(2) Studies of surveillance alone reserving treatment for those who recur [6].

In disseminated seminoma, cisplatin-based combination chemotherapy is highly effective and the standard regimen is the combination of cisplatin and etoposide [7].

The prognosis of patients with testicular non-seminoma is also excellent. There is still wide variation in the management of patients with stage I disease with options including surveillance, retroperitoneal node dissection or adjuvant chemotherapy [8]. Patients with small volume retroperitoneal metastases are treated either by retroperitoneal node dissection or by initial chemotherapy with surgery for residual masses [9]. Patients with advanced metastatic non-seminoma are treated with risk-related chemotherapy regimens, tailoring the aggressiveness of treatment to the prognosis. Major factors defining the prognosis include the tumour marker concentration, the number of lung metastases, involvement of liver, bone or brain, or the presence of a large mediastinal mass [10]. Trials in good prognosis metastatic non-seminoma have analysed the number of treatment cycles required, the role of bleomycin and the use of carboplatin rather than cisplatin. The standard approach is still the combination of bleomycin, etoposide and cisplatin, placing a limit on the total bleomycin dose to reduce the risk of pneumonitis. In advanced non-seminoma with poor prognosis, studies have addressed alternating chemotherapy, intensive cycling and high dose chemotherapy, but as yet, it is unclear that these approaches are superior to standard BEP chemotherapy. The contribution of high dose chemotherapy with blood stem cell support is being investigated, mainly in the context of salvage treatment of those who failed first line chemotherapy [11]. A trial under the coordination of the European Bone Marrow Transplant Group is comparing high dose chemotherapy with standard dose chemotherapy as first salvage treatment. Important issues in this highly curable group of tumours include long term consequences, not only of the tumour diagnosis but also of treatment, and long term follow up of treated patients is important.

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Recent Advances in the Management of Lymphoma

F. Cavalli

INTRODUCTION

THE NON-HODGKIN'S lymphomas (NHL) comprise a heterogeneous group of neoplasms that originate in lymphoreticular cells. Their incidence appears to be increasing annually, at least in the western hemisphere [1]. The reasons for this are not entirely clear, although there may be some contribution by patients infected with HIV. Lymphomas with T-cell immunology markers represent fewer than 15% of the cases in the western hemisphere, while they account for approximately half of the NHLs in Japan [1].

The management of malignant lymphoma is continuously evolving, and this evolution encompasses the biological understanding of the different entities and classifications as well as a better definition of treatment policies. In this summary, we will discuss new aspects which have recently begun to emerge in each of these areas.

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CLASSIFICATION

The histological categorisation of lymphoma has for many years been a source of frustration for both clinicians and pathologists. The lack of consensus on lymphoma classification causes problems and creates difficulties in interpretation of published studies. At the beginning of the 1980s, the NCI managed to establish a consensus with regard to the so-called working formulation for clinical usage (WF) [2]. However, after only a little more than 10 years, the WF appears outdated, primarily because it has been devised for B-cell lymphoma only, while much information has accumulated in the past 10 years on both B- and T-cell lymphomas, resulting in recognition of new entities and the refinement of previously recognised disease categories. It was, therefore, suggested that the WF be updated to include new entities, but this proved to be almost impossible. In fact, the WF was not intended by its authors to be a free-standing classification scheme, but rather a method for transposing between existing classifications. A second problem is that the WF categories were defined by survival data, based on a group of patients treated on chemotherapy protocols used in the 1970s. Finally, many of the advances in lymphoma in recent years have involved immunology and genetic studies which are not available on the WF material. Therefore, an international group of pathologists decided to establish a new classification in which they attempted to categorise diseases that are recognisable by the currently available morphology, immunology and genetic techniques [3]. A major advantage of this proposal, called the R.E.A.L. classification, relates to the frameowrk which is proposed for classifying all lymphoid neoplasms, including ALL, CLL, myeloma, hairy cell leukaemia, etc. Moreover, their review also describes several new clinical entities which have been recognised in recent years. Important examples are the mucosa-associated lymphoid tumour or MALT-lymphoma [4] and the mantle cell lymphoma [5]. Whether this new classification will prove clinically useful remains, however, to be seen and first doubts have already been expressed in a very critical editorial [6].

NEW ENTITIES

The progress achieved in the past decade can best be shown by presenting a few of the recently described entities.

Mantle cell lymphoma

The term mantle cell lymphoma represents the latest phase in a very long history. In the mid-1960s, Lennert described a group of NHLs composed predominantly of small cells with irregularly shaped and cleaved nuclei with no admixture of blast cells. In the Kiel Classification, this entity was called centrocytic lymphoma [7]. In the WF, it was included under the subtitle E, i.e., diffuse small cleaved lymphomas, which proved to be a rather heterogeneous group of diseases. The discovery of the *BCL-1* gene rearrangement and the common detection of the t(11;14) translocation has revived interest in this poorly understood lymphoma type, which is generally not accepted as such. Because of the presence of this genetic hallmark and the fact that the immunophenotype most closely resembles the cells of the mantle of secondary follicles, the term "mantle cell lymphoma" was recently proposed [8]. At a workshop of the European Lymphoma Task Force, a consensus was recently reached on the biological and clinical characteristics of this entity [5]. Since the median survival of patients with mantle cell lymphoma is of the order of 3.5 years, these lymphomas can no longer be considered as belonging to the low-grade lymphoma group, as was specified in the WF. The behaviour of mantle cell lymphoma seems to be halfway between that of low- and high-grade lymphomas, and new therapeutic strategies are urgently needed, since no curative treatment is presently available [5].

MALT lymphoma

Low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) are characterised by so-called lymphoepithelial lesions, whereby the epithelium is infiltrated by a heterogeneous population, including centrocyte-like cells (originating from marginal zone B-cells), monocytoid cells, small lymphocytes and plasma cells [4]. These are tumours of adults, with a slight female predominance. Many patients have a history of autoimmune disease or of Helicobacter gastritis. The majority present with localised stage I or II extranodal disease, involving glandular epithelial tissues of various sites, most frequently the stomach, although many other sites have been described [3]. Dissemination occurs in up to 30% of the cases, often in other extranodal sites, with long disease-free intervals. Localised tumours might be cured with local treatment. Recent studies suggest that proliferation in some early MALT type tumours might be antigen-driven [9] and that therapy directed at the antigen (*Helicobacter pylori* in gastric lymphoma) may result in the regression of early lesions [10]. When disseminated, they appear to be indolent and incurable. Transformation to large-cell lymphoma may occur. Immunophenotypes of this lymphoma express B cell-associated antigens and are characteristically CD5 and CD10. Importantly, no rearrangement of *BCL-1* or *BCL-2* has been seen [3].

Anaplastic large cell (CD_{80}) *lymphoma*

This tumour was originally recognised by application of the Ki-1 (CD30) antibody: tumours strongly expressing the antigen had a characteristic morphology, now known as anaplastic large-cell lymphomas (ALCL) [11]. Cytogenetic studies on a small number of cases have recently shown a t(2;5) translocation (12). The majority of tumours express one or more T-cell associated antigens, many express neither T nor B associated antigens, and a few cases express B-cell antigens [3].

There is growing evidence of two distinct clinical forms of primary ALCL, a systemic form, which is moderately aggressive but potentially curable with aggressive therapy, analogous to other large-cell lymphomas [13], and a primary cutaneous form, which appears to be indolent and incurable like all low-grade lymphomas [14].

TREATMENT

The management of patients with NHLs is primarily influenced by the tumour type and extent as well as by the physiological state of the patient. From a practical point of view, lymphoma can be subdivided into three groups: indolent lymphoma, whose average natural history is measured in years; aggressive lymphoma, whose average natural history is measured in months; and highly aggressive lymphoma, whose average natural history is measured in weeks. This scheme, proposed a few years ago by the NCI, is presented in Table 1.

We will discuss only the treatment of indolent and aggressive lymphomas, since most highly aggressive lymphomas are paediatric problems or are found in HIV-positive patients, and thus present special problems.

Indolent lymphoma

The optimal management of patients with indolent lymphoma still presents a substantial clinical challenge despite the high rate

Table 1. National Cancer Institute clinical schema for non-Hodgkin's lymphoma

Lymphomia group	Cell type
Indolent (median survival, years)	Small, lymphocytic
	Follicular, small-cleaved cell
	Follicular, mixed
	Diffuse, small-cleaved cells
	Diffuse, intermediately differentiated (or mantle zone)
	Cutaneous T-cell
Aggressive (median survival, months)	Follicular, large-cell
	Diffuse, mixed
	Diffuse, large-cell
	Diffuse, immunoblastic
	Other peripheral T-cell
Highly aggressive (median survival, weeks)	Diffuse, small non-cleaved cell (Burkitt's)
	Diffuse, small non-cleaved cell (non-Burkitt's)
	Lymphoblastic
	Adult T-cell leukaemia/lymphoma

of response to modern radio- and chemotherapy. In evaluating therapeutic responses, one should remember that spontaneous regressions occur in up to 25% of these patients [15]. Only 10–15% of patients with indolent lymphoma present with stages I or II disease. In general, radiation therapy is recommended for this minority and is particularly indicated for patients less than 40 years of age, a group with an 80% probability of remaining disease-free 10 or more years after adequate staging and irradiation [15]. At present, there is no role for combination chemotherapy in the management of early-stage indolent lymphoma, since three randomised studies failed to demonstrate a superiority of chemotherapy with irradiation over radiation therapy alone [16]. The precise treatment of choice remains undetermined for patients with advanced stage (III–IV) and with "unfavourable" stage II indolent lymphoma. Most patients will respond to single-agent and combination chemotherapy, radiation therapy and combined modality approaches. By and large, long-term results are similar with all modalities; responses are not durable, and almost all patients will ultimately relapse. Median duration of first remission averages 3 years [16]. Whether the long survival (more than 10 years) of patients achieving a CR or a very good PR with the first treatment is therapy-related or only indicates a favourable subset of patients selected out by treatment, remains to be ascertained. It is still unclear as to whether immediate treatment is necessary or whether, in the majority of patients, a "wait-and-see" period can precede eventual treatment [15]. A recent NCI trial comparing "wait-and-see" to median aggressive combination chemotherapy shows no survival difference [16]. Our current policy dictates an initial abstention of therapy in most patients with indolent lymphoma who fit into the following critical absence of B-symptoms: slow disease course, absence of mechanically induced symptoms, absence of disease-related abnormalities in the peripheral blood values. If there is any indication for therapeutic intervention, the exact modality is to be determined according to the nature of the problem.

The current lack of a curative approach to treatment of indolent lymphoma clearly shows the need for further improvement. The immunomodulator, α-interferon, has been shown to be more effective during the maintenance than the induction phase [17]. The use of high-dose chemotherapy (+ total body irradiation) supplemented by autologous bone marrow transplantation (ABMT) or peripheral stem cells is under investigation, mainly as consolidation for those in remission after conventional therapy for relapse [18].

More recently, two purine analogues, fludarabine and 2-chlorodeoxyadenosine (2-CDA), have shown very promising results in the treatment of indolent lymphoma [16]. More data are needed, however, to properly assess their merits especially as first-line treatment. An EORTC trial is presently comparing fludarabine to CVP as first line treatment in follicular lymphoma. In previously treated patients, both those purine analogues elicit a response rate of the order of 40–50%, but remission duration is generally shorter than 1 year. One concern is the immunodepressive nature of these drugs, especially as expressed in their decreasing the level of CD4 lymphoid cells, a condition which can last for a long period of time following the end of treatment [19].

Aggressive lymphoma

Historically, radiation therapy has been used as the primary treatment for patients with localised aggressive lymphoma. Nowadays, however, most centres will treat patients with fewer than three sites of disease and no bulky masses with CHOP for 3–6 cycles followed by (or alternated with) involved radiation therapy.

The management of patients with any factor associated with poor prognosis is similar to that of patients with advanced stage disease. In these latter cases, the most effective treatment is chemotherapy; numerous combination chemotherapy regimens have been developed in the past 15 years and designated first, second and third generation regimes [16]. This rapid development (especially during the last 15 years) and the many methodological differences in the reported series have created a certain amount of confusion [16]. However, the results of a recent American intergroup-study comparing CHOP to m-BACOD, MACOP and Pro-MACE-CytaBOM in almost 1200 patients show no differences among the four treatment arms [20]. While obviously disappointing, these and other similar data have led to a reappraisal of the importance of prognostic factors in determining the outcome of first-line treatment. These endeavours have already led to a proposal for an International Index, a prognostic system, which could in years to come replace the Ann Arbor Classification for aggressive lymphoma [21]. We, therefore, feel that the future lies with development of different treatment protocols for different risk groups of patients ("risk-adapted chemotherapy"). This is particularly necessary in view of the significant toxicity of the newer regimens, which have shown a toxic death rate of between 2 and 10%. Clearly, not all patients with aggressive lymphoma need to be exposed to this degree of toxicity. On the contrary, many cases with one or more unfavourable prognostic factors could be treated quite aggressively from the very beginning, for example by ABMT or high-dose chemotherapy supplemented by peripheral stem cells [16]. The relative merit of these latter approaches continues to be controversial; preliminary results of a recent randomised French study indicate that ABMT may be equivalent to a more "standard" consolidation chemotherapy in patients in first remission [22].

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Molecular Basis of Radioresistance

P.A. Coucke and N.E.A. Crompton

INTRODUCTION

IONISING RADIATION is known to induce DNA damage and especially double strand breaks (DSB). Subsequent biological responses, in particular repair, cell cycle arrest, and physiological cell death (apoptosis), necessitate recognition of the damage and subsequent mobilisation of a spectrum of proteins. It has been demonstrated that intracellular signalling via phosphorylation pathways govern biological response to radiation exposure [1–9]. We aim to discuss some of the molecular components now under intensive investigation, which are involved in these processes and which determine the genetic basis of radioresistance.

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IRRADIATION AND CELL CYCLE

There is substantial experimental evidence indicating that radioresistant cell lines tend to display longer division delays than their radiosensitive parents [6]. Regulation of cell cycle transition is therefore considered a keystone in ultimate radiation response. The eukaryotic cell cycle has various characteristic checkpoints regulating transition from G0 to G1 (called START), G1 to S and G2 to mitosis. Although radiation is able to induce different cell cycle arrests, most information has been gathered on G1/S and G2/M arrests which affect DNA damage repair [6].

One important factor in postirradiation G1 arrest appears to be p53 [4, 6]. The protein undergoes post-translational stabilisation after irradiation (no increase of mRNA). The p53 protein binds to a regulatory sequence controlling the expression of different genes activating muscle creatinine kinase, growth arrest and DNA damage-inducible GADD45 and GADD153; murine double minute *mdm-2* which plays a role in tp53 regulation; and of