non-small cell lung cancer (NSCLC)
dasatinib	BCR-ABL kinase and SRC-family kinases	Chronic myeloid leukaemia (CML) Acute lymphoblastic leukaemia

Substance	Target	Indications [a]
erlotinib	HER1/EGFR receptor	Non-small cell lung cancer (NSCLC) Pancreatic cancer
everolimus	mTOR	Neuroendocrine tumours of pancreatic origin Renal cell carcinoma (RCC) Subependymal giant cell astrocytoma associated with tuberous sclerosis complex
gefitinib	EGFR	Non-small cell lung cancer (NSCLC)
ibrutinib	Bruton's tyrosine kinase	Mantle cell lymphoma (MCL) Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) Waldenström's macroglobulinemia
imatinib	BCR-ABL tyrosine kinase	Chronic myeloid leukaemia (CML) Acute lymphoblastic leukaemia (ALL) Myelodysplastic/myeloproliferative diseases Gastrointestinal stromal tumours Dermatofibrosarcoma protuberans
lenvatinib	Vascular endothelial growth factor (VEGF) receptors	Endometrial carcinoma Differentiated thyroid cancer Renal cell carcinoma (RCC) Hepatocellular carcinoma (HCC)
midostaurin	FLT3 and KIT kinase	Acute myeloid leukaemia (AML) Aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms, or mast cell leukaemia
neratinib	EGFR, HER2 and HER4	Breast cancer
nilotinib	BCR-ABL tyrosine kinase	Chronic myeloid leukaemia Chronic myelogenous leukaemia
nintedanib	Vascular endothelial growth factor (VEGF) receptors	Non-small cell lung cancer (NSCLC)
olaparib	PARP-1, PARP-2, PARP-3	Ovarian cancer Breast cancer Adenocarcinoma of the pancreas Prostate cancer
osimertinib	EGFRs with certain mutations	Non-small cell lung cancer (NSCLC)
palbociclib	CDK 4 and 6	Breast cancer
pazopanib	Vascular endothelial growth factor (VEGF) receptors	Renal cell carcinoma (RCC) Soft tissue sarcoma
ribociclib	CDK 4 and 6	Breast cancer
sorafenib	Various tyrosine kinases and RAF kinases	Hepatocellular carcinoma (HCC) Renal cell carcinoma (RCC) Differentiated thyroid carcinoma
sunitinib	Multiple receptor tyrosine kinases	Renal cell carcinoma (RCC) Gastrointestinal stromal tumour (GIST) Pancreatic neuroendocrine tumours
trametinib	MEK1 and MEK2	Melanoma Anaplastic thyroid cancer Non-small cell lung cancer (NSCLC)
vemurafenib	BRAF	Melanoma

Source: NZ data sheets

[a] Indications relating to cancer in brief

2.2 Monoclonal antibodies (mAbs) [2]

In 1988, scientists identified CD20, a protein specific to mature B cells and found to be abundantly expressed on cancerous B cells in non-Hodgkin's lymphoma, but not on healthy immature B cells. Therefore, CD20 became the first target for monoclonal antibody therapy (mAb) and rituximab was the first mAb to be approved for the treatment of cancer. There are now mAbs directed to other targets such as EGFR and HER2 used in colorectal and breast cancers, respectively, and there are a number of other ways that mAbs are used in cancer therapy including antibody-drug conjugates, targeting pro-tumorigenic compounds in the microenvironment, bispecific T cell engagers, and immune checkpoint inhibitors. Monoclonal antibodies (excluding immune checkpoint inhibitors) approved for use in NZ are shown in Table 2.

Table 2: Monoclonal antibodies (excluding immune checkpoint inhibitors) approved in NZ, their targets and indications

Substance	Target	Indications [a]
bevacizumab	VEGF	Colorectal cancer Renal cell cancer Non-small cell lung cancer (NSCLC) Breast cancer Glioma Epithelial ovarian, fallopian tube or primary peritoneal cancer Cervical cancer
brentuximab vedotin	CD30	Hodgkin lymphoma T-cell lymphoma
cetuximab	EGFR	Colorectal cancer Squamous cell cancer of the head and neck
daratumumab	CD38	Multiple myeloma
gemtuzumab ozogamicin	CD33	Acute myeloid leukaemia
obinutuzumab	CD20	Chronic lymphocytic leukaemia (CLL) Non-Hodgkin lymphoma
pertuzumab	HER2	Breast cancer
pertuzumab + trastuzumab	HER2	Breast cancer
trastuzumab	HER2	Breast cancer Advanced gastric cancer
trastuzumab emtansine	HER2	Breast cancer
rituximab	CD20	Non-Hodgkin's lymphoma Chronic lymphocytic leukaemia

Source: NZ data sheets

[a] Indications relating to cancer in brief

2.2.1 Immune checkpoint inhibitors (ICIs) [3]

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target key receptor systems regulating T-cells and their ability to recognise and target tumours. These targets include the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor and the programmed death-1 (PD-1) receptor and its ligand PD-L1. Tumour cells can co-opt immune checkpoints to reduce T-cell activity and thus the immune response to cancer cells. ICIs restore T-cell activity, improving the immune response to tumour cells. Immune checkpoint inhibitors approved for us in NZ are shown in Table 3.

Table 3: Immune checkpoint inhibitors approved in NZ, their targets and indications

Substance	Target	Indications [a]
atezolizumab	PD-L1	Non-small cell lung cancer (NSCLC) Small cell lung cancer Urothelial carcinoma Breast cancer Hepatocellular carcinoma (HCC)
durvalumab	PD-L1	Urothelial carcinoma Non-small cell lung cancer (NSCLC) Small cell lung cancer Biliary tract cancer
ipilimumab	CTLA-4	Melanoma Renal cell carcinoma (RCC) Non-small cell lung cancer (NSCLC) Malignant pleural mesothelioma
nivolumab	PD-1	Melanoma Non-small cell lung cancer (NSCLC) Malignant pleural mesothelioma Renal cell carcinoma (RCC) Classical Hodgkin lymphoma Squamous cell carcinoma of the head and neck Urothelial carcinoma Hepatocellular carcinoma (HCC) Oesophageal cancer Gastro-oesophageal junction cancer Gastric cancer
pembrolizumab	PD-1	Melanoma Non-small cell lung cancer (NSCLC) Classical Hodgkin lymphoma Urothelial carcinoma Head and neck squamous cell cancer Microsatellite instability-high cancer Colorectal cancer Endometrial cancer Cervical cancer Cutaneous squamous cell carcinoma Renal cell carcinoma (RCC) Oseophageal cancer Breast cancer

Source: NZ data sheets

[a] Indications relating to cancer in brief

2.3 Tumour lysis syndrome [4-6]

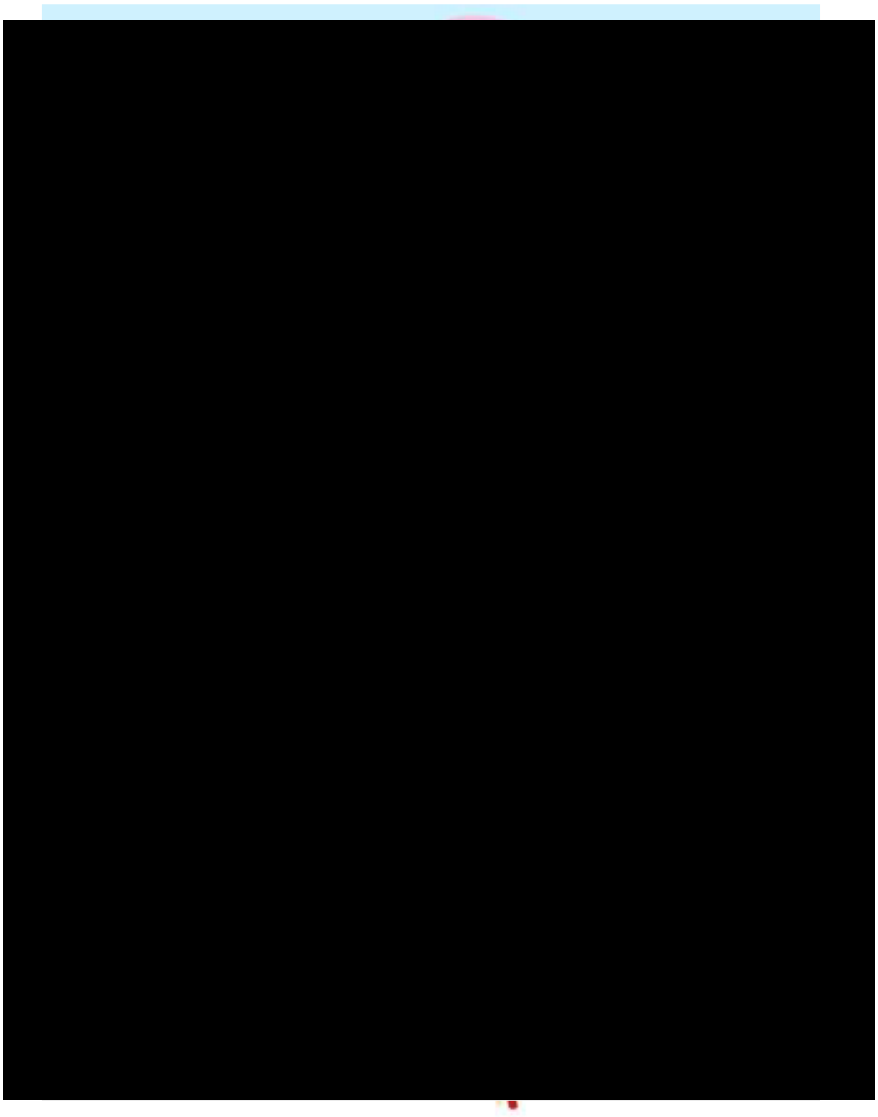
Tumour lysis syndrome (TLS) is caused by massive tumour cell lysis over a short period of time with release of large amounts of potassium, phosphate and uric acid into the systemic circulation. Deposition of uric acid and/or calcium phosphate crystals in the renal tubules can result in acute kidney injury (Figure 1).

Symptoms associated with TLS largely reflect the associated metabolic abnormalities (hyperkalaemia, hyperphosphatemia, hypocalcaemia). They include nausea, vomiting, diarrhoea, anorexia, lethargy, haematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope and possible sudden death.

The Cairo-Bishop definition proposed in 2004 for TLS is commonly used:

- Laboratory TLS is defined as any two or more of the following metabolic abnormalities and presents within three days before or seven days after instituting chemotherapy: hyperuricaemia, hyperkalaemia, hyperphosphatemia, hypocalcaemia.
- Clinical TLS is defined as laboratory TLS plus one or more of the following not directly or probably attributable to a therapeutic agent: increased serum creatinine concentration (≥1.5 times the upper limit of normal), cardiac arrhythmia/sudden death, or a seizure.

Figure 1: Pathogenesis of tumour lysis syndrome resulting in acute kidney injury



Source: Lupusoru et al (2022) [7]

TLS most often occurs after initiation of cytotoxic therapy in patients with high-grade lymphomas (particularly the Burkitt subtype) and acute lymphoblastic leukaemia. However, TLS can occur spontaneously and with other tumour types that have a high proliferative rate, large tumour burden or high sensitivity to cytotoxic treatment. The emergence of effective and targeted anticancer medicines used alone or in combination with conventional cytotoxic agents has led to an increase in the frequency and severity of TLS in haematologic cancers that previously were rarely associated with this complication, including:

- Venetoclax (B-cell lymphoma 2 inhibitor) used for chronic lymphocytic leukaemia, small lymphocytic leukaemia and acute myeloid leukaemia. Venetoclax can cause rapid reduction in chronic lymphocytic leukaemia.
- Obinutuzumab (anti-CD20 monoclonal antibody) used for chronic lymphocytic leukaemia and non-Hodgkin lymphoma.
- Dinaciclib (cyclin-dependent kinase inhibitor) for advanced acute lymphoblastic leukaemia or myeloid leukaemia (product not approved for use in NZ).
- Alvocidib (flavopiridol, cyclin-dependent kinase inhibitor) under study in intermediate-risk and high-risk acute myeloid leukaemia (product not approved for use in NZ).

TLS has also been observed in patients with cancers that were previously rarely associated with this complication.

2.3.1 Incidence [7]

The incidence of TLS varies from sporadic cases up to high incidence. However, even patients with tumours with low risk for TLS should be closely monitored as those with diseases such a multiple myeloma may develop TLS due to highly efficient modern anticancer therapy. There is a great heterogeneity in reporting the incidence of TLS mainly because most studies preceding the Cairo-Bishop criteria were retrospective and also because of the absence of uniform diagnostic criteria (some considering only clinical TLS as valid criteria).

A study including 788 adults and paediatric patients with acute leukaemia or non-Hodgkin's lymphoma demonstrated how incidence of TLS varied according to laboratory or clinical TLS – 18.9% vs. 5%, respectively. The incidences of laboratory and clinical TLS based on tumour type were 21.4% and 5.2% in acute lymphoblastic leukaemia (ALL), 14.7% and 3.4% in acute myeloid leukaemia (AML), and 19.6% and 6.1% in non-Hodgkin lymphoma, respectively. In other studies, TLS incidence varied from 26% in ALL to 32% in AML.

2.3.2 Risk factors [5, 7]

Many individual factors contribute to the overall risk of TLS, including older age, advanced stage of cancer, bulky disease, bone marrow involvement, mediastinal mass, high white blood cell count, high lactate dehydrogenase level, dehydration, concurrent medicines (other than cancer therapy), renal impairment, hepatomegaly or splenomegaly with tumour involvement and tumour infiltrating the kidneys.

Major risk factors, each of which contribute substantially and independently to the risk of clinical TLS, are bulk of disease, potential for cell lysis (a combination of tumour type, its proliferation rate, its chemosensitivity and intensity of initial therapy), and presentation (laboratory TLS at presentation, pre-existing AKI). Other comorbidities mentioned as important for TLS risk classification were baseline electrolyte abnormalities (hyperkalaemia, hyperphosphatemia, hyperuricemia), pre-existing cardiac or pulmonary conditions, and ability to receive hyperhydration.

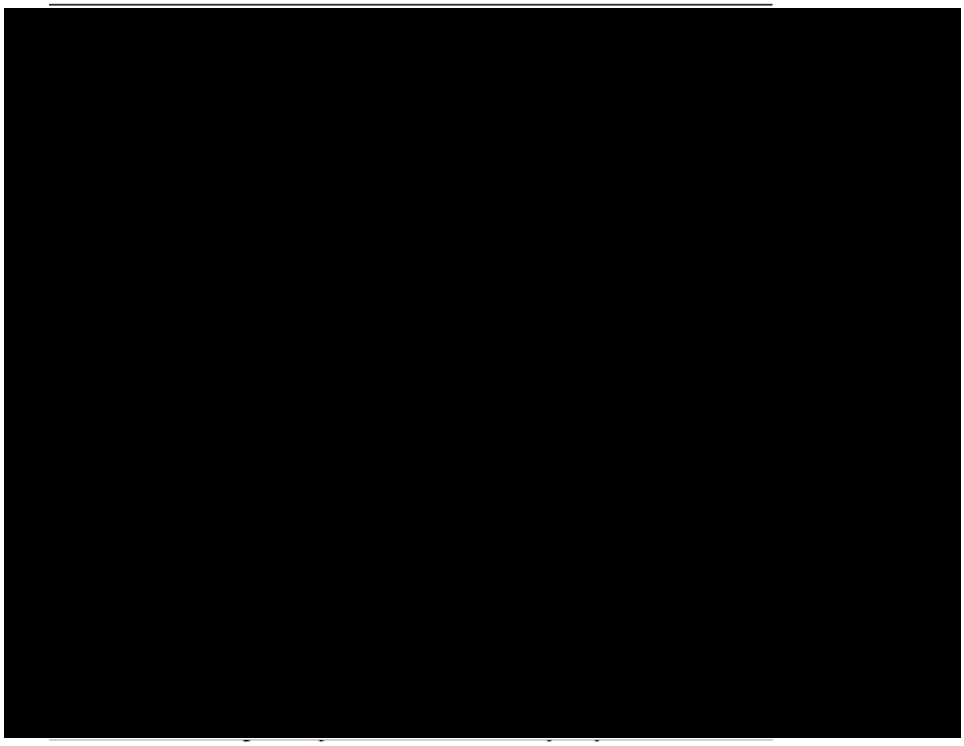
Several risk-stratification models for TLS have been developed and risk factors are summarised in Table 4.

Concern for TLS risk associated with specific anticancer agents is shown in Table 5. Panellists from the US TLS guidelines were in favour of using dose-escalation strategies for chemotherapeutic agents (for those with supporting data) to reduce the risk of TLS and noted that this strategy has considerably attenuated the risk of TLS with venetoclax treatment.

Table 4: Risk factors for tumour lysis syndrome

Source: Lupusoru et al (2022) [7]

Table 5: Degree of concern of TLS risk with chemotherapeutic agents



Source: Perissinotti et al (2023) [5]

Cases of catastrophic TLS in low-risk tumours are also described, for example, the reported cases of a patient receiving cetuximab for metastatic colon cancer [8], a patient with chronic leukaemia who developed TLS during the first 24 hours after starting imatinib [9], and a patient with renal cell carcinoma treated with sunitinib [10]. On the other hand, TLS incidence may be significantly reduced in high-risk tumours (eg, Burkitt's lymphoma) due to aggressive prophylactic therapy. Solid tumours that have been associated with TLS are shown in Table 6.

Table 6: Solid tumours associated with tumour lysis syndrome

Source: Lupusoru et al (2022) [7]

2.3.3 Monitoring and prophylaxis [5, 6]

Panellists from the US TLS guidelines agreed monitoring for TLS should begin prior to the first dose of therapy regardless of TLS risk and all patients should have baseline laboratory values. The panel considered urine output, potassium, phosphate, uric acid, calcium, creatinine, blood urea nitrogen and lactate dehydrogenase to be important parameters to monitor.

Panellists used cancer type, cancer stage, specific oncologic therapy and renal function in their determination of how often to monitor for TLS.

Aggressive hydration is a cornerstone of TLS prophylaxis and management as it allows for dilution of potentially harmful levels of solutes from tumour lysis. Therefore, the use of IV hydration and hypouricaemic agents (eg, allopurinol, rasburicase, febuxostat) are the main prophylactic strategies of TLS. The specific type of prophylaxis is generally selected based on the estimated risk of TLS.

Comments:

TLS could lead to serious outcomes (acute kidney injury, cardiac arrhythmias). Therefore, identifying patients at risk of TLS is important so that appropriate prophylactic measures and treatment can be started promptly.

TLS most commonly occurs after initiation of cytotoxic therapy in patients with high-grade haematological malignancies, but can also occur with other tumour types (eg, solid tumours).

2.4 Other reference texts

2.4.1 New Zealand Formulary (NZF)

The cytotoxic drugs chapter of NZF lists tumour lysis syndrome as an adverse effect noting that it occurs secondary to spontaneous or treatment-related rapid destruction of malignant cells. Patients at risk of tumour lysis syndrome include those with non-Hodgkin's lymphoma (especially if high grade and bulky disease), Burkitt's lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia (particularly if high white blood cell counts or bulky disease), and occasionally those with solid tumours. Pre-existing hyperuricaemia, dehydration and renal impairment are also predisposing factors. Features include hyperkalaemia, hyperuricaemia and hyperphosphatemia with hypocalcaemia; renal damage and arrhythmias can follow. Early identification of patients at risk and initiation of prophylaxis or therapy for tumour lysis syndrome are essential.

2.4.2 Best Practice Advocacy Centre (BPAC)

A 2015 article on improving the safety of community-based chemotherapy notes that rarer but serious adverse effects of chemotherapy that require immediate referral to secondary care include tumour lysis syndrome.

A 2020 article on biosimilars notes that severe reactions generally occurring within two hours of beginning the first infusion of Riximyo (rituximab) and Mabthera (rituximab) include tumour lysis syndrome.

2.5 Data sheets

2.5.1 New Zealand

Information on tumour lysis syndrome in NZ data sheets are shown in separate tables below for tyrosine kinase inhibitors (Table 7), monoclonal antibodies (excluding immune checkpoint inhibitors) (Table 8), and immune checkpoint inhibitors (Table 9).

Table 7: Tumour lysis syndrome information in tyrosine kinase inhibitor data sheets

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
acalabrutinib	Calquence	AstraZeneca	4.8	CLL in ELEVATE-TN study: Tumour lysis syndrome was reported in 2% of patients treated with CALQUENCE+G. No patients experienced TLS in the CALQUENCE monotherapy arm. ASCEND study: TLS was reported in patients treated with CALQUENCE and idelalisib plus rituximab with an incidence of 1% in both arms. The one patient experiencing TLS treated with CALQUENCE had Grade 3 TLS and bulky disease.	Y
afatinib	Giotrif	Boehringer Ingelheim	no	no	N
alectinib	Alecensa	Roche	no	no	N
axitinib	Inlyta	Pfizer	no	no	N
bortezomib	Velcade	Janssen-Cilag	4.4	Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.	Y
			4.8	Uncommon: tumour lysis syndrome	
					Y
carfilzomib	Kyprolis	Amgen	4.2	Adequate hydration is required prior to dosing in cycle 1, especially in patients at high risk of tumour lysis syndrome or renal toxicity.	Y

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
			4.4	Cases of tumour lysis syndrome (TLS), including fatal outcome, have been reported in patients who received Kyprolis. Patients with a high tumour burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in cycle 1, and in subsequent cycles as needed. Uric acid lowering drugs should be considered in patients at high risk for TLS (see section 4.2). Monitor for evidence of TLS during treatment including regular measurement of serum electrolytes, and manage promptly. Interrupt Kyprolis until TLS is resolved (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).	
			4.8	Summary of safety profile: Serious adverse reactions that may occur during Kyprolis treatment include: [...] tumour lysis syndrome Uncommon: Tumour lysis syndrome	
cobimetinib	Cotellic	Roche	no	no	N
crizotinib	Xalkori	Pfizer	no	no	N
dabrafenib	Tafinlar	Novartis	no	no	N
dasatinib	Sprycel	Bristol-Myers Squibb	4.8	Adverse reactions from clinical trials: Uncommon: tumour lysis syndrome	Y
erlotinib	Tarceva	Roche	no	no	N
everolimus	Afinitor	Novartis	no	no	N
gefitinib	Iressa	AstraZeneca	no	no	N
ibrutinib	Imbruvica	Janssen-Cilag	4.4	Tumour lysis syndrome (TLS) has been reported with IMBRUVICA therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.	Y
			4.8	Postmarketing data Very rare: Tumour lysis syndrome	
imatinib	Glivec	Novartis	4.4	Cases of tumor lysis syndrome (TLS) have been reported in patients treated with Glivec. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Glivec (see section 4.8 Undesirable effects).	Y

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
			4.8	Postmarketing reports: Rare: Tumor lysis syndrome Description of adverse reactions A causal relationship between tumor lysis syndrome and Glivec treatment is deemed possible, although some cases were confounded by concomitant medications and other independent risks (see section 4.4 Special warnings and precautions for use).	
lenvatinib	Lenvima	Eisai	no	no	N
midostaurin	Rydapt	Novartis	no	no	Y
neratinib	Nerlynx	Specialised Therapeutics	no	no	N
nilotinib	Tasigna	Novartis	4.2	Due to possible occurrence of Tumor Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with TASIGNA (see section 4.8).	Y
			4.4	Cases of tumor lysis syndrome (TSL) have been reported in patients treated with TASIGNA. For monitoring recommendations please refer to Dosage and method of administration section.	
			4.8	ADRs from spontaneous reports, literature (frequency not known) Frequency not known: Tumor lysis syndrome	
nintedanib	Ofev	Boehringer Ingelheim	no	no	N
olaparib	Lynparza	AstraZeneca	no	no	N
osimertinib	Tagrisso	AstraZeneca	no	no	N
palbociclib	Ibrance	Pfizer	no	no	N
pazopanib	Votrient	Novartis	4.4	Cases of TLS, including fatal cases, have been reported in patients treated with Votrient (see Section 4.8 Undesirable effects). Patients generally at risk of TLS are those with rapidly growing tumours, a high tumour burden, renal dysfunction, or dehydration. Preventative measures such as treatment of high uric acid levels and intravenous hydration should be considered prior to initiation of Votrient. Patients at risk should be closely monitored and treated as clinically indicated.	N

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
			4.8	Postmarketing data Unknown: Tumour lysis syndrome (including fatal cases); see section 4.4 Special warnings and precautions for use.	
ribociclib	Kisqali	Novartis	no	no	N
sorafenib	Nexavar	Bayer	4.4	Cases of tumour lysis syndrome, some fatal, have been reported in post-marketing surveillance in patients treated with sorafenib. Risk factors for tumour lysis syndrome include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.	N
			4.8	Postmarketing experience tumour lysis syndrome	
sunitinib	Sutent	Pfizer	4.4	Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Patients generally at risk of TLS are those with high tumour burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.	N
			4.8	Postmarketing experience Cases of tumour lysis syndrome (TLS), some fatal, have been reported in patients treated with sunitinib.	
trametinib	Mekinist	Novartis	no	no	N
vemurafenib	Zelboraf	Roche	no	no	N

[a] Only the innovator brand is included in the table

[b] Section 4.2 = dose and administration, section 4.4 = warnings and precautions, section 4.8 = undesirable effects

Table 8: Tumour lysis syndrome information in monoclonal antibody (excluding immune checkpoint inhibitors) data sheets

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
bevacizumab	Avastin	Roche	no	no	N
brentuximab vedotin	Adcetris	Takeda	4.4	Tumour lysis syndrome (TLS) has been reported with ADCETRIS. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.	Y
			4.8	Uncommon: tumour lysis syndrome	
cetuximab	Erbitux	Pharmacy Retailing	no	no	N
daratumumab	Darzalex	Janssen-Cilag	5.1	Mechanism of action: Daratumumab has been shown to inhibit the in vivo growth of CD38-expressing tumour cells. Based on in vitro studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) in malignancies expressing CD38.	Y
gemtuzumab ozogamicin	Mylotarg	Pfizer	4.2	Appropriate measures to help prevent the development of tumour lysis-related hyperuricaemia such as hydration, administration of antihyperuricaemic or other agents for treatment of hyperuricaemia must be taken (see Section 4.4 Special warnings and precautions for use).	Y
			4.4	In clinical studies with MYLOTARG, TLS was reported (see Section 4.8 Undesirable effects). Fatal reports of TLS complicated by acute renal failure have been reported in the postmarketing setting. In patients with hyperleukocytic AML, leukoreduction should be considered with hydroxyurea or leukapheresis to reduce the peripheral WBC count to below 30,000/mm3 prior to administration of MYLOTARG to reduce the risk of inducing TLS (see Section 4.2 Dose and method of administration). Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice. Appropriate measures to help prevent the development of tumour lysisrelated hyperuricaemia such as hydration, administration of antihyperuricaemic (e.g., allopurinol) or other agents for treatment of hyperuricaemia (e.g., rasburicase) must be taken.	
			4.8	ADRs from monotherapy studies and postmarketing: Common: Tumour lysis syndrome	

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
obinutuzumab	Gazyva	Roche	4.2	Prophylaxis and Premedication for Tumour Lysis Syndrome (TLS): Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 109 /L) and/or renal impairment (CrCl < 70 mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to start of Gazyva infusion as per standard practice (see section 4.4). Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.	Y
			4.4	Tumour lysis syndrome (TLS) has been reported with Gazyva. Patients who are considered to be at risk of TLS [e.g. patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 109 /L) and/or renal impairment (CrCl < 70 mL/min)] should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to the infusion of Gazyva as described in section 4.2. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines should also be followed, according to standard practice. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.	
			4.8	The most serious adverse drug reactions were: [...] Tumour Lysis Syndrome, which is more common in patients with a high tumour burden and/or a high circulating lymphocyte count and/or renal impairment (see section 4.4). ADRs associated with use of Gazyva in combination with different chemo regimens in multiple indications: Tumour lysis syndrome (common)	
pertuzumab	Perjeta	Roche	4.4	Tumour Lysis Syndrome (TLS) refers to the constellation of metabolic disturbances that may be seen after initiation of effective cancer treatment. It usually occurs in patients with high grade, bulky, rapidly proliferating, treatment-responsive tumours and in patients with acute haematological malignancies. To date, while no cases have been reported from controlled investigational clinical trials in more than 10,000 patients exposed to Perjeta cases suggestive of TLS have been reported in the postmarketing setting. There is no confirmed causal association between TLS and Perjeta in these cases, however patients at risk of tumour lysis syndrome should be monitored closely and appropriate precautions taken.	N

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
			4.8	Post marketing experience: Tumour lysis syndrome	
pertuzumab + trastuzumab	Phesgo	Roche	4.8	ADRs from pivotal trials and in the postmarketing setting: Tumour lysis syndrome (unknown)	N
trastuzumab	Herceptin	Roche	4.8	ADRs from clinical trials and postmarket setting: Tumour lysis syndrome (not known)	N
trastuzumab emtansine	Kadcyla	Roche	no	no	N
rituximab	Mabthera	Roche	4.2	Chronic lymphocytic leukaemia: Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to the start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome	Y
			4.4	Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia patients: Infusion-related Reactions: Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first MabThera infusion, were characterised by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 4.8) Rapid tumour lysis: MabThera mediates the rapid lysis of benign and malignant CD20 positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MabThera infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (>25 x 109 /L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent MabThera therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.	

Substance	Brand [a]	Sponsor	Section [b]	Wording	Indicated for haematological malignancy? (Y/N)
			4.8	Monotherapy - 4 weeks treatment: Some features of tumour lysis syndrome have also been observed. Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL): Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome.	

[a] Only the innovator brand is included in the table

[b] Section 4.2 = dose and administration, section 4.4 = warnings and precautions, section 4.8 = undesirable effects, section 5.1 = pharmacodynamic properties

Table 9: Tumour lysis syndrome information in immune checkpoint inhibitor data sheets

Substance	Brand [a]	Sponsor	Section [b]	DS wording	Indicated for haematological malignancy? (Y/N)
atezolizumab	Tecentriq	Roche	no	no	N
durvalumab	Imfinzi	AstraZeneca	no	no	N
ipilimumab	Yervoy	Bristol-Myers Squibb	4.8	SAEs reported in other ipilimumab monotherapy clinical trials: Rare: tumour lysis syndrome	N
nivolumab	Opdivo	Bristol-Myers Squibb	no	no	Y
pembrolizumab	Keytruda	Merck Sharp & Dohme	no	no	Y

[a] Only the innovator brand is included in the table

[b] Section 4.8 = undesirable effects

Comments:

In summary, the information on tumour lysis syndrome varies between no information to information in different data sheet sections (predominantly sections 4.4 and/or 4.8), and the extent of the information is also very variable.

In general, medicines used for haematological cancers are more likely to contain information on tumour lysis syndrome compared with those for solid tumours, though there are exceptions to this:

- Midostaurin (Rydapt), nivolumab (Opdivo), and pembrolizumab (Keytruda) indicated for haematological malignancy has no information on TLS. This is consistent with Australia, Canada and the US. The nivolumab (Opdivo) UK SmPC lists TLS in section 4.8.
- Pazopanib (Votrient), sorafenib (Nexavar), sunitinib (Sutent), and ipilimumab (Yervoy) not indicated for haematological malignancy has info on TLS.
- Acalabrutinib (Calquence) and Dasatinib (Sprycel) indicated for haematological malignancy only list TLS in section 4.8, with no information in section 4.4.
- Daratumumab (Darzalex) indicated for haematological malignancy has information on TLS in section 5.1 only.
- Pertuzumab (Perjeta) not indicated for haematological malignancy has information on TLS in sections 4.4 and 4.8. However, the pertuzumab + trastuzumab (Phesgo) and trastuzumab (Herceptin) data sheets have information in section 4.8 only, and the trastuzumab emtansine (Kadcyla) has no information on TLS.

3 SCIENTIFIC INFORMATION

3.1 Published literature

Some articles describing tumour lysis syndrome are shown below. Most are case reports with a few reviews. Note that this is not a complete literature review.

3.1.1 Tyrosine kinase inhibitors

TLS associated with **ibrutinib** monotherapy in a patient with relapsed mantle cell lymphoma was reported by Kaur and Swami (2017) [11], and Titus-Rains et al (2018) [12] described the occurrence of TLS in two patients initiated on ibrutinib. One patient had chronic lymphocytic leukaemia/small lymphocytic lymphoma and one patient and mantel cell lymphoma. Both developed laboratory and clinical TLS after initiation of ibrutinib. Causality assessment with the Naranjo ADR probability scale indicated one probable relationship and one possible relationship between ibrutinib and TLS. There were additional factors that may have confounded the laboratory and clinical factors observed, including baseline laboratory values and concurrent medicines. Both patients were managed with supportive therapies. Another case of a patient treated with ibrutinib (Imbruvica) for chemotherapy-resistant chronic lymphocytic leukaemia and small lymphocytic lymphoma who developed TLS was described by Brener et al (2020) [13]. The patient showed dramatic improvement in kidney function, uric acid and phosphorus after discontinuation of ibrutinib, a short course of rasburicase and two haemodialysis treatments.

Chang and Shih (2008) [14] described a patient with BCR-ABL (ela2) positive acute lymphoblastic leukaemia who developed tumour lysis syndrome (TLS) after 10-day treatment with **imatinib**. A further case of tumour lysis syndrome (TLS) after starting treatment with imatinib (Glivec) in a patient with chronic myelogenous leukaemia was described by Al-Kali et al (2009) [15]. Subsequently, Ondecker et al (2018) [16] presented a rare case of TLS following treatment of a large gastrointestinal stromal tumour (GIST) in a 63-year-old man. Imatinib was started for tumour size reduction prior to surgical intervention and in 5 days the patient developed metabolic derangements consistent with TLS. Imatinib was held and fluids, allopurinol and rasburicase were started. All metabolic abnormalities resolved in 3 days. Imatinib was restarted and he eventually underwent surgical intervention.

Hua et al (2013) [17] described TLS soon after treatment with hydroxyurea followed by **nilotinib** in two patients with chronic-phase chronic myelogenous leukaemia. The first patient co-presented with underlying mild-to-moderate renal insufficiency due to polycystic kidney disease. However, TLS resolved on discontinuation of nilotinib. The second patient had an exceedingly high white blood cell count and presented with disseminated intravascular coagulation and severe liver injury triggered by TLS, which developed after starting nilotinib and died of multiple organ failure.

A case report of **pazopanib**-related TLS in metastatic renal cell carcinoma was described by van Kalleveen et al (2018) [18]. A 58-year-old man with a history of poor prognosis metastasised clear cell renal cell carcinoma (mRCC) developed TLS within six days after initiating therapy with pazopanib. In this case, a low serum albumin (26 g/L) might have led to a higher free fraction of pazopanib which could have resulted in more toxicity.

Additionally, Narukawa et al (2020) [19] described a case of a patient who received pazopanib after nivolumab-induced TLS in a patient with metastatic renal cell carcinoma (mRCC). The 69-year-old female patient received pazopanib as fourth-line therapy after sunitinib, axitinib and nivolumab as first-, second- and third-line therapies, respectively. Two weeks after administration of pazopanib, she presented to the emergency room complaining of fatigue associated with nausea and diarrhoea. Consistent with TLS, her laboratory results showed hyperphosphatemia, hyperuricaemia, hypocalcaemia and possible acute kidney injury. The authors postulate the combination of pazopanib and prolonged effect of nivolumab may have

caused TLS, and advise careful observation is needed when administering tyrosine kinase inhibitors after immune checkpoint inhibitors.

Saylor et al (2007) [20] described a 56-year-old man who experienced tumour lysis syndrome (TLS) after treatment of a gastrointestinal stromal tumour with **sunitinib**. The authors note several factors predisposed the patient to TLS while taking sunitinib: he had a particularly aggressive tumour with a high rate of mitoses, his serum albumin was low due to his fistula output and the reduced plasma protein binding of sunitinib may have caused his effective dose to be much higher than anticipated. In addition, his tumour seemed highly sensitive to sunitinib, and he had undergone several recent blood transfusions and may have been experiencing a dangerous synergy between tumour cell lysis and high red cell turnover due to the fragility of transfused cells. The patient's tumour burden rapidly increased as sunitinib was held, but re-initiation of sunitinib carried a substantial risk of clinical deterioration. He was changed to comfort care and died peacefully 1 week later.

Salter et al (2022) [1] conducted a systematic review to determine the incidence of tumour lysis syndrome (TLS) with **tyrosine kinase inhibitors (TKIs) in haematologic malignancies**. A total of 57 publications were identified. Of these, 39 reported TLS as an adverse event. TLS was described as an adverse event among essentially all the subclasses of TKIs that are used to manage haematologic malignancies. Ibrutinib had the highest reported rate of TLS either when administered alone or in combination with other agents, following by the second generation Bruton's tyrosine kinase (BTK) inhibitor acalabrutinib. All generations of Bcr-Abl-targeted TKIs were the second most common subclass to be associated with TLS.

With respect to individual TKIs, the following agents were identified in the systematic review: acalabrutinib (n=6), bafetinib (n=1), dasatinib (n=6), gandotinib (n=1), gliterinib (n=3), ibrutinib (n=17), imatinib (n=13), nilotinib (n=5) ponatainib (n=2), ruxolitinib (n=1) and zanubrutinib (n=4).

There were 51 patients (1.8% based on total patients from the 57 studies) with TLS, of which 3 were fatal cases. Of the 51 patients, 25 (49%) received TKI monotherapy and the remaining 26 (51%) were on combination therapy with either immunomodulatory or chemotherapy.

The risk of TLS varied with respect to the haematologic malignancy. TLS occurred in three cases of acute myelocytic leukaemia (AML) and five cases of acute lymphoblastic leukaemia (ALL). This was not surprising given AML and ALL are associated with intermediate-to-high risk of TLS. Of the eight publications of lymphoma, four cases of TLS were reported in patients with mantle cell lymphoma (MCL), two of which were on combination therapy. The most common haematologic malignancy reported with TLS was chronic leukaemia, with 25 publications of TLS occurring in chronic lymphocytic leukaemia (CLL) and chronic myelocytic leukaemia (CML).

Comments:

TLS reported in patients with solid tumours who were treated with tyrosine kinase inhibitors were among the identified publications and included imatinib (Ondecker et al), pazopanib (Kalleveen et al, Narukawa et al) and sunitinib (Saylor et al). The solid tumours in these cases were GIST in 2 patients and mRCC in 2 patients.

3.1.2 Monoclonal antibodies

Fatal tumour lysis syndrome after irinotecan/5-FU/folinic acid/**bevacizumab**-containing therapy in a patient heavily pre-treated for metastatic colon cancer was described by Hentrich et al (2008) [21]. A 62-year-old man was diagnosed with colon cancer which metastasised to the right lung in 1996. He received several rounds of chemotherapy and surgical excision was performed. More than 10 years after the primary diagnosis of metastatic colon cancer, the patient presented with progressive bone and lung metastases. He received bevacizumab in combination with irinotecan, folinic acid and 5-FU. Over the next two days, massive signs of TLS developed. Despite vigorous hydration, urine alkalisation and rasburicase-based uricolytic therapy, the patient deteriorated and died of acute renal failure.

Krishnan et al (2008) [8] described a **cetuximab**-related tumour lysis syndrome in a 64-year-old male patient with metastatic colon carcinoma. The patient received cetuximab monotherapy and after 18 hours, his renal function started to deteriorate. His biochemical profile was consistent with acute tumour lysis syndrome. About 6 hours later, his renal function continued to deteriorate. The patient received a dose of rasburicase and his uric acid level decreased about 20 hours later. The patient eventually died due to complications of TLS. Haroon et al (2010) [22] reported on another case of cetuximab-related tumour lysis syndrome. A 60-year-old man was diagnosed with a moderately differentiated adenocarcinoma. Multiple liver metastases were found confined to its right lobe. He had the first session of a combined therapy with cetuximab and 5-fluorouracil, however, soon afterwards he presented with symptoms, signs and biochemistry suggestive of tumour lysis syndrome.

A case of an 83-year-old woman who developed TLS five days after FOLFIRI+cetuximab therapy was reported by Matsuyama et al (2015) [23]. The patient was diagnosed with a huge ascending colon cancer measuring 10 cm in diameter and with peritoneal dissemination. Following successful therapy with FOLFIRI alone, cetuximab was added and administered. On day-5, TLS was diagnosed with hyperuricaemia, hyperkalaemia, hyperphosphatemia and an increase in serum creatinine. Intravenous furosemide, volume loading and glucose-insulin therapy resulted in improvement of laboratory data in two days. However, she died on day-34 due to multiple organ failure caused by aspiration pneumonia following small intestine functional ileus.

A case of laboratory features of tumour lysis syndrome following **daratumumab** monotherapy was described in a letter to the editor by Shackleton et al (2020) [24]. The patient was an 83-year-old woman with relapsed/refractory light-chain multiple myeloma. She commenced bortezomib and dexamethasone and completed eight cycles but relapsed 3 months later. She commenced lenalidomide plus dexamethasone and five months later, her multiple myeloma again progressed and her treatment was adjusted to lenalidomide, cyclophosphamide and prednisolone. She remained stable for a further 15 months before being admitted to hospital to commence daratumumab monotherapy. Her laboratory abnormalities met the criteria for laboratory TLS (25% increase from baseline of uric acid and phosphate). A repeat 10% dose of daratumumab 10 days later with pre-treatment with dexamethasone and an oral leukotriene antagonist was well tolerated. She was subsequently treated with full-dose daratumumab 1 week later following IV hydration and pre-treatment with rasburicase. Although no clinical adverse reaction was observed, her blood results did again show evidence of laboratory TLS.

Xia et al 2023 [25] investigated the association between **CD20 monoclonal antibodies (mAbs) for chronic lymphocytic leukaemia (CLL)** and TLS by using post-marketing data from the US FDA's adverse event reporting system (FAERS) database. FDA-approved mAbs for CLL were included: obinutuzumab, rituximab, ofatumumab (CD20 mAbs), and alemtuzumab (CD52 mAb).

The study combined a frequentist reporting odds ratio (ROR), deemed significant if the lower limit of the 95% CI (ROR_{025}) is >1 with at least three cases, and the Bayesian information component (IC) deemed significant if the 95% credibility interval (IC_{025}) is >0. Venetoclax was used as the positive control due to its well-known association with TLS. In the primary analysis, the study calculated the ROR and IC by comparing mAbs with all other medicines reported in the FAERS database, and other anticancer medicines. In the secondary sensitivity

analyses, the IC was calculated by using all other anticancer medicines as the comparator accounting for potential confounders: removed high-frequency events recorded with CD20 mAbs such as neutropenia and infusion-related reactions, removed reports with concomitant nephrotoxic medicines, restricted analyses to reports where the agents were recorded as suspect and reported by healthcare professionals, excluded pre-existing diseases which may increase risk of TLS, and used the standardised MedDRA query (SMQ) broad search (including 39 preferred terms) to better reflect co-reported features.

From 2004 to 2022, the study detected 8616 TLS reports in FAERS. There were 7780 TLS cases with anticancer medicines, in which 197, 368, 41 and 14 TLS reports were with obinutuzumab, rituximab, ofatumumab and alemtuzumab, respectively. The study detected disproportionality signals for obinutuzumab, rituximab, ofatumumab and alemtuzumab when compared to all medicines as well as to other anticancer agents (Table 10). After sensitivity analyses, disproportionality signals for obinutuzumab, rituximab and ofatumumab remained consistently robust, whereas the reporting of alemtuzumab became insignificant in the two analyses (Table 11). For the time to onset (TTO) analysis, the median onset time of TLS was 4.5, 1.5 and 2.5 days for rituximab, obinutuzumab and ofatumumab, respectively.

Table 10: TLS with mAbs in CLL: primary disproportionality analysis

[redacted]

Table 11: TLS with mAbs in CLL: sensitivity disproportionality analysis

[redacted]

The authors note 3 key novel findings were identified:

1. TLS appears to be a class effect of CD20 mAbs (obinutuzumab, rituximab, ofatumumab).
2. The disproportionality signal of TLS emerged with various monotherapy and combinational therapy for CLL.
3. Onset of TLS was early (within 5 days) with serious outcomes (death and hospitalisation) recorded in 21.1% and 54.6% of cases, respectively.

Comments:

TLS reported in patients with solid tumours who were treated with monoclonal antibodies (excluding immune checkpoint inhibitors) were identified and included bevacizumab in combination with irinotecan, folinic acid and 5-FU (Hentrich et al) and cetuximab (Krishnan et al, Haroon et al, Matsuyama et al). The solid tumours in these cases were colon cancer in 3 patients and adenocarcinoma in the remaining patient.

3.1.2.1 Immune checkpoint inhibitors (ICIs)

Carrier et al (2020) [26] described a case of tumour lysis syndrome (TLS) in a 55-year-old woman with metastatic triple-negative breast cancer who had received multiple lines of chemotherapy and developed TLS after receiving combined chemoimmunotherapy. She presented to the medical centre with generalised body weakness, sleepiness, anorexia and oliguria 6 days after her first dose of combined chemoimmunotherapy with nab-paclitaxel (100 mg/m^2) and **atezolizumab** (840 mg). Grade 2 TLS was diagnosed based on Cairo-Bishop criteria, promptly treated with IV hydration and a single dose of rasburicase. Her symptoms completely resolved within 4 days. The authors state massive destruction of tumour cells through selective PD-L1 binding by atezolizumab may explain the occurrence of TLS and they believe TLS was purely due to immunotherapy because the patient had previously received multiple lines of chemotherapy without any evidence of subsequent TLS. At the time of publication, rare cases of TLS had been described in patients who received immunotherapy. Fa'ak et al (2019) [27] reported a case in which TLS occurred after the initial dose of atezolizumab for metastatic urothelial cancer. By searching PubMed, the authors identified 4 case reports of TLS from 2014 to 2018: two cases after a single dose of nivolumab [28, 29] and two cases after atezolizumab [30, 31].

A case of TLS in a 79-year-old male patient with metastatic melanoma of the right maxillary sinus and multiple liver metastases who received a single dose of **nivolumab** was described by Sugimoto et al (2020) [32]. Eight days after the nivolumab dose, the patient experienced impaired consciousness accompanied by abnormal laboratory and electrocardiographic findings. He was diagnosed with TLS. Laboratory and electrocardiographic findings improved immediately after continuous hemodiafiltration, however the patient died 22 days after receiving nivolumab. Autopsy revealed massive tumour necrosis in the liver.

A case of TLS following a single dose of nivolumab for relapsed small-cell lung cancer (SCLC) was described by Hayes et al (2021**)** [33]. An 86-year-old female with a history of widely metastatic SCLC with metastasis to the liver, bone and lymph nodes presented to the hospital following a fall due to weakness, dizziness, slurred speech, nausea, vomiting and abdominal pain occurring 6 days after receiving her first nivolumab infusion. After extensive evaluation, the patient was diagnosed with TLS with hyperkalaemia, acute renal failure, hyperphosphatemia and hypocalcaemia. She was treated aggressively with intravenous fluids, rasburicase and sodium polystyrene sulfate (Kayexalate) which resulted in rapid improvement of her electrolytes and renal function. However, despite this and overall symptomatic improvement, over the course of several days, the patient's condition rapidly deteriorated with increasing dyspnoea, lethargy, confusion and eventually death. The authors searched for case reports of TLS with checkpoint blockade therapy as shown in Table 12.

Table 12: Individual case reports of tumour lysis syndrome following checkpoint inhibitor therapy

Avelino et al (2022) [34] described a case of a man in his 60s with squamous cell carcinoma of the lung with brain metastasis treated with **pembrolizumab** who subsequently developed T-cell prolymphocytic leukaemia. He was transferred to hospital with worsening dyspnoea, suspected hyperviscosity syndrome and tumour lysis syndrome. He was intubated and admitted to the critical care unit. Emergent leucapheresis was started due to worsening renal function in the setting of tumour lysis and hyperviscosity syndromes. He continued to deteriorate and required continuous renal replacement therapy. He eventually died from haemodynamic decompensation.

A real-world pharmacovigilance study of **immune checkpoint inhibitor (ICI)**-associated TLS using the US FDA's adverse event reporting system (FAERS) was conducted by Wang et al (2021) [35]. The authors retrieved 164 TLS cases where patients were treated with anti-CTLA-4 (n=14), anti PD-1/PD-L1 (n=113) or anti CTLA-4 + PD-1 (n=37) therapies between the 1st quarter of 2004 and 4th quarter of 2020. The mean TLS onset time associated with anti-CTLA-4, anti PD-1/PD-L1 and anti CTLA-4 + PD-1 was 6 (IQR: 2-39.5), 9 (IQR: 2-40) and 20 (IQR: 7.5-37.75) days, respectively. Four algorithms for signal detection were used with the criteria for each algorithm shown in Table 13. The signal values of combined therapy were higher than those of monotherapies (Table 14). The authors conclude ICI therapies could induce TLS in both solid and haematological malignancies.

Table 13: Criteria of four algorithms for signal detection

Table 14: Detected signals of TLS related to ICIs by four algorithms

[redacted]

3.2 CARM data

There are a total of six individual case reports of tumour lysis syndrome in the CARM database. Of these six reports, one reported lenalidomide as the suspect and two cases were with venetoclax. The remaining three cases involved a tyrosine kinase or monoclonal antibody. [redacted]

- 097340: A patient of unknown age and gender was treated with IV bortezomib and experienced tumour lysis syndrome.
- 110863: A 74-year-old female patient was treated with cyclophosphamide, rituximab and fludarabine [redacted] Other co-suspect medicines included a hydrocortisone-containing skin lotion and oral promethazine. The patient experienced tumour lysis syndrome [redacted]
- 120678: A 70-year-old male experienced tumour lysis syndrome with IV obinutuzumab. [redacted]

4 DISCUSSION AND CONCLUSIONS

Tumour lysis syndrome (TLS) is caused by massive tumour cell lysis with release of large amounts of potassium, phosphate and nucleic acids into the bloodstream. This results in hyperuricaemia, hyperkalaemia, hyperphosphatemia and hypocalcaemia, and could lead to acute kidney injury (AKI) and cardiac arrythmias which could be life-threatening.

TLS most commonly occurs after initiation of cytotoxic therapy in patients with high-grade haematological malignancies, such as acute leukaemia and Burkitt's lymphoma, but can also occur with other tumour types that have a high proliferative rate, large tumour burden, or high sensitivity to cytotoxic therapy.

The incidence of TLS is unclear, partly due to an absence of uniform diagnostic criteria for diagnosis. However, modern cancer therapy with targeted medicines used alone or in combination with conventional cytotoxic agents has led to an increase in the frequency. Identifying patients at risk for TLS is important so that proper prophylactic and curative treatment can be instituted.

Tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) are commonly indicated to treat various types of cancer, including haematological cancers and solid tumours. Because TLS commonly occurs after initiation of cytotoxic treatment, there is a possibility that TKIs and mAbs could cause TLS when treatment is started in patients with cancer.

The literature describing TLS in association with TKIs or mAbs is very sparse and mostly consist of case reports.

TLS is currently listed in the NZ data sheet for some of these medicines and the extent of the information varies between different medicines.

5 ADVICE SOUGHT

The Committee is asked to advise on the following:

- Whether information on tumour lysis syndrome should be included in data sheets for all tyrosine kinase inhibitors and monoclonal antibodies used in cancer treatment. Note that the actions for monitoring for tumour lysis syndrome qualifies for addition to section 4.4 (warnings and precautions) as well as section 4.8 (undesirable effects). However, addition to section 5 (pharmacological properties) is not considered acceptable.

6 REFERENCES

1. Salter, B., et al., *Tyrosine kinase inhibitors and tumor lysis syndrome in hematologic malignancies: A systemic review.* Eur J Haematol, 2022. **109**(2): p. 166-181.
2. Zahavi, D. and L. Weiner, *Monoclonal Antibodies in Cancer Therapy.* Antibodies (Basel), 2020. **9**(3).
3. New Zealand Formulary. *Cytotoxic drugs*. 01 November 2023 [accessed 15 November 2023]; Available from: https://nzf.org.nz/nzf_4381.
4. UpToDate. *Tumor lysis syndrome: Pathogenesis, clinical manifestations, definition, etiology and risk factors*. 24 May 2022 [accessed 10 November 2023]; Available from: https://www.uptodate.com/contents/tumor-lysis-syndrome-pathogenesis-clinical-manifestations-definition-etiology-and-risk-factors.
5. Perissinotti, A.J., et al., *Expert consensus guidelines for the prophylaxis and management of tumor lysis syndrome in the United States: Results of a modified Delphi panel.* Cancer Treat Rev, 2023. **120**: p. 102603.
6. UpToDate. *Tumor lysis syndrome: Prevention and treatment*. 01 April 2022 [accessed 13 November 2023]; Available from: https://www.uptodate.com/contents/tumor-lysis-syndrome-prevention-and-treatment.
7. Lupușoru, G., et al., *Tumor Lysis Syndrome: An Endless Challenge in Onco-Nephrology.* Biomedicines, 2022. **10**(5).
8. Krishnan, G., K. D'Silva, and A. Al-Janadi, *Cetuximab-related tumor lysis syndrome in metastatic colon carcinoma.* J Clin Oncol, 2008. **26**(14): p. 2406-8.
9. Keane, C., A. Henden, and R. Bird, *Catastrophic tumour lysis syndrome following single dose of imatinib.* Eur J Haematol, 2009. **82**(3): p. 244-5.
10. Michels, J., et al., *Sunitinib inducing tumor lysis syndrome in a patient treated for renal carcinoma.* Invest New Drugs, 2010. **28**(5): p. 690-3.
11. Kaur, V. and A. Swami, *Ibrutinib-associated tumor lysis syndrome in a patient with mantle cell lymphoma: A case report.* J Oncol Pharm Pract, 2017. **23**(3): p. 235-239.
12. Titus-Rains, K.S., J.N. Brown, and J.M. Hammond, *Ibrutinib-associated tumor lysis syndrome in chronic lymphocytic leukemia/small lymphocytic lymphoma and mantle cell lymphoma: A case series and review of the literature.* J Oncol Pharm Pract, 2018. **24**(7): p. 544-549.
13. Brener, Z.Z., H. Brener, and A. Losev, *Bruton's tyrosine kinase inhibitors and the kidney: Focus on ibrutinib.* J Oncol Pharm Pract, 2020. **26**(7): p. 1735-1737.
14. Chang, H. and L.Y. Shih, *Imatinib-induced tumor lysis syndrome: report of a case and review of the literature.* Chang Gung Med J, 2008. **31**(5): p. 510-4.
15. Al-Kali, A.F., S. Tfayli, A., *Tumor lysis syndrome after starting treatment with Gleevec in a patient with chronic myelogenous leukemia.* Journal of Clinical Pharmacy and Therapeutics, 2009. **34**: p. 607-610.
16. Ondecker, J., G. Kordic, and K. Jordan, *Tumour lysis syndrome: a rare side effect of imatinib therapy for GIST.* BMJ Case Rep, 2018. **11**(1).
17. Hua, J., et al., *Tumor lysis syndrome soon after treatment with hydroxyurea followed by nilotinib in two patients with chronic-phase chronic myelogenous leukemia.* Int J Hematol, 2013. **98**(2): p. 243-6.

18. van Kalleveen, M.W., M. Walraven, and M.P. Hendriks, *Pazopanib-related tumor lysis syndrome in metastatic clear cell renal cell carcinoma: a case report.* Invest New Drugs, 2018. **36**(3): p. 513-516.
19. Narukawa, T., et al., *Pazopanib after Nivolumab-Induced Tumor Lysis Syndrome in a Patient with Metastatic Clear-Cell Renal Cell Carcinoma.* Case Rep Oncol, 2020. **13**(1): p. 249-254.
20. Saylor, P.J. and T.R. Reid, *Tumor lysis syndrome after treatment of a gastrointestinal stromal tumor with the oral tyrosine kinase inhibitor sunitinib.* J Clin Oncol, 2007. **25**(23): p. 3544-6.
21. Hentrich, M., et al., *Fatal tumor lysis syndrome after irinotecan/5-FU/folinic acid/bevacizumab-containing therapy in a patient heavily pretreated for metastatic colon cancer.* Acta Oncol, 2008. **47**(1): p. 155-6.
22. Haroon, M., et al., *A case of cetuximab-related tumour lysis syndrome in metastatic rectal carcinoma.* NDT Plus, 2010. **3**(3): p. 271-272.
23. Matsuyama, S., et al., *[Tumor lysis syndrome after FOLFIRI+cetuximab for ascending colon cancer].* Nihon Shokakibyo Gakkai Zasshi, 2015. **112**(4): p. 714-20.
24. Shackleton, L., et al., *Laboratory features of tumour lysis syndrome following daratumumab monotherapy in relapsed/refractory multiple myeloma.* EJHaem, 2020. **1**(1): p. 312-314.
25. Xia, S., et al., *Tumor Lysis Syndrome with CD20 Monoclonal Antibodies for Chronic Lymphocytic Leukemia: Signals from the FDA Adverse Event Reporting System.* Clin Drug Investig, 2023. **43**(10): p. 773-783.
26. Carrier, X., S. Gaur, and A. Philipovskiy, *Tumor Lysis Syndrome After a Single Dose of Atezolizumab with Nab-Paclitaxel: A Case Report and Review of Literature.* Am J Case Rep, 2020. **21**: p. e925248.
27. Fa'ak, F., D. Vanegas, and K.M. Osei, *A Case Report of Atezolizumab Induced Tumor Lysis Syndrome.* Am J Case Rep, 2019. **20**: p. 785-789.
28. Brunnhoelz, D.W., J., *Acute tumor lysis syndrome after anti-pd-1 immunotherapy nivolumab for metastatic melanoma.* Journal of Molecular Oncology Research, 2017. **1**(1): p. 5-6.
29. Sater, H.A., et al., *A case report of inflammatory syndrome presenting as tumor lysis syndrome after single dose of nivolumab.* J Cancer Prev Curr Res, 2017. **8**(2): p. 00271.
30. Brunnhoelzl, D.W., M; Trepet, R; Wang, J, *Tumor Lysis Syndrome Following a Single Atezolizumab Infusion for Metastatic Urothelial Carcinoma Involving Both Upper and Lower Tract.* Archives in Cancer Research, 2017. **5**(1): p. 1-5.
31. Herbst, R.S., et al., *Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients.* Nature, 2014. **515**(7528): p. 563-7.
32. Sugimoto, S., et al., *Tumor lysis syndrome in a patient with metastatic melanoma treated with nivolumab.* Clin J Gastroenterol, 2020. **13**(5): p. 935-939.
33. Hayes, S.M., C. Wiese, and R. Schneidewend, *Tumor Lysis Syndrome following a Single Dose of Nivolumab for Relapsed Small-Cell Lung Cancer.* Case Rep Oncol, 2021. **14**(3): p. 1652-1659.
34. Avelino, A.R., et al., *T-cell prolymphocytic leukaemia associated with immune checkpoint inhibitor (pembrolizumab).* BMJ Case Rep, 2022. **15**(3).
35. Wang, L., et al., *Immune Checkpoint Inhibitor-Associated Tumor Lysis Syndrome: A Real-World Pharmacovigilance Study.* Front Pharmacol, 2021. **12**: p. 679207.