

Certification after Treatment for Malignancy of the Immune System Civil Aviation

ALL CLASS ONE ASSESSMENTS SHALL BE REFERRED TO THE UK CAA'S AUTHORITY MEDICAL SECTION (AMS).

CLASS TWO ASSESSMENTS MAY BE REFERRED TO THE UK CAA'S AMS BY THE AME. FOR CLASS TWO CERTIFICATION:

- Fitness for Class 1 OML is considered equivalent to unrestricted Class 2 certification.
- Class 2 certification with an Operational Safety pilot Limitation (OSL) is possible for all tumour types of the immune system provided the overriding prerequisites for certification have been satisfied.

Introduction

The assessment of an individual's fitness to fly after treatment for a malignancy of the immune system is complex as such tumours are a heterogeneous group and vary markedly in terms of clinical patterns of spread, response to treatment, sites of relapse and prognosis. There are more than 25 diseases classified as lymphoid malignancies in the current World Health Organization classification (Table 1).

Table 1.

Modern Classification of Malignancies Involving the Immune System (according to the World Health Organisation (WHO))

Precursor cell Lymphoma

Lymphoblastic lymphoma

T-cell

B-cell

Peripheral B-cell Neoplasms

- B-chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B prolymphocytic lymphoma
- Lymphoplasmacytic lymphoma
- Mantle cell lymphoma
- Follicular lymphoma
- Marginal zone B-cell lymphoma
 - Extranodal (MALT)
 - Nodal
- Hairy cell leukaemia
- Diffuse large B-cell lymphoma
- Burkitt lymphoma and Burkitt-like lymphoma
- Plasmacytoma and myeloma

Peripheral T And NK Cell Neoplasms

- T prolymphocytic leukaemia
- T cell granular lymphocytic leukaemia
- Aggressive NK cell leukaemia
- Mycosis fungoides and Sezary syndrome
- Peripheral T-cell lymphoma not otherwise characterised
- Angioimmunoblastic T-cell lymphoma
- Extranodal NK/T cell lymphoma of nasal and nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic gamma delta T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Anaplastic large cell lymphoma (T/null cell)
 - Primary systemic type
 - Primary cutaneous type
- Adult T-cell lymphoma/leukaemia (HTLV1 positive)

Hodgkin's Lymphoma

Legend HTLV = Human T-cell Lymphoma/Leukaemia Virus 1

NK = Natural Killer

WHO = World Health Organisation

MALT = Mucosa-Associated Lymphoid Tissue

A detailed oncology report will be required and the following criteria should be satisfied before certification can be considered:

Prerequisites for Certification

- Normally a minimum of 6 weeks since completion of radiotherapy. If radiotherapy has been given to the chest and cardiac tissue included within the radiation field, cardiac evaluation should be satisfactory;
- Minimum of 2 months since completion of chemotherapy (excluding anthracyclines);
- Minimum of 6 months since completion of anthracycline chemotherapy, and cardiac evaluation should be satisfactory;
- Satisfactory haematological parameters Haemoglobin >12g/dl (male) or >11.5g/dl (female), Platelets >100,000/mm³, (or > 50,000 mm³ provided the trend is upwards and thrombocytopaenia is secondary to therapy and not disease), White Cell Count (WCC) > 3,000/mm³ and Neutrophils >1,000/mm³;
- In continuing clinical remission without symptoms of potential flight safety importance;
- No history of central nervous system involvement;
- No continuing side-effects from treatment;
- 6 monthly Full Blood Count (to include WCC and differential) and Biochemical Profile (to include Liver Function Tests) for 5 years then annually (exception - see group G below);
- Regular clinical follow up is being undertaken and satisfactory reports submitted to the Authority Medical Section.

Certificatory Assessment

Malignancies of the immune system, including lymphoid leukaemias, may be grouped according to potential for long-term complete remission ('cure') and prolonged relapse-free survival (Table 2). All assessments are after treatment for primary disease except where specifically stated. A longer time period should normally elapse before returning to flying after treatment for relapse than is required after primary treatment.

The prognosis for some patients within a particular diagnostic category may be very different from the median and an assessment of prognostic factors can allow a more accurate prediction of the probability of relapse-free-survival, event-free-survival and overall survival. These probabilities will change with time as the clinical condition progresses. In addition transformation to a higher grade of lymphoma may occur. Relevant clinical information should be taken into account on a continuous basis when considering fitness for pilot certification.

The 'potential cure' for each group is an 'average' for the diagnoses listed. Within each group an individual may be assessed as having a better prognosis (good prognostic factors) or worse prognosis (adverse prognostic factors) than the 'average'. This may allow an earlier return to certification or delay the return to flying, according to individual circumstances. Relapses may present with an acute incapacitating event such as a retinal bleed, neuropathy, seizure or abdominal pain. However, it is more likely to be associated with symptoms such as fatigue, fever, sweats, headache, nausea, vomiting or diarrhoea. Any of these could adversely affect flight safety.

Certification following treatment for Lymphoid Malignancy

Group	Potential Cure Rates	Diagnosis	Minimum time to certification after completion of treatment	
			Class 1 OML Class 2 Unrestricted	Class 1 Unrestricted
Group A	>80%	MZ MALT (stage I/II) DLBC (stage I/II) ALCL (stage I/II) Solitary Plasmacytoma	Once pre-requisites satisfied	2-6 months (dependent on type of chemotherapy)
Group B	50%	Primary Mediastinal Lymphoma	6 months	2 years
Group C	30%	DLBC (stage III/IV) ALCL (stage III/IV) including ALK negative MZ MALT (stage III/IV)	1 year	2 years
Group D	30%	Burkitt's/Burkitt-like Lymphoma Pre-B Lymphoblastic Lymphoma/Leukaemia B-cell Lymphoblastic Lymphoma/Leukaemia Multiple myeloma (post BMT-csd)	2 years	3 years
Group E	10-20%	Pre-T ALL Pre-T LBL Mantle cell lymphoma (2 years symptom free)	2 years	3 years
Group F	<10% and moderately aggressive	Other Peripheral T-cell and NK Lymphoma/Leukaemia Adult T-cell Lymphoma (HTLV+) Mantle Cell Lymphoma Multiple Myeloma (Other) Subcutaneous panniculitis T-cell lymphoma	5 years See text	N/A
Group G	Considered incurable using current therapy but indolent	Follicular Lymphoma SLL B-cell CLL Lymphoplasmacytic Lymphoma T-cell Prolymphocytic Leukaemia T-cell Granular Lymphocytic Leukaemia Hairy Cell Leukaemia MZ B-cell Lymphoma (nodal/splenic)	See text	See text
Group H	A miscellaneous group with a generally good prognosis	Primary Cutaneous Lymphoma	Once wound healed	Once wound healed
Group I	Poor prognosis	Mycosis fungoides/Sezary syndrome	See text	See text
Group J	> 60%	Hodgkin's lymphoma	6 months	2 years

Legend	ALCL ALK	Anaplastic Large Cell Lymphoma Anaplastic Lymphoma Kinase	
	BMT-csd	Bone Marrow Transplantation – compatible sibling donor	
	CLL	Chronic Lymphocytic Leukaemia	
	DLBC	Diffuse Large B-cell Lymphoma	
	HTLV	Human T-cell Lymphoma/Leukaemia Virus 1	
	MZ	Marginal Zone Lymphoma	
	MALT	Mucosa-Associated Lymphoid Tissue	
	N/A	Not applicable	
	NK	Natural Killer	
	Pre-T ALL	Precursor T-cell Lymphoblastic Leukaemia	
	Pre-T LBL	Precursor T-cell Lymphoblastic Lymphoma	
	SLL	Small Lymphocytic (B-cell) Lymphoma	

Group F

Most of these conditions have a very poor prognosis and relapse is common. However, in some, a durable remission may be achieved and individual consideration can be given to cases that have been in continuous remission for 3 years.

Group G

A remission of an indolent lymphoma may be complete or associated with the presence of small amounts of residual disease after treatment. Licence holders with a good partial remission (minor residual bone marrow involvement or a small amount of residual lymphadenopathy present on Computerised Tomography (CT) scan), which is not progressive, may be certificated. Persistent evidence of liver involvement or palpable enlargement of the spleen will disqualify.

Follicular lymphoma

A 3 monthly full blood count to include a differential white cell count and biochemical profile to include liver function tests is required. Six-monthly follow up is acceptable after 5 years complete remission.

a) Certification After Primary Treatment

This may be possible if the International Prognostic Index (IPI) is low and there is no evidence of progressive disease.

Class 1 OML at 3 months

Unrestricted at 1 year

Class 2 Unrestricted at 3 months

b) Certification After Treatment for Relapse

This may be possible if the relapse was only nodal, performance status was good and serum lactate dehydrogenase was normal at the time of relapse. Additionally for Class 1, if the relapse occurred within 3 years of previous treatment, an OML will be applied to the licence. Thereafter unrestricted certification is only possible if sustained remission is achieved (more than 3 years).

Class 1 OML at 3 months

Unrestricted at 2 years (unless initial remission period < 3 years)

Class 2 Unrestricted at 3 months

Chronic Lymphocytic Leukaemia/Small Lymphocytic (B-cell) Lymphoma

a) Stable Stage A disease – not requiring treatment

Certification is possible as soon as the disease can be shown to be stable and non-progressive.

Class 1 Unrestricted at 3 months

Class 2 Unrestricted at 3 months

b) Certification after Primary Treatment

Treatment may be indicated for progressive Stage A (lymphocytosis alone or with a small amount of lymphadenopathy) or Stage B + (with substantial lymphadenopathy, splenomegaly, hepatomegaly or cytopaenias). If a good partial remission is achieved with treatment and there is no evidence of progressive disease, certification may be possible.

Class 1 OML at 3 months

Unrestricted at 1 year

Class 2 Unrestricted at 3 months

Marginal Zone B-cell Lymphoma (nodal/splenic)

Class 1 OML at 2 years

Unrestricted at 3 years

Class 2 OSL once pre-requisites for certification satisfied

Unrestricted at 2 years

Lymphoplasmacytic Lymphoma

Certification is not possible if the performance status is poor at presentation, if two or more cytopaenias are present or there is hepato/splenomegaly.

a) Stable early disease not requiring treatment

Certification is possible if there is a low IPI at presentation and the disease can be shown to be stable and non-progressive.

Class 1 OML at 3 months

Unrestricted at 1 year

Class 2 Unrestricted at 3 months

b) Certification after Primary Treatment

Certification is possible for those who achieve a complete or good partial remission.

Class 1 OML at 6 months

Unrestricted at 2 years

Class 2 OSL once pre-requisites for certification satisfied

Unrestricted at 6 months

Hairy cell Leukaemia

a) Stable early disease not requiring treatment

Class 1 OML at 3 months

Unrestricted at 1 year

Class 2 Unrestricted at 3 months

b) Certification after Primary Treatment

Certification is possible for those who achieve a complete or good partial remission following interferon therapy. A relapse less than 3 years after treatment and requirement for chemotherapy will disqualify.

Class 1 OML at 2 years

Unrestricted at 2 years

Class 2 OSL once pre-requisites for certification satisfied

Unrestricted at 2 years

Group H

Primary Cutaneous Lymphoma

When primary therapy or treatment for relapsing lymphoma only involving the skin has been completed, and at least a partial remission has been achieved with recovery from any complications of therapy, unrestricted Class 1 certification is possible.

Group I

Sezary syndrome and Mycosis fungoides

This is characterised by involvement of the blood and bone marrow and in view of the poor prognosis requires more careful consideration. In those who achieve a stable, good partial remission following primary treatment certification may be considered.

Group J

Hodgkin's Lymphoma

The overall survival of patients with Hodgkin's lymphoma depends on stage (10 year survival 95% for stage IA, 60% for stage IV) and prognostic factors at presentation. Adverse prognostic factors include serum albumin <4 g/dl, haemoglobin <10.5 g/dl, <45 years, male, WCC >15,000/mm³, lymphocytes <600/mm³.

80% of relapses occur within the first 2-3 years after treatment. Relapses are extremely unlikely to present with symptoms that cause sudden incapacitation.

Substantial improvements in radiotherapy and combination chemotherapy during the late 20th Century dramatically increased survival. The use of autologous stem cell transplantation has recently provided a further treatment option for relapse and approximately 50% will achieve prolonged survival using this method.

Long term follow up is important as radiotherapy and chemotherapy both result in an increased risk of second malignancy, either a solid tumour or a further lymphoid malignancy, beyond ten years after treatment. The relative risk is higher for younger patients as malignancy is uncommon in this age group.

Prolonged Long-Term Complete Remission

Unrestricted Class 1 is possible for all tumour types of the immune system if a period of 5 years or more has elapsed since completion of treatment with no evidence of relapse of disease during this period.

Bone Marrow Transplantation

Fitness for recertification after bone marrow transplantation will be dependent on the individual circumstances. Lack of adverse prognostic features and the underlying diagnosis will be important and, in the case of allogeneic transplantation, the lack of continuing graft-versus-host disease or immunosuppression.

Autologous Stem Cell Transplantation:

Class 1 OML at 1 year after transplantation

Unrestricted at 2 years after transplantation

Class 2 Unrestricted at 1 year after transplantation

Allogeneic transplantation:

Class 1 OML at 2 years after transplantation

Unrestricted at 3 years after transplantation

Class 2 OSL at 1 year after transplantation

Unrestricted at 2 years after transplantation

Definitions

International Prognostic Index (IPI)

The IPI is the scoring system frequently used as a prognostic indicator for lymphoid malignancies. It takes the clinical features at presentation into account. The overall prognosis is related to the histological diagnosis (World Health Organization classification) and the IPI.

Prognostic Factor	Score
Age < 60 years	0
Age > 60 years	1
Stage I-II	0
Stage III-IV	1
Serum Lactate Dehydrogenase Low	0
Serum Lactate Dehydrogenase High	1
Number of extranodal sites <2	0
Number of extranodal sites >2	1
Performance Status 0-1	0
Performance Status 2+	1

A **Low** score = 0-2

A High score = 3 - 5

Staging System

The accepted staging system is a modification of the Ann Arbor staging system.

Stage I 1 lymph node site involved;

Stage II 2 or more lymph node sites involved either above or below the diaphragm;

Stage III nodal sites involved both above and below the diaphragm;

Stage IV extranodal sites such as bone marrow, lung and liver involved in addition to the

above.

NB When there is only a single localised extranodal site of involvement such as salivary gland, thyroid, orbit, testis, tonsil, stomach or cervix, the appropriate stage would be annotated with E "Patients who present with weight loss or fever/sweats are classified as having B symptoms" (designated B).

Performance Status

Performance status is scored according to the Eastern Co-operative Oncology Group Scale (Ref: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.):

- 0 Fully Active
- 1 Ambulatory
- 2 Confined to bed/chair <50% of the daytime
- 3 Confined to bed/chair >50% of the daytime
- 4 Totally confined to bed/chair