Treatment of malignant lymphoma

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Summary

Malignant lymphomas are increasing in frequency for unknown reasons. We know today that they constitute a big family of tumours of lymphoproliferative origin, which can be very different one from the other in terms of morphology, biology, and clinical behaviour. Some of them need very specific treatments and it is therefore important that a clear diagnosis is obtained and that the treatment is administered by specialised doctors. Although the new WHO classification has abolished the concepts of low-grade and high-grade lymphomas, it remains true that some lymphomas exhibit indolent behaviour and cannot be cured, while other aggressive lymphomas can be cured by modern therapy. The cornerstone of treatment remains chemotherapy and, to a minor extent, radiotherapy. New treatment modalities such as the use of monoclonal antibodies, high-dose therapy or allogenic transplantation have improved the treatment results in the last decade. In this article we offer a summary of the most important concepts which are of interest for practising physicians.

Key words: malignant lymphoma, treatment

Introduction

The treatment of patients with malignant lymphoma is gaining interest in the medical community for several reasons: firstly, an impressive increase in the incidence (approximately doubled in the last 20 years) [1], so that what used to be a rare disease is encountered more and more in medical practice. Secondly, new treatments have been developed for lymphoma such as monoclonal antibodies, antisense molecules and allogenic bone marrow transplants. A third reason for growing interest is the increasing proportion of patients being cured. Treatments are becoming simpler, are often performed in an outpatient setting, and general practitioners are therefore more often involved.

The purpose of this article is to review the most common forms of treatments used against malignant lymphoma and to review their indications for the different histological subtypes. We do not pretend to cover all the details of rare histologies and special treatments, but wish to give an overview of the most common entities and treatment algorithms, which should allow the internist to be updated in this field.

Classification and staging

The classification of malignant lymphomas has changed at least once every decade. This has made it difficult for general practicioners and even for oncologists who do not deal daily with these issues, to remain up to date. Therefore, it is useful to briefly review the newest classification, which was published by the World Health Organization [2]. The latter is based on cytological and histological characteristics, but also takes into account the immunophenotype of tumour cells, cytogenetics and molecular alterations, as well as clinical behavior, with the purpose of defining separate entities which could be looked at as "single diseases". Since it has become clear that a number of disease groups with different names (lymphoid leukaemias, myeloma, Hodgkin's disease, non-Hodgkin's lymphomas) are in fact all neoplasms derived from lymphoid cells, they have all been grouped by the WHO in a classification of lymphoid neoplasms (table 1). Nevertheless, for practical and historical reasons, these disease groups continue to be treated in quite a different way, and in this review we will limit our discussion to the so-called non-Hodgkin's lymphomas, which include about 30 diseases of both B- and T-cell lineage. The new classification avoids the grouping of diseases into low- or high-grades, which was previously based either on cytological appearance (ie, in the Kiel Classification [3]), with differentiated cells being classified as low-grade, and undifferentiated cells

Table 1

Proposed WHO classification of lymphoid neoplasms.

B-Cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukaemia/lymphoma (precursor B-cell
acute lymphoblastic leukaemia)
Mature (peripheral) B-cell neoplasms*
B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (½ villous lymphocytes)
Hairy cell leukaemia
Plasma cell myeloma/plasmacytoma
* Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma (½ monocytoid B cells)
* Follicular lymphoma
* Mantle-cell lymphoma
* Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt cell leukaemia

T-cell and NK-cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukaemia (precursor T-cell
acute lymphoblastic leukaemia)
Mature (peripheral) T-cell neoplasms*
T-cell prolymphocytic leukaemia
T-cell granular lymphocytic leukaemia
Aggressive NK-cell leukaemia
Adult T-cell lymphoma/leukaemia (HTLV11)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
* Mycosis fungoides/Sezary syndrome
Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, T/null cell, primary systemic type

Hodgkin's lymphoma (Hodgkin's disease)
Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

Common entities are shown in boldface type. Entities discussed more in detail in this review are marked with*

classified as high-grade, or based on clinical behaviour as in the International Working Formulation (IWF) which included tumours with longer survival in the low-grade category and those with shorter survival in the high-grade [4]. The latter classification rather sought to acknowledge the fact that entities exist, for example mantle-cell lymphoma, which appear low-grade microscopically but which most often behave aggressively in clinical practice.

Treatment modalities for malignant lymphomas

Types of treatment (see table 2)

Surgery, one of the most important therapeutic tools in oncology, has a limited role in the treatment of lymphoma. Of course all diagnoses should be made on sufficient tissue (reaching diagnoses based on fine-needle aspiration specimens should be absolutely avoided!), which means surgical biopsy. Debulking, a procedure which has shown in many tumours (for example ovarian cancer) to clearly improve survival proportionally to its extent, has been proven not to have the same role in such a very chemo- and radio-sensitive disease as lymphoma. For some particular forms of lymphoma, for example gastric lymphoma limited to the stomach, surgery was the primary form of treatment until a few years ago, but this principle is no longer accepted [5]. For primary intestinal lymphoma, however, there are no studies witch clearly demonstrate that surgery is unnecessary [6].

Radiotherapy historically had a very important role, having been the first treatment capable of inducing long-lasting remission and even cure a number of patients at the beginning of the previous century. It's role remains very important in the treatment of Hodgkin's disease [7], while in non-Hodgkin's lymphoma, where localised disease is less frequent and tumour spread less predictable, its role is more and more confined to the exceptional cases of stage I diseases or for the consolidation of remission in patients initially presenting with bulky disease. The reluctance to use radiotherapy comes from long-term observational data, especially in Hodgkin's lymphoma, showing an important increase in second tumour incidence for patients having received radiotherapy, particularly when combined with chemotherapy [8]. A new form of targeted radiotherapy is nowadays entering clinical practice: radio-immunotherapy, ie,

Table 2

Treatment Strategies for NHL.

Strategy	main characteristic
Surgery	needed for diagnosis, usually not useful for treatment except in some case of primary lymphoma of the stomach.
Radiotherapy	local therapy, indicated for consolidation of bulky disease, rescue therapy. Short and long-term side effects (such as mucositis or radio-induced sarcoma).
Chemotherapy	necessary in most clinical settings, frequently complicated by neutropenic fever, mucositis, alopecia etc. can cause late side effects (cardiomyopathy, leukaemia, pulmonary interstitiopathy).
High-dose myelo-ablative chemotherapy	applies high dose of cytotoxic followed by stem cell rescue, can obtain remission in partially chemo-resistant lymphoma, complicated with major adverse effects and death in 5%.
Immunotherapy	increasing importance for passive immunotherapy associated with chemotherapy or as monotherapy. Allergic reactions are rare.
Allogenic bone marrow transplant	principal mechanism of action is a graft versus lymphoma effect with high cure rate but also high treatment-related mortality (up to 50%). Difficulty to find the appropriate marrow donor.

monoclonal antibodies directed against lymphoma specific antigens (for example CD20 or CD22) which are bound to a radio-isotope (for example ^{131}Iodine or ^{90}Yttrium), leading to selective irradiation of the tumour cells. Examples of these substances are now commercially available (at least in the USA) as Tositumomab (Bexxar®) and Ibritumomab tiuxetan (Zevalin®) [9], the latter is now available in Switzerland.

Chemotherapy has been used for many decades and many drugs have been shown to be active in lymphomas. Among them are the alkylating agents, which were the first class of drugs showing activity (such as Chlorambucil, Melphalan and Cyclofosfamide). Anthracyclins or anthracyclin-like drugs as Doxorubicine and Mitoxantrone are also important drugs, as are Etoposide, Vincristine and Vinblastine. Steroids are frequently used for the treatment of lymphoid malignancies: their activity is explained by the induction of apoptosis in normal and pathological lymphoid cells. Other drugs such as Ifosfamide, Cisplatin, Citarabine, high-dose Methotrexate and more recently Gemcitabine have shown activity as well. These latter drugs are rather used in second line treatment, but new protocols are being developed, which try to integrate them in the first line in an attempt to achieve higher remission rates.

High-dose myelo-ablative chemotherapy is an extension of the use for some of the above-mentioned drugs, developed thanks to the improvements in the understanding of the biology of haematopoiesis. New techniques of haematopoietic stem cell collection and transplantation, make it possible to apply myelo-ablative doses of some cytotoxics (such as alkylating agents or carboplatin), exploiting the dose-response relationship, which causes the death of a partially chemoresistant cell by applying a much higher dose of cytotoxic. The permanent myelo-ablation that follows can be reversed by the re-infusion of previously collected autologous haematopoietic stem cells. This technique has become a new standard for the rescue of patients with relapsed Hodgkin's disease and high-grade non-Hodgkin's lymphoma [10, 11].

Immunotherapy is a concept including a number of strategies all aiming at improving patients immune reaction against lymphoma cells. The first

of these was the use of Interferon-a, a molecule of which the mechanism of action remains partially unknown, but which is thought to stimulate the immune system reactivity against foreign tissues and cells. In some particular situations, the association of Interferon with chemotherapy or its use as maintenance after chemotherapy has shown clinical benefit [12]. Nevertheless, due to the high cost, the uncertain benefit and the often important side effects of the drug, the use of Interferon has never entered routine clinical practice in many countries. If treatment with Interferon could be considered to act by an "immunomodulatory" mechanism, another strategy, defined by some as "passive immunotherapy", consists of infusing the patient with antibodies directed against antigens present on the surface of lymphoma cells. Techniques of humanising antibodies [13] (so that only the variable component of the antibody is of murine origin, while the majority of the molecule is human) has allowed antibody treatment to successfully enter clinical practice. A number of these antibodies have been and are still being developed, but the anti-CD20 antibody Rituximab has already gained widespread use in clinical practice. Rituximab has shown activity in all B-cell lymphomas, either used in monotherapy or combined with chemotherapy. Other monoclonal antibodies available on the market are the anti-CD52 antibody Campath 1H, active against both B- and T-CLL, and the T-cell antibody Denileukin diftitox (Ontak®), active on cutaneous T-cell lymphomas [14]. Allogeneic bone marrow transplant is also considered an immunologically based treatment: this treatment is based on the graft vs. lymphoma effect, in which the intact immune system of the donor recognises lymphoma cells of the host as foreign and elicits an immune response against them. The recently developed technique of "mini-allogeneic transplant", in which the patient does not receive a myelo-ablative preparative treatment, but only an immunosuppression followed by donor cell infusion, is completely based on this principle [15]. Results of this treatment are favourable for chronic myeloid leukaemia and for acute leukaemia in the elderly, while for the treatment of lymphoma we only have data from preliminary pilot trials, which nevertheless showed encouraging results.

Table 3

Staging and risk assessment.

| CT-scan of the abdomen chest X-ray or a CT-scan of the chest. |
| PET is recommended in curative setting. |
| Bone marrow aspirate and biopsy. |
| Diagnostic spinal tap directly in high-risk patients [patients with more than two adverse parameters according to international prognostic index (IPI)] with e.g. involvement of bone marrow, testis, the spine, or the base of the skull. |
| Complete blood count, routine blood chemistry including LDH and uric acid, β_2-microglobulin. |
| Screening test for HIV and hepatitis B and C. |
| Protein electrophoresis is recommended for B-cell lymphomas. |

Table 4

Incidence of lymphomas.

Diagnosis	% of NHL
Diffuse large B-cell	30,6
Follicular lymphoma	22,1
MALT	7,6
Peripheral T-cell lymphomas (PTL)	7,6
PTL, NOS	3,7
Nasal NK/T	1,4
Angioimmunoblastic T-cell	1,2
Enteropathy-type	<1
Hepatosplenic	<1
Adult T-cell leukaemia	<1
CLL/SLL	6,7
Mantle cell lymphoma	6,0
Mediastinal large B-cell lymphoma	2,4
Anaplastic large cell lymphoma/T-null	2,4
Burkitt lymphoma/Burkitt-like	2,5
Nodal marginal zone lymphoma	1,8
Percursor T-cell lymphoblastic	1,7
Lymphoplasmacitic lymphoma	1,2
Others	7,4

Defining the treatment algorithm

The most important factors determinant for the choice of treatment are: histology, localisation, stage of disease, concomitant diseases and several prognostic indicators of risk: lactate dehydrogenase level (LDH), number of involved lymph-node regions, general well being of the patient. These elements help define whether the disease is potentially curable. If "yes", as for a diffuse large B-cell lymphoma in a young patient, a programme with the highest chance of cure is constructed, accepting that relevant side effects will arise. In these cases treatments are rather standardised and are subject to minimal variation depending on country and centre. A different situation is the case in which the chance of cure is very small. Here a lot of variation exists and much depends on doctors' and patients' preferences. For an incurable disease (for example follicular lymphoma in an advanced stage), many options are available. There are two schools of thought on the approach to incurable lymphoma: some clinicians consider that these patients should be treated considering quality of life as the main endpoint. Treatments are selected in a sequence which starts with less toxic approaches, allowing patients to live with a better quality of life. More aggressive treatments are kept for a later evolution. Other physicians believe that more aggressive treatments should be used first, because these obtain a long first remission, avoiding repeated relapses for longer; moreover this approach potentially improves the overall survival and creates the possibility for potentially curing some of these patients, particularly when treatments can achieve complete remission at the molecular level. Still, only a small number of randomised studies exist addressing this question, and their results are equivocal.

Treatment of nodal B-cell lymphomas

B-cell lymphomas represent the great majority of non-Hodgkin's lymphomas. Their clinical behaviour varies from very aggressive as in the case of Burkitt or lymphoblastic lymphoma to very indolent diseases as with follicular lymphoma. The details of the treatment algorithm for each of these diseases is beyond the scope of this review. We will limit our discussion to 3 entities, which are at the same time more common and more illustrative of the possible strategies for treating lymphoma.

Treatment of follicular lymphoma

Follicular lymphoma is the prototype of indolent lymphomas and is also the most frequently occurring (approximately 30%). Its clinical course is usually slow; the median survival is of 9–10 years [16]. Clinically the disease usually presents at an advanced stage with lymph nodes involved above and below the diaphragm, with bone marrow involvement in half of the cases. Very rarely the disease is discovered at an early stage with only one or two lymph node stations involved; in this case a curative approach should be attempted, with radiotherapy of the involved field [17]. Follicular lymphoma is characterised by the over expression of the anti-apoptotic Bcl-2 protein, which is the consequence of a translocation occurring between chromosome 14 and 18. This translocation can be detected with molecular biological tests allowing for the detection of minimal residual disease even

in the absence of histologically or cytologically demonstrated lymphoma [18]. If the patient is without symptoms a "wait-and-see" policy is usually an adequate practice without worsening the prognosis [19]. A number of treatments can obtain remission in follicular lymphoma: the disease is very sensitive to radiation, to alkylating agents (for example Chlorambucil or Cyclofosfamide), and longer response duration can be obtained by combining several agents (for example CVP = Cyclophosfamide, Vincristine, Prednisone, or CHOP = Cyclofosfamide, Doxorubicine, Vincristine, and Prednisone) [20]. Interferon has shown to greatly improve disease-free survival and even overall survival, either if added to chemotherapy or if used as maintenance after chemotherapy [12]. High dose chemotherapy with autologous stem cell transplantation can induce remission in an important number of patients even if heavily pre-treated, and might induce a molecular remission potentially lasting for a prolonged time [21]. There is controversy on the timing of application of this modality: some retrospective data suggest that first line high-dose therapy can prolong life, while similar comparisons from other centres do not confirm these observations [22, 23]. A recently published randomised trial, which was unfortunately closed before the planned number of patients were accrued, suggested that autologous transplantation can improve survival [24]. Another treatment, which obtains an important remission rate and a relevant molecular remission rate, is the anti-CD20 monoclonal antibody Rituximab. This antibody acts probably via several mechanisms of action including antibody-dependant cell cytotoxicity, the activation of complement and a direct effect on stimulating apoptosis. When used alone this drug obtains a 50% response rate while the combination of Rituximab with chemotherapy obtains a response rate around 90% which lasts for many years [25]. Fludarabine is a purine analogue particularly active in low-grade lymphomas. Recent data of the combination of Fludarabine, alkylating agents and Rituximab have shown very long disease-free survival, but we still have no demonstration of its effects on overall survival [26]. To summarise, we have a number of active agents and strategies for follicular lymphoma but none of these have been shown to be curative. The decision on how to choose the first line treatment (soft or aggressive) and how to use each of these possibilities is dependent on doctors' and patients' preferences. Follicular lymphoma being an incurable disease, experimental treatment to achieve cure is permitted in very motivated patients. Allogeneic transplantation is one of these possibilities and has been studied in younger patients as first line or at first relapse. Data from small case series with selected patients are available and shows promising results [27, 28]. However, further evidence is needed before this strategy can be considered as part of the standard treatment.

Treatment of diffuse large B-cell lymphoma (DLBCL)

This entity is the prototype of curable lymphoma. It is the most frequent form of non-Hodgkin's lymphoma and can be diagnosed either in a localised or in a diffuse form. For localised disease a combination of chemotherapy and radiotherapy has been advocated as standard for a long time. Recent studies seem to suggest that chemotherapy alone given for 6 to 8 cycles can be equivalent or even superior to the combination of chemo- and radiotherapy [29, 30]. The avoidance of radiotherapy can be of clinical benefit for the patients, particularly for localisations where radiation can have unpleasant long-term side effects, for example xerostomia after irradiation of the head and neck region, heart failure after irradiation of the mediastinum, or even life-threatening complications such as chemio-radioinduced sarcoma. In advanced disease the standard treatment remains the poly-chemotherapy CHOP-regime. In the last 30 years, many new drug combinations have been tried to improve the results obtained with CHOP, but have failed to do so [31]. The demonstration that high-dose therapy with autologous stem cell transplantation can cure patients in relapse, which were not curable by conventional chemotherapy [32], have prompted researchers to study the use of this strategy as first line, particularly for patients with adverse prognostic factors. Unfortunately, even though a first retrospective evaluation had suggested that this strategy could be useful, prospective studies failed to demonstrate that high-dose therapy improved survival in the high-risk category. High-dose treatment therefore remains experimental as first line for all patients, while it has become the standard treatment for patients of this histology in relapse, if younger than 60 years of age. After two decades of stagnation in the results of DLBCL treatment, very recently three different modifications of the CHOP regimen have suggested a 10–15% increase in the five year overall survival: the addition of Rituximab [33], the addition of Etoposide [34], and the intensification of the dose by the administration of CHOP every two, instead of every three weeks, thanks to the addition of granulocyte colony stimulating factor (G-CSF) [35]. These data need to be consolidated by confirmatory studies. The role of allogeneic transplants in high-grade lymphomas is still experimental and limited to patients who either relapse after autologous transplants, and to patients who have a high risk of relapse and a HLA compatible family donor. The role of radiotherapy in advanced disease is now controversial: traditionally, localisations with bulky disease at diagnosis were irradiated at the end of the treatment even after obtaining complete remission. Recent data have questioned this practice [36].

Treatment of mantle cell lymphoma

Mantle cell lymphomas have a low grade appearance histologically but behave aggressively

clinically, with a median overall survival of three years. It is an incurable disease and no treatment type has been proven to be superior in terms of overall survival [37]. First line treatment often obtains remission and more intensive treatment (for example CHOP) obtains a higher proportion and a longer duration of remission than for example monotherapy with chlorambucil [38]. Rituximab has only a 30% response rate when used as monotherapy but can greatly improve disease-free survival and even overall survival [39], when used in combination with chemotherapeutic drugs. High-dose therapy with autologous stem cell transplantation used in first line significantly improves event-free survival but has not yet been shown to improve overall survival [40]. Given the relatively short disease-free survival induced by "soft" treatments (such as alkylating agent or Rituximab alone), it is common practice, at least in patients with good general health at the outset, to start treatment with a combination therapy such as CHOP or even with high-dose therapy and autologous stem cell transplantation, with the purpose of obtaining the longest-possible disease-free interval and with the hope of improving survival, as is suggested by retrospective studies. Mantle cell lymphoma is a disease mostly affecting elderly people (median age at diagnosis is 65 years) so that this aggressive approach is only possible in a small number of cases. For all other patients the treatment is often decided "ad hoc" and depends on comorbidity.

Treatment of primary extra-nodal lymphomas

Even though in the majority of lymphoma cases the treatment algorithm is decided based on histology and prognostic factors as well as patient age and general health, special attention must be paid to lymphomas arising outside the lymphatic system, because some primary localisations need a different treatment strategy than for the same histological entities arising in lymph-nodes [41]. Examples of these are lymphomas arising in salivary glands, in the lachrymal glands, in the thyroid, in the breast, and in bone; they are all rather rare. Here we will discuss some examples paying particular attention to cases such as lymphoma arising in the stomach and in the central nervous system. Other frequent extra-nodal lymphomas are T-cell lymphomas arising in the skin, such as Mycosis Fungoides and Sezary syndrome.

Treatment of gastric lymphoma

Lymphomas arising in the stomach mainly show two histologies: MALT lymphomas or diffuse large B-cell lymphomas. Large-cell lymphomas of the stomach could be a transformation of MALT lymphomas and there are arguments in favour of this pathogenetic pathway [42]. MALT (Mucosa Associated Lymphoid Tissue) is lymphatic tissue which is normally absent from a particular mucosa (in this instance gastric mucosa), and develops following an antigenic stimulus (in the stomach chronic infection by Helicobacter pylori). While MALT develops and proliferates in the stomach mucosa, it can undergo sequential mutations which finally lead to the transformation to lymphoma, – a MALT lymphoma [43]. It was described in the last decade that the eradication of the "catalytic" Helicobacter pylori infection, can lead to a macroscopic and microscopic remission, so that the impression was first raised that MALT lymphomas could be cured with antibiotics alone. More recent molecular biology data have nevertheless shown that the lymphoma clone can remain in the stomach even after microscopic eradication of the disease and may in some cases lead to relapse [44]. MALT lymphomas are very indolent diseases and even without eradication the survival of these patients ranges from 10 to 20 years, raising the question as to whether a definitive eradication of the disease is really necessary or at what price it should be obtained. Cure of gastric MALT lymphoma can be obtained by gastrectomy or by gastric irradiation, both with relevant side effects and impact on quality of life [45]. As an alternative it can be proposed to first treat the disease with antibiotics only, and, in case of relapse, treat by single agent alkylating agents or single agent rituximab, (both have shown to be very active), and to reserve more aggressive treatment such as surgery and radiotherapy for resistant disease [46]. This is an acceptable option because the possibility of the disease spreading outside the stomach is relatively small.

For aggressive gastric lymphoma a stomach-preserving treatment is nowadays recommended: either chemotherapy alone, or chemotherapy plus radiation as in any other localised high-grade lymphoma.

Treatment of primary central nervous system (CNS) lymphomas

CNS lymphomas can be of various histology, but the most frequent is the DLBCL whose incidence has risen since the HIV pandemic: in fact, CNS lymphomas are often associated with this infection. Nevertheless there has been an unexplained increase in non-HIV related CNS lymphomas in the last decade, which is higher than the overall increase in nodal lymphomas. Radiotherapy has long remained the standard treatment for this disease, but with disappointing results: response rates rose up to 80%, but no patients were cured and the response duration was in the range of 1–2 years [47]. The observation that high doses of Methotrexate or high doses of Ara-C could pass the blood-brain-barrier introduced an important

change in the treatment of this disease. These forms of chemotherapy were first used to rescue patients in relapse after brain irradiation, but subsequently were increasingly used in first line treatment, mainly followed by radiotherapy. The scheme with the best therapeutic index seems today to be the first line administration of high dose Methotrexate until complete remission, followed by consolidation radiotherapy. Retrospective data suggest that consolidating with further chemotherapy based on high dose Ara-C could further increase the cure rate and the duration of response [48, 49]. Toxicity, mainly in the form of cognitive impairment and dementia, the incidence of which is related to patients' age, remains a great concern of these treatment schemes.

Treatment of the Mycosis fungoides and Sezary syndrome

These tumours are composed by predominantly small T-lymphocytes infiltrating the epidermis, producing multiple cutaneous plaques or nodules, or alternatively present the aspect of a generalised erythema. Systemic involvement is rare for Mycosis fungoides: its 5 years survival is over 85%. Sezary syndrome is a more generalised form of the disease involving organs outside the skin and defined by the presence of tumour cells in the peripheral blood, an aggressive course due to visceral involvement and a median survival at 5 years of only 10%.

Treatment is usually not curative but can produce long-lasting remissions. Initial management of early stage disease should consider topical therapy such as PCNU (topical alkylating agent) or phototherapy, either alone or in combination with Psoralen (PUVA) [50]. Radiotherapy, which was the first treatment reported in 1902, is still a valid treatment option (today electron-beam radiotherapy), particularly for patients with less than 10% skin involvement. Systemic treatment for advanced stages or relapses after local therapy includes corticosteroids and a number of single agent cytostatic drugs. The median relapse-free survival is usually short, with a median of 6 months. Interferon-α is also a treatment option but is frequently complicated by unpleasant side effects [51]. A new treatment option is the fusion protein Denileukin diftitox (Ontak®), designed to direct the cytocidal action of diphtheria toxin to cells which express the IL-2 receptor. The high affinity form of this receptor is usually found only on activated T lymphocytes, activated B lymphocytes and activated macrophages. Malignant cells expressing one or more of the subunits of the IL-2 receptor are found in certain leukaemias and lymphomas including cutaneous T-cell lymphoma, explaining the activity of the drug in these diseases [52]. The humanised antibody CAMPATH-1H, directed against the surface protein CD 52 (expressed on the surface of normal and malignant B and T lymphocytes), has also been shown to be beneficial.

Conclusion

In conclusion, lymphomas are a very heterogeneous family of neoplastic diseases of lymphoid origin, which require specific diagnostic procedures and therapeutic interventions. Many of them can be cured, and in many cases survival can be prolonged. The very rapid evolution in this field makes it advisable to refer patients with lymphoma to a specialist in the field.

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