Non-Hodgkin's lymphoma

NICE guideline: short version

Draft for consultation, January 2016

This guideline covers the diagnosis and management of non-Hodgkin's lymphoma in adults and young people (16 years and older). There are a number of different subtypes of non-Hodgkin's lymphoma, and diagnosis can be complex. Improvements in understanding of the biology of non-Hodgkin's lymphoma have led to more specific and targeted treatments. The subtypes covered in this guideline are diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, MALT lymphoma, Burkitt lymphoma and peripheral T-cell lymphoma. Treatments include radiotherapy, immunochemotherapy and stem cell transplantation.

Who is it for?

- Healthcare professionals who diagnose and treat people with non-Hodgkin's lymphoma.
- People with non-Hodgkin's lymphoma, their families and carers.

This version of the guideline contains the draft recommendations, context and recommendations for research. Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the guideline committee's discussion and the evidence reviews (in the full guideline), the scope, and details of the committee and any declarations of interest.

Contents

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Diagnosis

Type of biopsy

1.1.1 Consider an excision biopsy as the first diagnostic procedure for people with suspected non-Hodgkin's lymphoma at first presentation.

1.1.2 In people with suspected non-Hodgkin's lymphoma for whom the risk of a surgical procedure outweighs the potential benefits of an excision biopsy, consider a needle core biopsy procedure. Take the maximum number of cores of the largest possible calibre.

1.1.3 For people with suspected non-Hodgkin's lymphoma in whom a diagnosis is not possible after a needle core biopsy procedure, offer an excision biopsy (if surgically feasible) in preference to a second needle core biopsy procedure.

1.1.4 Pathology departments should ensure that tissue is conserved when handling needle core biopsies.

Diagnosing B-cell lymphomas: gene testing strategies

1.1.5 Consider using FISH (fluorescence in situ hybridisation) to identify a *MYC* rearrangement in all people newly presenting with histologically high-grade B-cell lymphoma.

1.1.6 If a *MYC* rearrangement is found, use FISH to identify the immunoglobulin partner and the presence of *BCL2* and *BCL6* rearrangements.

Stratifying high-grade B-cell lymphomas using laboratory techniques

1.1.7 Do not use immunohistochemistry to assess the prognostic value associated with cell of origin in people with diffuse large B-cell lymphoma.

1.1.8 Interpret FISH results (*MYC*, *BCL2* and *BCL6* rearrangements) in the context of other prognostic factors (particularly the person's age and International Prognostic Index [IPI]).

1.1.9 Explain FISH results and their potential prognostic value to people with B-cell lymphoma.

1.2 Staging using FDG-PET-CT (fluorodeoxyglucose-positron emission topography-CT)

Confirming staging

1.2.1 Offer FDG-PET-CT imaging to confirm staging for people diagnosed with:

- stage I diffuse large B-cell lymphoma by clinical and CT criteria
- stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field
- stage I or II Burkitt lymphoma with other low-risk features.

1.2.2 Do not routinely offer FDG-PET-CT imaging to confirm staging for people diagnosed with:

- diffuse large B-cell lymphoma that is stage II or above
- follicular lymphoma that is non-localised stage II or above
- mantle cell lymphoma
- MALT lymphoma (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue)
- Burkitt lymphoma with high-risk features, or stage III or IV.

Assessing response to treatment for diffuse large B-cell lymphoma

1.2.3 Do not routinely offer FDG-PET-CT imaging for interim assessment during treatment for diffuse large B-cell lymphoma.

End-of-treatment assessment

1.2.4 Offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:

- diffuse large B-cell lymphoma
- Burkitt lymphoma.

1.2.5 Do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:

- follicular lymphoma
- mantle cell lymphoma
- MALT lymphoma.

1.2.6 Consider FDG-PET-CT imaging to assess response to treatment before autologous stem cell transplantation for people with high-grade non-Hodgkin's lymphoma.

1.3 Management of follicular lymphoma

First-line treatment for early-stage follicular lymphoma

1.3.1 Offer involved field radiotherapy as first-line treatment to people with localised stage IIA follicular lymphoma.

1.3.2 Consider 'watch and wait' (observation without therapy) as first-line treatment for people with stage IIA follicular lymphoma who are asymptomatic and for whom treatment with a single radiotherapy volume is not suitable.

1.3.3 Offer the same treatment as for advanced-stage (stages III and IV) disease to people with stage IIA follicular lymphoma who are symptomatic and for whom radiotherapy is not suitable.

Consolidation therapy

1.3.4 Offer consolidation with autologous stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial) who have not already had a transplant and who are fit enough for transplantation.

1.3.5 Consider consolidation with allogeneic stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial):

- who are fit enough for transplantation **and**
- for whom a suitable donor can be found **and**
- when autologous stem cell transplantation has not resulted in remission or is inappropriate (for example, because stem cell harvesting is not possible).

Treating advanced-stage asymptomatic follicular lymphoma

1.3.6 Offer rituximab induction therapy[1] to people with advanced-stage (stages III and IV) follicular lymphoma who are asymptomatic.

Treating advanced-stage symptomatic follicular lymphoma

1.3.7 Rituximab, in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP)
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi) or
- chlorambucil

is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people. [This

[1] At the time of consultation (January 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The evidence reviewed for the guideline supports the standard dosage of 4 doses of 375 mg/m^2 at weekly intervals.

recommendation is from Rituximab for the first-line treatment of stage III-IV follicular lymphoma (NICE technology appraisal guidance 243).]

Treating advanced-stage relapsed or refractory follicular lymphoma

The recommendations in this section are from Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (NICE technology appraisal guidance 137).

1.3.8 Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma.

1.3.9 Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab.

1.3.10 Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

Treating transformed follicular lymphoma

1.3.11 Consider consolidation with autologous stem cell transplantation for people with transformation of previously diagnosed follicular lymphoma that has responded to treatment and who are fit enough for transplantation.

1.3.12 Consider consolidation with autologous or allogeneic stem cell transplantation for people with transformation of follicular lymphoma who need more than 1 line of treatment for a response and who are fit enough for transplantation.

1.3.13 Do not offer consolidation with high-dose therapy and autologous or allogeneic stem cell transplantation to people presenting with concurrent diagnoses of follicular lymphoma and diffuse large B-cell lymphoma that have responded to first-line treatment.

1.4 Management of MALT lymphoma

First-line treatment

Gastric MALT lymphoma: localised disease

1.4.1 Offer 1 or more lines of *Helicobacter pylori* eradication therapy, without any concurrent therapy, to people with *H. pylori*-positive gastric MALT lymphoma.

1.4.2 Consider *H. pylori* eradication therapy for people with *H. pylori*-negative gastric MALT lymphoma.

1.4.3 Consider 'watch and wait' (observation without therapy) for people with gastric MALT lymphoma that responds clinically and endoscopically to *H. pylori* eradication therapy but who have residual disease shown by surveillance biopsies of the stomach, unless high-risk features are present.

1.4.4 For people with residual MALT lymphoma after *H. pylori* eradication therapy who are at high risk of progression [*H. pylori*-negative at initial presentation or t(11:18) translocation], consider a choice of the following, in discussion with the person:

- chemotherapy (for example, chlorambucil or CVP) in combination with rituximab **or**
- gastric radiotherapy.

1.4.5 For people with progressive gastric MALT lymphoma, offer a choice of:

- chemotherapy (for example, chlorambucil or CVP) in combination with rituximab **or**
- gastric radiotherapy.

Gastric MALT lymphoma: disseminated disease

1.4.6 Offer *H. pylori* eradication therapy to people with disseminated *H. pylori*-positive gastric MALT lymphoma, as described in the NICE guideline on gastro-oesophageal reflux disease and dyspepsia in adults.

1.4.7 Offer chemotherapy (for example, chlorambucil or CVP) in combination with rituximab to people with disseminated gastric MALT lymphoma who need treatment – for example, people who are symptomatic or with threatened vital organ function.

1.4.8 Consider 'watch and wait' (observation without therapy) for people with disseminated gastric MALT lymphoma who are asymptomatic and do not have threatened vital organ function.

Non-gastric MALT lymphoma

1.4.9 For people with non-gastric MALT lymphoma, take into account the following before recommending any treatment:

- site of involvement and potential for organ dysfunction
- whether it is localised or disseminated
- the morbidity associated with any treatment proposed
- the person's overall fitness.

1.4.10 Offer chemotherapy (for example, chlorambucil or CVP) in combination with rituximab to people with non-gastric MALT lymphoma for whom radiotherapy is not suitable or who have disseminated disease and need treatment.

1.4.11 Consider radiotherapy for people with localised disease sites of non-gastric MALT lymphoma, irrespective of stage.

1.4.12 Consider 'watch and wait' (observation without therapy) for people with clinically non-progressive localised non-gastric MALT lymphoma that is unlikely to result in vital organ dysfunction, who are asymptomatic and for whom radiotherapy is not suitable.

1.5 Management of mantle cell lymphoma

First-line treatment

1.5.1 Offer chemotherapy in combination with rituximab as first-line treatment for people with advanced-stage mantle cell lymphoma who are symptomatic. Take the person's fitness into account when deciding on the intensity of chemotherapy.

1.5.2 Consider cytarabine-containing immunochemotherapy for people with advanced-stage mantle cell lymphoma who are fit enough to tolerate an intensive approach.

1.5.3 Consider radiotherapy for people with localised stage I or II mantle cell lymphoma.

1.5.4 Consider 'watch and wait' (observation without therapy) until disease progression for people with clinically non-progressive mantle cell lymphoma who are asymptomatic and for whom radiotherapy is not suitable.

1.5.5 Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable. [This recommendation is from Bortezomib for previously untreated mantle cell lymphoma (NICE technology appraisal guidance 370).]

Consolidation therapy

1.5.6 Consider consolidation with autologous stem cell transplantation for people with chemosensitive mantle cell lymphoma (that is, there has been at least a partial response to induction chemotherapy) who are fit enough for transplantation.

Maintenance strategies

1.5.7 Consider maintenance rituximab[2], every 2 months until disease progression, for people with newly diagnosed mantle cell lymphoma who are not fit enough for high-dose chemotherapy and where there has been a response to R-CHOP-based immunochemotherapy.

1.5.8 Consider maintenance rituximab[3], every 2 months for 3 years, for people with newly diagnosed mantle cell lymphoma who are in remission after cytarabine-based induction and high-dose chemotherapy.

1.6 Management of diffuse large B-cell lymphoma

Radiotherapy in first-line treatment

1.6.1 Consider consolidation radiotherapy delivering 30 Gy to sites involved with bulk disease at diagnosis for people with advanced-stage diffuse large B-cell lymphoma that has responded to first-line immunochemotherapy. For each person, balance the possible late effects of radiotherapy with the possible increased need for salvage therapy if it is omitted, and discuss the options with them.

First-line treatment of CD20-positive diffuse large B-cell lymphoma

The recommendations in this section are from Rituximab for aggressive non-Hodgkin's lymphoma (NICE technology appraisal guidance 65).

1.6.2 Rituximab is recommended for use in combination with a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for the first-line treatment of people with CD20-positive diffuse large-B-cell

[2] At the time of consultation (January 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The evidence reviewed for the guideline supports a dosage of 375 mg/m^2 every 2 months until disease progression.

[3] At the time of consultation (January 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The evidence reviewed for the guideline supports a dosage of 375 mg/m^2 every 2 months for 3 years.

lymphoma at clinical stage II, III or IV. Rituximab is not recommended for use when CHOP is contraindicated.

1.6.3 The clinical and cost effectiveness of rituximab in patients with localised disease (Stage I) has not been established. It is recommended that rituximab be used in these circumstances only as part of ongoing or new clinical studies.

1.6.4 A specialist in the treatment of lymphomas should supervise the use of rituximab in combination with CHOP for the treatment of diffuse large-B-cell lymphoma.

Central nervous system prophylaxis

1.6.5 Explain to people with diffuse large B-cell lymphoma that they have an increased risk of central nervous system lymphoma if the testis, breast, adrenal gland or kidney is affected.

1.6.6 Explain to people with diffuse large B-cell lymphoma that they may have an increased risk of central nervous system lymphoma if they have 2 or more of the following, and that the level of risk increases with the number of factors involved:

- elevated lactate dehydrogenase (LDH)
- age over 60 years
- poor performance status (ECOG score of 2 or more)
- more than one extranodal site involved
- stage III or IV disease.

1.6.7 Offer central nervous system-directed prophylactic therapy to people with diffuse large B-cell lymphoma:

- that involves the testis, breast, adrenal gland or kidney **or**
- who have 4 or 5 factors associated with increased risk of central nervous system relapse (see recommendation 1.6.6).

1.6.8 Consider central nervous system-directed prophylactic therapy for people with diffuse large B-cell lymphoma who have 2 or 3 factors that are associated with increased risk of central nervous system relapse (see recommendation 1.6.6).

Salvage therapy

1.6.9 Offer salvage therapy with multi-agent immunochemotherapy to people with relapsed or refractory diffuse large B-cell lymphoma who are fit enough to tolerate intensive therapy:

- explain that this is primarily to obtain sufficient response to allow consolidation with autologous or allogeneic stem cell transplantation, but is also beneficial even if not followed by transplantation
- consider R-GDP immunochemotherapy, which is as effective as other commonly used salvage regimens and less toxic.

1.6.10 Offer consolidation with autologous stem cell transplantation to people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial response to chemotherapy) who are fit enough for transplantation.

1.6.11 Consider consolidation with allogeneic stem cell transplantation for people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial response to chemotherapy):

- that relapses after autologous stem cell transplantation **or**
- in whom stem cell harvesting is not possible.

1.7 Management of Burkitt lymphoma

First-line treatment

1.7.1 Offer intensive immunochemotherapy to people with Burkitt lymphoma who are fit enough to tolerate it. Consider using one of the following:

- R-BFM
- R-CODOX-M

- R-HyperCVAD (HDMTX)
- R-LMB.

1.7.2 For people with low-risk Burkitt lymphoma, consider using the less intensive DA-EPOCH-R regimen, alone or supplemented with intravenous and/or intrathecal methotrexate.

1.7.3 Offer less intensive immunochemotherapy to people with Burkitt lymphoma who are not fit enough to tolerate intensive chemotherapy Consider using one of the following, alone or supplemented with intravenous and/or intrathecal methotrexate:

- R-CHOP
- R-CHEOP
- DA-EPOCH-R.

1.8 Management of peripheral T-cell lymphoma

First-line treatment

1.8.1 Consider CHOP chemotherapy as first-line treatment for people with peripheral T-cell lymphoma.

Consolidation therapy

1.8.2 Consider consolidation with autologous stem cell transplantation for people with chemosensitive peripheral T-cell lymphoma (that is, there has been at least a partial response to first-line chemotherapy) who are fit enough for transplantation.

1.9 Information and support

1.9.1 To help people with non-Hodgkin's lymphoma (and their family members or carers as appropriate) to make decisions about care, follow the recommendations in the NICE guideline on patient experience in adult NHS services and the recommendations about patient-centred care in the NICE guideline on improving outcomes in haematological cancers. Pay particular attention to the following areas:

- establishing the best way of communicating with the person
- timing and format of information
- information about treatment, including benefits, short-term risks and late effects
- financial support and benefit advice
- fertility issues
- sexual function
- support groups
- access to wellbeing services.

1.9.2 Give people with non-Hodgkin's lymphoma (and their family members or carers as appropriate) detailed information about the nature and purpose of diagnostic and staging tests, including:

- bone marrow biopsies
- central line insertion
- core and excision biopsies
- CT and PET-CT scans
- lumbar punctures.

1.9.3 If 'watch and wait' (observation without therapy) is suggested for a person with non-Hodgkin's lymphoma:

- explain to them (and their family members or carers as appropriate) about what this involves and why it is being advised
- address any increased anxiety that results from this approach.

1.9.4 Explain (at an appropriate time) to people with low-grade non-Hodgkin’s lymphoma (and their family members or carers as appropriate) about the possibility of transformation to high-grade lymphoma.

1.9.5 Ensure that people with non-Hodgkin’s lymphoma have:

- a named key worker at diagnosis and during treatment **and**
- contact details for the specialist team after treatment.

1.9.6 Discuss exercise and lifestyle advice with people with non-Hodgkin's lymphoma from diagnosis onwards.

1.10 Follow-up for people with diffuse large B-cell lymphoma

1.10.1 For people in complete remission after first-line treatment with curative intent for diffuse large B-cell lymphoma:

- consider regular clinical assessment for the first 3 years after completing treatment
- offer urgent appointments to people who experience a recurrence of lymphoma symptoms or new symptoms that suggest disease relapse
- do not offer LDH surveillance for detecting relapse
- do not offer routine surveillance imaging (including chest X-ray, CT and PET-CT) for detecting relapse in people who are asymptomatic
- consider stopping regular clinical assessment aimed at detecting relapse for people in ongoing complete remission 3 years after completing treatment.

1.11 Survivorship

1.11.1 Provide end-of-treatment summaries for people with non-Hodgkin's lymphoma (and their GPs). Discuss these with the person, highlighting personal and general risk factors, including late effects related to their lymphoma type and/or its treatment.

1.11.2 Offer education to people with non-Hodgkin's lymphoma when they complete treatment about how to recognise possible relapse and late effects of treatment.

1.11.3 At 3 years after a person with non-Hodgkin's lymphoma completes a course of treatment, consider switching surveillance of late effects of treatment to nurse-led or GP-led services.

Context

Non-Hodgkin's lymphoma is the sixth most common cancer in the UK. There are many different subtypes of the disease, with markedly different clinical courses and

requirements for therapy. Diagnosing non-Hodgkin's lymphoma and the precise subtype is challenging, and optimising the diagnostic process is central to improved management. Significant improvements in our understanding of the biology of non-Hodgkin's lymphoma have contributed to improved diagnosis and also allowed for more targeted therapies.

The treatment of non-Hodgkin's lymphoma has been a beacon for the development of specific treatment strategies (now applied to many other forms of cancer), but paradoxically there is a paucity of large randomised clinical trials to define best practice in treating the various subtypes. As a consequence there are considerable differences between centres and countries in the ways in which some subtypes of the disease are diagnosed and managed.

There have been some improvements in outcome for people with non-Hodgkin's lymphoma in the last decade, but these have been relatively modest and there is still a need for improvement. This is a rapidly developing field, with a number of new therapies proving to be exciting in initial studies. It is too soon, however, to judge their long-term impact, and ongoing assessment of these new agents compared with standard therapy will be needed.

This guideline covers adults and young people (16 years and older) who are referred to secondary care with suspected non-Hodgkin's lymphoma, or who have newly diagnosed or relapsed non-Hodgkin's lymphoma. It addresses a number of areas where there is uncertainty or variation clinical practice, in relation to diagnosing non-Hodgkin's lymphoma and management of the subtypes at different times in the course of the disease. It is not intended as a comprehensive guide to diagnosing and treating lymphomas. Topics include the best type of biopsy for diagnosis, genetic testing, the role of FDG-PET-CT imaging in staging, patient information needs and survivorship. Management of the more common subtypes is covered: that is, follicular lymphoma, MALT lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma and peripheral T-cell lymphoma.

This guideline aims to facilitate standardisation of practice in treating non-Hodgkin's lymphoma. But because of the rapid development of new therapies as a result of

improved understanding of the biology of the disease, continual re-evaluation will be essential.

More information

To find out what NICE has said on topics related to this guideline, see our web pages on blood and bone marrow cancers and complications of cancer .

Recommendations for research

The guideline committee has made the following recommendations for research.

1 Factors predicting outcomes for people with high-grade transformation of follicular lymphoma

In people with high-grade transformation of follicular lymphoma, which biological and clinical factors predict good outcomes with immunochemotherapy alone?

Why this is important

Before rituximab, it was accepted that high-grade transformation of follicular lymphoma to diffuse large B-cell lymphoma portended a poor prognosis. Recent data suggests that although transformation remains an important clinical event, outcomes have improved. It is unclear which people are likely to do well with conventional treatment (such as R-CHOP) and which people may benefit from intensive treatment with, for example, high-dose therapy and autologous stem cell transplantation. Many factors are likely to influence outcome, including clinical factors (such as age, stage at transformation and extranodal involvement at transformation), radiological findings (such as early improvement of disease identified using an interim FDG-PET-CT scan) and molecular factors (such as certain driver mutations present at transformation, the presence of *MYC* translocation and response of circulating tumour DNA to treatment). A better understanding of which factors are associated with high-risk or low-risk disease would enable therapy to be tailored to the person's needs, reducing unnecessary toxicity for people at low risk and reserving intensive therapy for people at high risk. Outcomes of interest include progression-free survival and overall survival in subgroups defined by clinical factors, radiological findings and molecular analyses.

2 Radiotherapy in first-line treatment of diffuse large B-cell lymphoma

In people presenting with diffuse large B-cell lymphoma and sites of bulky disease, are outcomes improved by radiotherapy to the those sites following a full course of chemotherapy?

Why this is important

The role of radiotherapy to sites of original bulky disease in treating diffuse large B-cell lymphoma is uncertain. Some clinical teams will consider radiotherapy in this setting while others will not because of concerns about morbidity and late effects of treatment. In a recent randomised trial of chemotherapy in people with diffuse large B-cell lymphoma over 60 years old, people having radiotherapy were identified and compared with a cohort having no radiotherapy. Significant improvements in event-free, progression-free and overall survival were seen in the group having radiotherapy. These results have encouraged some teams to reconsider radiotherapy for bulky diffuse large B-cell lymphoma. A definitive randomised trial is needed to address this question. Outcomes of interest include overall survival, disease-free survival, progression-free survival, treatment-related mortality, treatment-related morbidity, health-related quality of life, patient satisfaction, patient preference and overall response rate (complete or partial remission).

ISBN: