

DECISION MAKING AND PROBLEM SOLVING

Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up

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ABSTRACT

The Italian Society of Hematology (SIE), the Italian Society of Experimental Haematology (SIES) and the Italian Group for Bone Marrow Transplantation (GITMO) commissioned a project to develop practice guidelines for the initial work-up, therapy and follow-up of classical Hodgkin's lymphoma. Key questions to the clinical evaluation and treatment of this disease were formulated by an Advisory Committee, discussed and approved by an Expert Panel (EP) composed of senior hematologists and one radiotherapist. After a comprehensive and systematic literature review, the EP recommendations were graded according to their supporting evidence. An explicit approach to consensus methodologies was used for evidence interpretation and for producing recommendations in the absence of a strong evidence. The EP decided that the target domain of the guidelines should include only classical Hodgkin's lymphoma, as defined by the WHO classification, and exclude lymphocyte predominant histology. Distinct recommendations were produced for initial work-up, first-line therapy of early and advanced stage disease, monitoring procedures and salvage therapy, including hemopoietic stem cell transplant. Separate recommendations were formulated for elderly patients. Pre-treatment volumetric CT scan of the neck, thorax, abdomen, and pelvis is mandatory, while FDG-PET is recommended. As to the therapy of early stage disease, a combined modality approach is still recommended with ABVD followed by involved-field radiotherapy; the number of courses of ABVD will depend on the patient risk category (favorable or unfavorable). Full-term chemotherapy with ABVD is recommended in advanced stage disease; adjuvant radiotherapy in patients without initial bulk who achieved a complete remission is not recommended. In the elderly, chemotherapy regimens more intensive than ABVD are not recommended. Early evaluation of response with FDG-PET scan is suggested. Relapsed or refractory patients should receive high-dose chemotherapy and autologous hemopoietic stem cells transplant. Allogeneic transplant is recommended in patients relapsing after autologous transplant. All fertile patients should be informed of the possible effects of therapy on gonadal function and fertility preservation measures should be taken before the initiation of therapy.

Key words: Hodgkin's lymphoma, clinical guidelines.

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Introduction

During the last decades, survival of patients treated for classical Hodgkin's lymphoma (HL) has improved substantially and, to date, the overall cure rate for this neoplasm is about 80-85%.¹ Improvement in the outcome is mostly due to the development of more active chemotherapy (CT) regimens, of a more accurate radiotherapy (RT) and of a rational combination of the different

treatment modalities. Unfortunately, however, the risk of treatment-related morbidity and mortality is still significant,^{2,3} and modern therapies should attempt to maximize the chance of cure, while minimizing late toxicity. In order to offer the best available treatment to patients with lymphoma, the Italian Society of Haematology (SIE), the Italian Society of Experimental Haematology and the Group for Bone Marrow Transplantation (GITMO) supported the development of clinical practice guide-

lines for initial work-up, therapy and follow-up of the different lymphoma categories. Three of these guidelines have already been published, namely for nodal indolent lymphoma,⁴ nodal diffuse large B-cell lymphoma,⁵ and extranodal lymphoma of the lung and mediastinum.⁶ The guidelines produced for initial work-up, treatment and follow-up of patients with classical HL are illustrated in this paper.

Design and Methods

Organization and design

The organization and design of this project have been reported in a previous paper on guidelines for the management of nodal indolent non-Hodgkin's lymphoma.⁴ The first search of evidence databases was performed in May 2007 and updated throughout the project. The full reference list (including abstracts of full papers) is available from marcettim@smatteo.pv.it.

The grading system chosen for present guidelines is that developed by the Scottish Intercollegiate Guidelines Network (SIGN). Recommendations are therefore graded as grade A if supported by consistent and applicable level 1 evidence (at least one level 1++ trial or some consistent level 1+ trials), as grade B if derived from consistent results of level 2++ studies or extrapolated from level 1+/1++ trials, as grade C if supported by grade 2+ studies that could be applied directly to the object population and provided consistent results, or level 1++ studies from different populations (translated evidence), and as grade D when supported by poor quality evidence or evidence extrapolated from level 2+ studies, and thus sustained mainly by experts' opinion. Updating of the present guidelines is expected within two years.

Definitions

The Expert Panel (EP) agreed on the following definitions that are used in these guidelines:

Histological variants of Hodgkin's lymphoma and age categories

Two histological variants of HL have been defined by the WHO classification:⁷ the classical variant that includes nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte depletion histologies and the nodular lymphocyte predominant variant. In the first consensus meeting, the EP agreed to address only the classical and to exclude the lymphocyte predominant variant. HL developing in HIV-positive patients was also excluded.

Staging

Staging terminology is according to the Ann Arbor criteria, modified at the Cotswolds meeting.⁸ These criteria are illustrated in Table 1 and define limited (early stage) and advanced disease. Early stage disease includes patients with clinical stage I and II, further subdivided according to the EORTC criteria⁹ into favorable and unfavorable subgroups (Table 2).

Risk scoring system for advanced disease

The scoring system for advanced stage we will refer to in the text is that defined by Hasenclever *et al.*¹⁰ In this sys-

tem, the variables with an adverse prognostic impact are: age > 45 years, male gender, stage IV, Hb <10.5 g/dL, albumin <4 g/dL, leukocytes $\geq 15 \times 10^9/L$, lymphocytes $< 0.6 \times 10^9/L$ (or <8% in the differential count). Table 3 indicates the percent of patients belonging to each prognostic group in the original cohort, with the respective 5-year progression free survival (PFS).

Response assessment

The response criteria utilized in this paper are those updated by Cheson *et al.*¹¹ and illustrated in Table 4.

Radiotherapy

Table 5 defines the fields of irradiation in the different types of radiotherapy.

Table 1. The Ann Arbor/Cotswolds staging system.

Stage	Involvement
I	Single lymph node region (I) or one extralymphatic site (I _e)
II	Two or more lymph node regions on the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions on the same side of the diaphragm (II _e)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (III _e)
IV	Diffuse involvement of one or more extralymphatic organs or sites

A: no systemic symptoms.
B: presence of at least one of these symptoms: unexplained weight loss > 10% baseline during the six months prior to staging; recurrent unexplained fever >38°C; recurrent night sweats.

Bulky tumor: either a single mass exceeding 10 cm in the largest diameter or a mediastinal mass exceeding one third of the maximum transverse trans-thoracic diameter measured on a standard posterior-anterior chest X-ray at the level of the T5-T6 intervertebral disk.

Table 2. Early stage Hodgkin's lymphoma: favorable and unfavorable subgroups according to EORTC criteria.

Subgroup	Prognostic factors
Favorable	Stage I and II with ≤ 3 nodal involved areas, and age <50 years, and MT ratio <0.33, and ESR <50 without B symptoms, or ESR <30, with B symptoms
Unfavorable	Stage II with ≥ 4 nodal involved areas, or age ≥ 50 years, or MT ratio ≥ 0.33 or ESR ≥ 50 without B symptoms, or ESR ≥ 30 with B symptoms

ESR: Erythrocyte Sedimentation Rate; MT: mediastinum/thorax.

Table 3. International Prognostic System for advanced stage Hodgkin's lymphoma.¹

N. of risk factors ²	% of total	5-yr FFP %
0	7	84
1	22	77
2	29	67
3	23	60
4	12	51
≥ 5	7	42

FFP: freedom from progression. ¹According to Hasenclever *et al.* *N Engl J Med*, 1998.¹⁰
²For description of risk factors, see Design and Methods (Risk scoring system).

Table 4. Up-dated response criteria for lymphoma.¹

Type of response	Definition	Lymph nodes	Spleen, liver	Bone marrow
Complete remission				
	Disappearance of all evidence of disease	Masses of any size permitted if FDG-PET negative	Not palpable; nodules disappeared	Infiltrate cleared on repeated biopsy
Partial remission				
	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to six largest masses; no increase in size of other nodes. One or more FDG-PET positive at previously involved sites	≥ 50% decrease in SPD of nodules; no increase in size of liver or spleen	
Stable disease				
	Failure to attain CR or PR	FDG-PET positive at prior sites of disease and no new sites on CT scan or FDG-PET		
Relapse or progression				
	Any new lesion or increase by ≥50% of previously involved sites	Appearance of a new lesion or ≥50% increase in longest diameter of a previous node ≥ New FDG-PET positive lesion	≥50% increase in the SPD of any previous lesion	New or recurrent involvement

FDG: fluorodeoxyglucose; PET: positron emission tomography; PR: partial response; CR: complete remission; CT: computed tomography; SPD: sum of the product of diameters. ¹Modified from Cheson et al. *J Clin Oncol*, 2007.¹¹

Results

Initial work-up

The EP addressed the issue of which tests and evaluations should be carried out before the start of therapy (initial work-up), in order to choose the more appropriate treatment strategy and to allow for adequate response evaluation. Initial work-up for HL has evolved over the last 40 years. As long as irradiation was the main therapy, the most accurate assessment of the initial disease extension was essential; this requirement, in the absence of accurate imaging techniques, led in the 70s to the application of invasive procedures such as staging laparotomy with splenectomy and bipedal lymphangiography. In the 80s, the increased role of chemotherapy, the lesser extension and intensity of RT, and the assessment of the adverse effects of laparotomy with splenectomy (0.5% mortality, 10% morbidity with an increased risk of secondary leukemia)¹² led to the abolishment of laparotomy from the initial disease inventory of HL. In the meantime, both the availability and accuracy of imaging techniques have improved substantially, with the introduction of high-resolution computed tomography (CT scan), nuclear magnetic resonance (NMR), positron emission tomography with fluoro-deoxyglucose (FDG-PET), and the combination of CT scan and PET imaging (CT-PET). In particular, high-resolution CT scan has brought the advantage of eliminating the influence of respiratory motion, of a higher scanning speed, and of whole body scanning during the peak contrast enhancement (in the ideal conditions, spiral CT can detect lymph nodes of 5-7 mm of diameter). Randomized trials on comparative efficacy of these modern techniques for the best initial work-up of HL are lacking; therefore, recommendations on this matter can only be derived from consensus among experts.

Table 5. Radiotherapy fields.

Definitions	Fields of irradiation
Involved nodal	Initially involved lymph nodes
Involved field	Initially involved nodal regions (cervical, mediastinum, supraclavicular, axilla, para-aortic, spleen, iliac, inguinal)
Extended field	Initially involved and contiguous nodal regions
Mantle	Bilateral cervical, supraclavicular, infraclavicular, axillary nodes, and mediastinum (including the bilateral hilar regions) ± the spleen
Subtotal nodal	Mantle + Para-aortic nodal regions
Inverted Y	Para-aortic, iliac and inguinal node regions
Total nodal	Mantle + Inverted Y

The EP indicated the methods to define the initial extension of disease and the tests to evaluate co-morbidities and/or particular clinical conditions. As to the first category, all patients affected with classical HL should undergo at diagnosis a complete blood count, renal and liver function tests, serum albumin and lactic dehydrogenase determinations, and erythrocyte sedimentation rate evaluation. The initial extension of disease should be evaluated through a volumetric CT scan of neck, thorax, abdomen, and pelvis and the presence of systemic symptoms must be carefully assessed according to the classical criteria. Antero-posterior or chest X-ray, with calculation of the ratio of mass to thorax diameters, is necessary to define mediastinal involvement as bulky or not. In patients with B symptoms and/or advanced stage disease and/or blood count abnormalities, monolateral bone marrow biopsy should be performed. As to the co-morbidities, patients should be tested for HBV, HCV and HIV. Cardiac function should be evaluated with ultrasound bidimensional measurement of left ventricular

ejection fraction; this procedure is simpler and less expensive than angio-scintigraphy in detecting even slight abnormalities of left ventricular function. Women of fertile age should undergo a pregnancy test before starting therapy. Thyroid function assessment through TSH, FT3 and FT4 evaluation is recommended in candidates for neck irradiation, together with accurate dental survey and care. Pregnancy tests in women and fertility counseling to patients of reproductive age are also recommended.

A further issue was raised by the EP on the clinical application of FDG-PET scan before the initiation of therapy. Should baseline FDG-PET scan be performed in all patients with HL? Should CT-PET be preferred to PET scan? The panel indicated that FDG-PET scan before the initiation of therapy (baseline FDG-PET) is strongly recommended, although not mandatory. Baseline FDG-PET is necessary for a PET-aided response assessment during treatment and, when available, the combined CT-PET is to be preferred to standard FDG-PET. The EP put a warning on the risk of upstaging through CT-PET and recommended that for investigational purposes, FDG-PET images should be centrally reviewed, preferably in the Digital Imaging and Communications in Medicine (DICOM) format.

Recommendations

- The following initial evaluations should be performed in all patients [grade D]:

- (i) assessment of systemic symptoms;
- (ii) whole blood count;
- (iii) serum albumin;
- (iv) serum LDH;
- (v) erythrocyte sedimentation rate;
- (vi) HBV, HCV and HIV serology;
- (vii) standard chest X-ray, with mass to thoracic diameter ratio;
- (viii) CT scan of the neck, thorax, abdomen and pelvis;
- (ix) bidimensional ultrasound evaluation of left ventricular ejection fraction;
- (x) pregnancy test in women of fertile age.

- Monolateral bone marrow biopsy should be performed in patients with B symptoms and/or stage III/IV disease and/or blood count abnormalities [grade D].

- Whole body FDG-PET or CT-PET is recommended [grade C].

- Dental care and thyroid function (FT3, FT4, TSH) assessment should be performed in patients candidate to neck irradiation [grade D].

- Reproductive counseling should be offered to all patients of fertile age [grade D].

First-line therapy for early stage disease

The main issue addressed by the EP concerned the best initial therapeutic approach. To reach their conclusions, the experts extensively analyzed large randomized clinical trials conducted in the last 15 years, whose results have been published as full papers¹³⁻²¹ or as abstracts.²²⁻²⁵ A number of cohort studies,^{3,26,27} and the results of Cochrane analysis on chemotherapy, RT and combined modality for HL²⁸ have also been considered. For decades, RT has been the standard of care for patients with early stage HL. However, the significant risk of relapse after RT alone (even in favorable subgroups) and the abandonment of

staging laparotomy have substantially reduced the role of RT as the sole treatment in early stage Hodgkin's lymphoma. The results of large randomized studies comparing RT alone versus combined modality therapy (CMT) have recently been published.¹³⁻¹⁶ These studies include a SWOG trial,¹³ the German Hodgkin Study Group (GHSG) HD7 trial,¹⁴ and the EORTC H7 and H8 studies.^{15,16} The SWOG study has compared subtotal nodal irradiation (STNI) with a combined modality therapy consisting of chemotherapy (three courses of doxorubicin and vinblastine) followed by STNI. The 5-year freedom from progression (FFP) was significantly longer in the CMT compared to the RT alone group (93 vs. 70%). Likewise, the GHSG HD7 trial has demonstrated that CMT with two courses of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) followed by extended-field radiotherapy (EF-RT) is superior to EF-RT alone in patients with early stage favorable Hodgkin's lymphoma. In the EORTC trials H7 and H8, RT alone was compared to CMT in favorable patients. In the H7 trial, STNI was randomly compared to six courses of EBVP (epirubicin, bleomycin, vinblastine and prednisone) followed by IF-RT. The results of this trial indicated that the combination of EBVP and IF-RT could replace STNI as standard treatment. In the H8 trial, favorable patients were randomly assigned to either STNI alone or three courses of MOPP-ABV (mechlorethamine, vincristine, procarbazine, and prednisone alternated to doxorubicin, bleomycin, and vinblastine) plus IF-RT. The CMT proved to be superior to RT alone in terms of disease control and overall survival. Sufficient data allow the conclusion that RT alone may no longer be recommended.

A number of randomized studies have compared different CT regimens combined with different RT schedules.¹⁵⁻¹⁹ In the H7-U trial,¹⁵ unfavorable patients were randomly assigned to six courses of EBVP+IF-RT or to six courses of MOPP-ABV+IF-RT; the latter combination proved to be significantly superior. In the H8-U trial,¹⁶ six courses of MOPP-ABV+IF-RT were compared to four courses of MOPP-ABV+STNI, and to four courses of MOPP-ABV+IF-RT. The 5-year event-free survival rates were similar in the three groups (84, 87 and 88%, respectively); these results are in favor of a reduction from six to four courses of chemotherapy in this category of patients to limit toxicity.

Radiation field size has prospectively been studied in the combined modality approach. The HD8 GHSG trial¹⁷ has shown in unfavorable patients that, after two courses of COPP (cyclophosphamide, vincristine, procarbazine, prednisone) alternated with ABVD, IF-RT (30 Gy) was equally effective and less toxic when compared to EF-RT (30 Gy). A randomized study from the Milan Cancer Institute¹⁸ reinforced this notion comparing IF-RT versus EF-RT after four courses of ABVD. These studies have clearly demonstrated that the efficacy of IF-RT was not inferior to EF-RT in terms of relapse-free survival (RFS), FFP and overall survival (OS), even in unfavorable patients, with significantly lower toxicity. The EP has therefore concluded that four courses of ABVD followed by IF-RT may be considered the standard treatment of limited disease and that the recommended dose of irradiation is 30 Gy. In the four-arm randomized HD10 and HD11 trials,^{22,23} the GHSG is comparing the efficacy of different

amounts of CT followed by different IF-RT doses. Results of an interim analysis have recently been presented in the abstract form. In favorable patients,²² four courses of ABVD followed by IF-RT (30 or 20 Gy) were compared with two courses of ABVD followed by IF-RT (30 or 20 Gy); in unfavorable patients,²³ four courses of ABVD followed by +IF-RT (30 or 20 Gy) were compared to four courses of standard-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) + IF-RT (30 or 20 Gy). No differences between the four arms have so far been observed, either in favorable or unfavorable groups. The EP has therefore suggested that a further reduction compared to the standard of both chemotherapy and RT may be tested, but only in a controlled clinical trial setting.

The H9-U EORTC study is trying to identify the best CT regimen to use in a combined modality approach in unfavorable patients.²⁴ This randomized study compares four versus six courses of ABVD versus four courses of standard BEACOPP followed by IF-RT (30-36 Gy). Interim results indicate equivalent efficacy for the three arms, with less toxicity for ABVD compared to BEACOPP.

Hodgkin's lymphoma survivors who have been treated with chest RT are at increased risk of cardiovascular and/or pulmonary complications.^{29,32} Late toxicity of RT may include coronary alterations, myocardial and pericardial fibrosis, valvular abnormalities, conduction disturbances, and pulmonary fibrosis, with restrictive syndrome; the risk of toxicity is significantly enhanced by the combination of RT with CT containing doxorubicin and bleomycin. In the attempt to avoid RT-related toxicity, randomized studies have compared CT alone to combined modality therapy in patients with non-bulky early-stage Hodgkin's lymphoma.^{20,21,25} Besides, CT alone with ABVD has been utilized in a Spanish phase II trial.²⁶ In the Memorial Hospital study,²⁰ six courses of ABVD alone have been compared to six courses of ABVD followed by IF-RT (36 Gy); no significant differences in remission duration, FFP or OS were found between the two arms. A study from the National Cancer Institute of Canada and Eastern Cooperative Oncology Group²¹ has compared ABVD alone (four to six courses) to a strategy including chemotherapy and radiation therapy and found no difference in OS; 5-year FFP was slightly superior in patients given adjuvant RT; however, this advantage was counteracted by deaths from causes other than progression of Hodgkin's lymphoma. Finally, the EORTC H9-F trial²⁵ has compared EBVP alone with EBVP+IF-RT (20 Gy) or EBVP+IF-RT (36 Gy) in favorable patients. The 4-year event-free survival was 69% for EBVP alone vs. 85% and 87% for EBVP+20 Gy or 36 Gy IF-RT, respectively.

Based on the results of these trials, the EP agreed that, at the moment, there is no evidence of non-inferiority for CT alone compared to combined modality therapy, and forwarded these recommendations.

Recommendations

- *Patients with favorable early stage disease, according to the EORTC criteria, should receive chemotherapy with 3 to 4 courses of ABVD, followed by involved-field radiotherapy. The recommended dose of irradiation is of 30 Gy [grade A].*

- *Shortened chemotherapy with 2 courses of ABVD followed by*

low-dose (20 Gy) IF-RT can be offered to favorable patients in a clinical trial setting [grade B].

- *Patients with unfavorable early stage disease, according to the EORTC criteria, should receive chemotherapy with 4 to 6 courses of ABVD followed by involved-field radiotherapy (30 Gy, with additional 6 Gy to the bulk) [grade B].*

First-line therapy for advanced stage disease

The questions addressed by the EP concerned the optimal up-front therapy, the type and number of courses of CT, and the possible role of RT. To reach their conclusions, the experts have analyzed the results of randomized clinical trials, either as full papers³³⁻⁴⁵ or abstracts,⁴⁶⁻⁴⁸ and of meta-analyses of randomized clinical trials.^{49,50}

Evidence for the efficacy of chemotherapy to cure advanced Hodgkin's lymphoma has derived from studies initiated more than 35 years ago, with the introduction into the clinical practice of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy.⁵¹ The 25-year updated results of MOPP regimens indicate a cure rate of about 50%.⁵² After the introduction of the ABVD chemotherapy, a randomized study³³ demonstrated that MOPP+RT+MOPP was inferior to ABVD+RT+ABVD and two randomized studies^{34,35} that MOPP alone was inferior in terms of failure free survival compared to the alternating use of MOPP and ABVD. The alternating MOPP and ABVD approach has therefore become the standard of therapy; randomized trials failed to demonstrate any difference between the alternating and the hybrid modality.^{36,37}

In a US intergroup trial,³⁸ ABVD alone has subsequently been shown to be superior to MOPP alone and to be equivalent to the alternating MOPP and ABVD; hence, the ABVD has become the preferred induction therapy in advanced Hodgkin's lymphoma. Up-front ABVD has further been tested versus the hybrid MOPP/ABV in a US trial,³⁹ versus the Stanford V regimen and the MOPP/EBV/CAD program in an Italian co-operative study,⁴⁰ and versus alternating or hybrid multi-drug regimens such as ChIVPP/PABIOE and ChIVPP/EVA in a UK study.⁴¹ In all these trials, hybrid regimens did not show any superiority over ABVD alone which therefore emerged as the best regimen based on equivalent efficacy and lower toxicity. This conclusion, however, is challenged by a 37% failure rate after ABVD and an 18% death rate in a median follow-up of five-years (about half of total deaths were due to progressive disease).³⁹ Meanwhile, the 15-year updated CALGB study has shown for the ABVD group a 50% failure-free and a 65% overall survival,⁴² the mature results of the Stanford V regimen have been published,³³ and an Intergroup trial has compared Stanford V vs. ABVD±RT (this study has been closed to accrual for one year and results are pending).

The BEACOPP regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) has been introduced by the German Hodgkin Study Group in its baseline and dose-escalated variants, with a substantial increase of dose-density and dose-intensity compared to ABVD and hybrid regimens. In the HD9 randomized trial,⁴³ alternating COPP and ABVD have been compared with baseline and dose-escalated BEACOPP. Radiotherapy (36 Gy) was administered on sites of bulky

disease or on residual disease after chemotherapy. At five years, a significant superiority was demonstrated in freedom from treatment failure (FFTF) and OS for dose-escalated BEACOPP (87%) versus baseline BEACOPP (76%) and the alternating COPP/ABVD (69%) program. Dose-escalated BEACOPP was associated with a significantly greater toxicity compared to baseline BEACOPP and COPP/ABVD. The 10-year up-date of the HD9 study⁴⁶ confirms that BEACOPP escalated chemotherapy produced a significant improvement in long-term FFTF and OS compared to both COPP/ABVD and baseline BEACOPP and this advantage is particularly evident in the subset of poor prognosis patients, as defined by the International Prognostic Score.¹⁰

Only a direct comparison between ABVD and BEACOPP may indicate the gold standard therapy for advanced stage Hodgkin's lymphoma. A number of randomized studies are being conducted to compare ABVD with BEACOPP; at the moment, however, only data in the form of Abstracts are available.^{47,48} The preliminary results of the HD2000 trial,⁴⁷ suggest a superiority of BEACOPP over ABVD in terms of FFP but not of OS. In the IIL-GITIL-Michelangelo study,⁴⁸ ABVD (6-8 courses) or BEACOPP (4 escalated+4 baseline) first-line chemotherapy, plus pre-planned high-dose salvage, produced a comparable 3-year outcome. BEACOPP as up-front therapy scored a superior 3-year FFP (87 vs. 71%); however, freedom from second progression (92 vs. 87%) and OS (90 vs. 91%) were comparable to ABVD as up-front therapy. Altogether, no significant differences have so far emerged in the OS between ABVD and more intensive regimens, even though differences favoring dose intensive programs have been observed in the CR rate and progression free survival. The EP concluded that there is not yet any direct evidence that BEACOPP produces a significantly longer overall survival compared to ABVD.

Number of courses

There are no randomized trials on the optimal number of courses of CT in advanced disease. The US Intergroup study³⁸ demonstrated that 6-8 courses of ABVD were equivalent to 12 courses of the alternating MOPP and ABVD regimens, and indicated 6-8 courses of ABVD as the standard amount of CT. However, both the EORTC-GELA using ABVD and the GHSG using BEACOPP consider that 8 courses still remain the standard. A randomized comparison between 6 and 8 courses has not been conducted and 6 courses cannot at the moment be considered the standard for all patients with advanced stage disease. The EP concluded that there are no reasons to administer more than 8 courses of ABVD and recommends 6-8 courses; the choice of limiting to 6 the total number of courses will be prospectively supported by the demonstration of early FDG-PET-negativity (after two cycles of ABVD).

The role of RT

A meta-analysis of 16 randomized studies indicated a potential advantage of IF-RT after MOPP or MOPP-like regimens, whereas this advantage was not evident after ABVD or ABVD-like regimens, either in terms of RFS or OS.^{49,50} A randomized EORTC study⁴⁴ demonstrated that

consolidation with IF-RT did not improve the outcome in patients in complete remission after 6-8 courses of alternating MOPP and ABV, and a randomized GELA trial⁴⁵ that consolidation with IF-RT was not superior to two additional cycles of chemotherapy. The EP concluded that in patients achieving complete remission with chemotherapy, additional radiotherapy does not improve the overall results. Even the utility of irradiation to areas of initial bulky disease in patients achieving complete remission with adequate anthracycline-containing regimens is controversial. The value of FDG-PET scan may emerge as a means to select patients to be irradiated; at the moment, however, the EP did not reach a consensus.

Recommendations

- Patients with advanced stage disease should receive 6-8 courses of ABVD as first-line therapy [grade A].
- The use of MOPP or MOPP-like regimens is not recommended; nor is the use of alternating or hybrid regimens (MOPP-ABVD; MOPP-ABV; MOPP-EBV-CAD; ChLVPP-EVA; ChLVPP-PABIOE) [grade A].
- First-line escalated BEACOPP cannot be recommended as a standard, but only in controlled clinical trials. This recommendation is based on the currently available limited evidence of superiority compared to ABVD and because of a significantly higher toxicity [grade B].
- Patients without initial bulky disease achieving CR with anthracycline-containing chemotherapy should not receive adjuvant radiotherapy [grade A].
- A consensus on the utility of adjuvant radiotherapy to areas of initial bulk in patients achieving CR with anthracycline-containing chemotherapy was not reached.

Treatment of elderly patients

The less favorable prognosis of Hodgkin's lymphoma in the elderly is mostly due to the higher toxicity induced by treatment in an advanced age compared to younger patients; this substantially impairs the dose intensity of chemotherapy and eventually lessens its efficacy.^{54,55} Moreover, cardiovascular, respiratory and/or metabolic co-morbidities are important determinants of the less favorable prognosis of Hodgkin's lymphoma in the elderly.^{56,57} The EP defined as *elderly* patients over 70 years and addressed the question of whether a conventional strategy or a reduced-intensity approach is more appropriate for this category of patients.

Hodgkin's lymphoma is infrequent in the elderly and prospective randomized studies in this group of patients are lacking. The EP recommendations are, therefore, based on the analysis of retrospective studies or on data extracted from sub-groups of elderly patients enrolled into trials originally designed for younger patients. Data extrapolated from the HD8 GHSG study⁵⁸ indicate that in patients with early stage disease, without co-morbidities, 2-4 courses of chemotherapy with ABVD followed by limited radiotherapy are well tolerated and produce a high complete remission rate. Extended RT has a negative impact in elderly patients and only limited RT should therefore be adopted as adjuvant to chemotherapy in this category of patients.

In the advanced disease, it is evident from retrospective studies that elderly patients without limiting co-morbidities

ties can benefit, with acceptable toxicity, from conventional chemotherapy with 6 courses of ABVD or doxorubicin-containing regimens and that remission and relapse rates are comparable to those of younger patients.⁵⁹⁻⁶¹ At variance, the analysis of a sub-group of patients older than 65 years recruited into the HD9 GHSG trial (HD9 elderly) showed that baseline BEACOPP produced a 21% death rate due to severe toxicity.⁶² Regimens more intensive than ABVD are difficult to tolerate in advanced age and should therefore be avoided, even in patients with no limiting comorbidities. As far as bleomycin is concerned, a higher rate of pulmonary toxicity was reported in patients older than 40 years compared to younger patients by the CALGB (38% vs. 22%) and the Mayo Clinic (33% vs. 11%).^{59,63} A thorough evaluation and surveillance of respiratory function is recommended before and during ABVD chemotherapy in elderly patients, and caution should be used when administering growth factors during bleomycin-containing chemotherapy. Regimens with reduced intensity compared to ABVD are better tolerated; however, this advantage is counterbalanced by the lower remission rate and the higher relapse rate compared to standard dose regimens.^{57,64} Reduced-intensity chemotherapy, with or without limited RT, should be adopted in patients older than 80 years, as well as in those with severe co-morbidities (frail patients), where the most sensible goal of therapy should be to preserve a good quality of life with a palliative approach.

Recommendations

- Elderly patients with early-stage disease and no limiting comorbidities should receive a short chemotherapy regimen with ABVD (2-4 courses) followed by involved field radiotherapy [grade C].
- Elderly patients with advanced disease and no limiting comorbidities should be treated with 6 courses of ABVD [grade C]
- Patients older than 65 years should not receive the BEACOPP regimen (either baseline or escalated) due to its relevant toxicity [grade B].
- Elderly patients with limiting co-morbidities (frail) should be treated with reduced-intensity chemotherapy regimens or with a palliative approach to preserve a good quality of life [grade C].

Evaluation of response and monitoring

Patients should be restaged after the completion of first-line therapy. As a rule, all sites involved at the diagnosis should be restaged with appropriate methods. Physical examination and volumetric CT scan remain the cornerstones of the evaluation of response to therapy. The FDG-PET has recently been added as a sensitive tool for the assessment of response to first-line therapy. A systematic review of 13 studies for a total of 408 patients indicated that FDG-PET has a sensitivity of 84% (CI: 71-92) and a specificity of 90% (CI: 84-94) in detecting viable tumor after therapy.⁶⁵ The timing of FDG-PET is critical because post-therapy inflammatory changes may persist for two to three months after irradiation; to minimize the impact of confounding factors, FDG-PET should therefore be done at least two weeks after the end of chemotherapy and eight to 12 weeks after the completion of RT.^{11,66} Moreover, in advanced Hodgkin's lymphoma, early FDG-PET evaluation after two cycles of chemother-

apy has recently proved to be highly predictive of outcome and to be independent from the IPS variables.^{67,68} Therefore, the EP suggests that early FDG-PET be done to evaluate response to CT; even though data on the outcome of a PET-oriented therapy are not yet available. Besides, the FDG-PET scan is recommended as part of response evaluation at the end of treatment, if residual masses are present. For the definition of CR, masses of any size are permitted if they are FDG-PET negative after therapy.^{11,66}

As to CR monitoring, the EP addressed the issues of timing for visits, blood count and biochemistry, and of modalities of follow-up. No consensus was reached on the utility of FDG-PET in the follow-up because of the possibility that fibrosis, granulomatosis or unrelated neoplastic conditions may be responsible for false FDG-PET positivity, as documented in patients with mediastinal lymphoma.⁶⁹ On the whole, the EP reached a consensus on the following recommendations.

Recommendations

- Early evaluation of response (i.e. after 2 courses of ABVD) with FDG-PET scan is suggested, even though a treatment approach based on early FDG-PET findings cannot yet be recommended outside of a clinical trial setting [grade C].
- Patients in complete remission should receive complete blood count and physical examination every 3-4 months for the first two years, every six months for the next three years and every 12 months until at least ten years from the end of treatment [grade C].
- Patients in complete remission should receive neck-chest-abdominal-pelvic CT every six months for two years, then annually up to five years from the end of treatment, and depending on clinical circumstances, thereafter [grade C].
- Annual breast cancer screening is recommended in patients older than 35 years who were given radiotherapy above the diaphragm [grade C].
- Cardiovascular monitoring is recommended for all patients [grade C].
- Monitoring of thyroid function (FT3, FT4, TSH) is recommended in patients treated with neck irradiation [grade C].
- Reproductive counseling is recommended [grade C].

Therapy of relapsed and resistant disease

About 20-25% of patients with advanced Hodgkin's lymphoma do not achieve a complete remission with up-front standard chemotherapy (primary resistant disease), and a proportion of remitters are expected to relapse at different time intervals from complete remission. It has long been observed that the length of remission after first-line therapy has a significant effect on the success of subsequent salvage treatment; therefore, relapses are defined as early if they occur within 12 months from remission or late when they occur beyond this term. The choice of the best salvage approach should rely on the evaluation of prognostic factors and clinical characteristics of patients. The issues addressed by the Panel concerned the efficacy of second-line conventional dose chemotherapy in resistant and relapsing patients, the role of high-dose chemotherapy followed by autologous stem cell transplant (ASCT), and the role of allogeneic hemopoietic stem cell transplant (allo HSCT). The role of RT in limited residual disease was also addressed.

The role of conventional-dose chemotherapy

Conventional-dose chemotherapy has virtually no curative potential in patients with resistant or early relapsing Hodgkin's lymphoma.^{70,71} In contrast, patients with a late relapse may be sensitive to conventional-dose CT, and retreatment with initial chemotherapy may produce a second complete remission.^{72,73} In patients with early relapse or resistant to up-front therapy, the role of conventional-dose CT as salvage therapy is two-fold: to achieve a maximum tumor reduction before high-dose chemotherapy (debulking), and to efficiently mobilize progenitor cells into peripheral blood (PBPC) for subsequent autologous rescue. Conventional dose chemotherapy can also be used in patients who are not candidates for ASCT because of age and/or poor performance status. Several regimens of different intensity and toxicity have been developed; the more widely utilized include DHAP⁷⁴ (cisplatin, high-dose cytarabine and dexametasone), ICE⁷⁵ (ifosfamide, carboplatin, etoposide), and IGEV⁷⁶ (ifosfamide, gemcitabine, vinorelbine). No randomized studies are available comparing the relative efficacy of these different regimens.

The role of high-dose chemotherapy followed by autologous hemopoietic stem cell transplant

Evidence for the superiority of high-dose therapy followed by autologous stem cell transplant over conventional-dose therapy in young (less than 60 years) patients with relapsing and refractory disease has come from two randomized studies carried-out by the British National Lymphoma (BNLI) group and the European Blood and Marrow Transplantation (EBMT) group, respectively.^{77,78} In the BNLI trial, patients were treated with conventional dose mini-Beam (carmustine, etoposide, cytarabine, and melphalan) or high-dose BEAM with autologous stem cell transplant; the actuarial 3-year event-free survival was significantly better in patients who received high-dose therapy (53% vs. 10%). In the EBMT trial, patients relapsed after chemotherapy were randomly assigned to four courses of mini-Beam+dexamethasone (dexa-mini-Beam) or two courses of dexa-mini-Beam followed by BEAM and ASCT; the final analysis showed that FFP was significantly higher in the BEAM+ASCT group (55% vs. 34%). However, in neither of these two studies was an overall survival advantage observed for the transplant group. Non-randomized studies comparing autograft to conventional salvage therapy include the Stanford experience,⁷³ with a 4-year progression-free survival of 52% and 19% for transplant and standard dose chemotherapy, respectively, and the French Transplant Registry case-control study⁷⁹ with a 6-year PFS of 25% for transplant versus no survival for conventional chemotherapy. The reduction of transplant-related mortality (TRM) from the 10-15% of early experiences to less than 3% of recent studies, has led to a widespread acceptance of high-dose chemotherapy followed by autologous stem cell transplantation as standard of care for patients with relapsed or primary resistant Hodgkin's lymphoma. In all experiences, the outcome of patients receiving ASCT for relapsed disease is significantly better than that of patients with primary refractory disease and the number of lines of therapy before the transplant adversely affects its outcome. Eligibility criteria include age less than 65 years and absence of concomitant

diseases that can be precipitated by the high-dose procedure. Mature results of ASCT in first relapse indicate a PFS ranging from 45% to 77%, with an OS from 50 to 80%;⁸⁰⁻⁸⁴ results are significantly better when a second remission or a minimal disease status is achieved before ASCT, and demonstrate that ASCT is able to cure more than half of the patients in first chemosensitive relapse. As to the timing, the ASCT should be performed at first relapse, with the possible exception of patients with a late (more than three years after remission), and/or a single site (documented by FDG-PET, if available) relapse who can do as well with conventional dose chemotherapy.

The role of allogeneic hemopoietic stem cell transplant

Allogeneic HSCT was first explored in selected individuals with advanced Hodgkin's lymphoma,^{85,86} and proved that some patients, who had failed many lines of therapy, did survive long-term. One explanation for this result, is the combined anti-tumor effect of CT and RT with the immunologic effect of the graft-versus-lymphoma reaction. Four studies have reported the results of myeloablative allogeneic HSCT in Hodgkin's lymphoma, respectively from Seattle,⁸⁵ the International Bone Marrow Transplant Registry,⁸⁶ the Johns Hopkins University,⁸⁷ and the European Group for Blood and Marrow Transplantation.⁸⁸ The total number of patients reported is 373, with a cumulative incidence of TRM of 52%. The OS is 44%, and the PFS 20%, with a 57% relapse rate, despite the use of high-dose chemotherapy and radiotherapy.

The development of reduced intensity conditioning regimens (RIC) in the late 90s provided a new opportunity to use allo HSCT in Hodgkin's lymphoma. Several studies have been published on the outcome of patients receiving allo HSCT after RIC regimens;⁸⁹⁻⁹⁴ the main results are illustrated in Table 6. As shown by a recent direct comparison,⁹⁵ RIC transplants are associated with a significantly lower TRM compared to myeloablative transplants, with a 10% improvement in PFS and OS; nonetheless, the risk of relapse still remains a problem. Best results are obtained in patients with a Karnofsky score greater than 80 and a chemosensitive disease; this observation raises the issue of considering an allogeneic HSCT before the end stage of the disease. Results of transplants from HLA identical sib-

Table 6. Results of the reduced intensity conditioning allogeneic stem cell transplantation.

Institutions	N. of pts	Early TRM %	Cumulative TRM %	PFS %	OS %	Relapse %	Ref. #
EBMT, 2002	311	17	27	26	46	64	89
UKCG, 2005	49	4	16	39	55	43	90
MDAH, 2005	58	2	15	32	64	55	91
SPCP, 2006	40	12	25	32	48		92
GITMO, 2007	32	3	3		32	81	93
FHCRC, 2007	27	11	39	18	51	47	94
Total	485	8	21	29	49	62	

TRM: transplant-related mortality; PFS: progression-free survival; OS: overall survival.
EBMT: European group for Blood and Marrow Transplantation; UKCG: United Kingdom Cooperative Group; MDAH: M.D.Anderson Hospital; SPCP: Spanish Cooperative Panel; GITMO: Gruppo Italiano Trapianto Midollo Osseo; FHCRC: Fred Hutchinson Cancer Research Center.

lings, unrelated donors and haploidentical family members are comparable,⁹⁴ with the evidence of a graft-versus-Hodgkin effect that can be beneficial in terms of PFS.⁹⁵

The role of radiotherapy for limited residual disease

Radiotherapy may have a role as salvage in stages IA-IIA, when failure is limited to the initial nodal sites of disease (documented by the FDG-PET, if available), and prior RT has not been delivered on the area. In addition, RT (30-36 Gy) to residual nodal disease may be recommended in patients with a very good partial response after first-line chemotherapy with ABVD, Stanford V or BEACOPP regimens for advanced disease, and in patients with residual disease after salvage therapy with ASCT. In primary refractory disease, RT may have only a palliative role.

Recommendations

- *Patients younger than 60-65 years, with relapsed disease or refractory to first-line therapy should receive a second-line chemotherapy for debulking, followed, in chemosensitive patients, by high-dose chemotherapy and the infusion of autologous stem cells from peripheral blood or bone marrow [grade A].*

- *Second-line chemotherapy should consist of non cross-resistant regimens such as IGEV, DHAP, ICE, or other ifosfamide - and/or cytarabine-containing chemotherapy [grade B].*

- *It is recommended that the patient and family be screened for HLA identical or partially identical donors. The search for an unrelated donor is recommended in patients for whom a suitable family donor is not available [grade D].*

- *An allogeneic stem cell transplant is recommended in patients relapsing after an autologous transplant and in patients refractory to 1-2 lines of therapy or with early relapses, who failed to collect a suitable number of autologous stem cells from peripheral blood and bone marrow. A reduced-intensity conditioning is recommended and peripheral blood stem cells are to be preferred to bone marrow [grade C].*

- *Reduction of tumor mass is recommended before the preparative regimen for an allogeneic transplant [grade C].*

- *A myeloablative conditioning regimen is not recommended as standard approach, but it may be considered in selected young patients with primary refractory disease [grade C].*

- *For patients relapsing more than three years after first complete remission, prognostic factors such as stage of disease at relapse or systemic symptoms are to be considered to make a decision between conventional dose chemotherapy or high-dose chemotherapy followed by autologous stem cell transplant [grade D].*

- *Radiotherapy can be recommended for limited residual nodal disease in patients with a very good partial response after 6-8 courses of chemotherapy [grade B] or with residual nodal disease after ASCT [grade D].*

Fertility preservation

Fertility may be transiently or permanently affected by cancer treatment. Infertility is a late effect of great importance as it influences different domains of survivorship.⁹⁶ Therefore, a guidance about fertility preservation methods and related issues in people treated for Hodgkin's lymphoma is warranted. Two large studies have recently analyzed this problem in men⁹⁷ and women⁹⁸ treated for Hodgkin's lymphoma. The EORTC study analyzed ferti-

ty in male patients treated with various combinations of radiotherapy and chemotherapy, with or without alkylating agents, or with radiotherapy alone for early-stage Hodgkin's lymphoma. Follicle-stimulating hormone (FSH) plasma levels were measured at least 12 months after the end of treatment to assess post-treatment potential fertility. The proportion of elevated FSH was 3% and 8% in patients treated with radiotherapy only or with non-alkylating-containing chemotherapy such as ABVD or EBVP, and 60% in those treated with alkylating-containing regimens such as MOPP or BEACOPP. The GHSG analyzed the menstrual status in a large cohort of women treated with BEACOPP regimen (either baseline or escalated) for advanced disease and the influence on amenorrhea of age and use of oral contraceptives during chemotherapy. Amenorrhea was significantly more frequent after dose-escalated BEACOPP compared to standard BEACOPP, in women older than 30 years and in those who did not take oral contraceptives during chemotherapy. The EP addressed the issues of which information patients should receive about their fertility potential after therapy for Hodgkin's lymphoma and of which fertility preservation techniques should be adopted in fertile patients before the initiation of therapy. The literature review found many cohort studies, case series and case reports, but relatively few randomized or definitive trials examining the success and the impact of fertility preservation methods. The Panel noted that the infertility risk is in most studies reported as rate of azoospermia or amenorrhea, even though these are only surrogate measures of infertility.

Patient counseling

All patients of fertile age who are candidates to chemotherapy and/or radiotherapy for Hodgkin's lymphoma must be advised of the risk that treatment can permanently impair fertility. The EP recommended that the most recent data on the potential gonadic damage of therapy be clearly illustrated to the patients. In particular, male patients candidate to the ABVD chemotherapy (a chemotherapy without alkylating agents) should know that oligospermia may occur in less than 10%, with full recovery in almost all of them; female patients should expect amenorrhea to occur in about 5%, with recovery in about 75% of them, according to the age (almost full recovery in patients younger than 30 years). Patients candidate to chemotherapy containing alkylating agents and procarbazine such as baseline or dose-escalated BEACOPP, should know that the risk of azoospermia is about 90%,⁹⁹ with no difference between patients treated with baseline versus dose-escalated BEACOPP, and that of continuous amenorrhea more than 50%.⁹⁸ Candidates to high-dose chemotherapy and hemopoietic stem cell transplant (either autologous or allogeneic) should be warned that this approach may be quite gonadotoxic and that premature ovarian failure is less prevalent when patients are conditioned with reduced-intensity regimens.¹⁰⁰ At the same time, the prospective measures that can be taken to limit the risk of gonadic damage should be illustrated. The EP recommendations are in accordance with those recently forwarded by the American Society of Clinical Oncology on fertility preservation in cancer patients.¹⁰¹

Fertility preservation in men

The EP reviewed available data on the different measures to preserve fertility in men. These measures include sperm cryopreservation, testicular hormonal suppression and testicular tissue cryopreservation. The available evidence indicates that sperm cryopreservation is an effective method of fertility preservation.¹⁰¹⁻¹⁰³ The sperm must be collected before the initiation of treatment and the multiple samples generally needed to collect a suitable sperm quantity should not substantially delay the initiation of chemotherapy. Sperm quality may be poor in advanced Hodgkin's disease with systemic symptoms, even before treatment.¹⁰⁴ Nonetheless, even men with reduced sperm count and motility may be candidates for sperm cryopreservation because the modern techniques of assisted reproduction may not require a large quantity of sperm to be successful.¹⁰¹ In contrast, gonadoprotection through hormonal suppression is not effective in preventing sterility induced by chemotherapy.¹⁰⁵ Although this conclusion is drawn from small studies and the experience in Hodgkin's lymphoma is scanty, the EP agreed that hormonal therapy is not able to preserve fertility in men who are treated with gonadotoxic drugs such as the alkylating agents. Testicular tissue or spermatogonial cryopreservation and transplantation are still in their very early phase of experimentation and can not, at the moment, be recommended.

Fertility preservation in women

The EP reviewed available data on the different measures to preserve fertility in women. These measures include ovarian suppression, and oocyte or ovarian tissue cryopreservation. There is not yet any conclusive evidence regarding the efficacy and safety of ovarian suppression through oral contraceptives and/or gonadotropin-releasing hormone (GnRH) as a method to maintain fertility in women during chemotherapy. Data are mostly derived from small observational studies with menstruation, not fertility, as end-point measure. Some of these studies report resumption of menses and/or pregnancies after ovarian suppression.^{106,107} A GHSG study has investigated the menstrual status in a large series of women treated with different protocols for early and advanced stage disease,⁹⁶ and conclusively observed that amenorrhea was most pronounced in patients who had not taken oral contraceptives during chemotherapy. Oocyte cryopreservation requires sustained ovary stimulation before oocyte harvesting. This technique exposes patients to short-term high estrogen levels during the stimulation and may substantially delay the initiation of chemotherapy. Also, the overall pregnancy rate after this procedure is, at the moment, very low and further research is needed to improve its efficiency. Ovarian tissue cryopreservation does not require ovarian stimulation and follicles can be cryopreserved with good efficiency.¹⁰¹ There have been reports of live births from ovarian transplantation.¹⁰⁸ However, experience with this technique is still very limited and it can only be prospected as a forthcoming procedure.

If pelvic irradiation is part of the therapeutic program (in cases of primary subdiaphragmatic Hodgkin's lymphoma), the ovaries should be surgically or laparoscopically moved

away from the field of irradiation (oophorectomy) during RT and repositioned after the end of treatment. The overall success rate of this procedure in preserving menstrual function is about 50%.¹⁰⁹

The EP concluded that there is uncertain evidence of the efficacy of ovarian suppression to preserve fertility and still insufficient experience on forthcoming options such as ovarian or oocyte cryopreservation.

Recommendations

- *Fertile patients should be informed of the potential fertility damage produced by chemotherapy and/or radiotherapy [grade D].*
- *Male patients should be offered sperm cryopreservation as a measure to preserve their fathering potential [grade D].*
- *Female patients should be offered estro-progestinic therapy to reduce the risk of amenorrhea and oocyte or ovary tissue cryopreservation to reduce the risk of infertility (still an experimental procedure) [grade D].*
- *Female patients should be advised to adopt effective contraceptive methods in order to avoid pregnancies in the three years after the end of chemotherapy [grade D].*

Discussion

This paper provides practice guidelines for the clinical management of patients with classical Hodgkin's lymphoma. Recommendations are issued that cover a large domain including decisions on which tests and evaluations are to be performed before therapy, how to approach first-line therapy, how to evaluate the response, how to monitor patients after therapy, and how to treat refractory and relapsed patients. Recommendations on fertility preservation are also provided. Literature was retrieved from January 1995 to June 2008 in a systematic manner according to explicit criteria for quality and strength, and a panel of experts used a literature systematic review to compare specific therapies. However, in the process of guideline production, interpretation of evidence, consensus on its grading, and consensus on clinical key questions not supported by good evidence played a critical role. The theoretical value of the experts consensus approach to influence clinical practice is the assumption that knowledgeable experts have an implicit and comprehensive mastery of scientific and practical information that would yield the most appropriate recommendations. The result is that 5 out of the 35 recommendations were supported by level 1 scientific evidence and received grade A, while 11 were supported by consensus only and were explicitly marked with a grade D.

A comparison and summary of currently available evidence-based guidelines on Hodgkin's lymphoma is shown in Table 7. Since recommendations for the initial work-up of patients before treatment are largely based on the clinical practice of panelists and are not supported by high-level evidence, somewhat different approaches have been envisioned. These apply particularly to the selection of patients in whom a bone marrow biopsy may be mandatory as initial work-up, to the use of CT scan of the neck to detect nodal involvement, and to the use of left ventricular ejection fraction before and after therapy to evaluate

Table 7. A comparison between recommendations of the different available guidelines (first part).

Guidelines	ESMO 2008	NCCN 2008	SIE-SIES-GITMO
Initial work-up			
	<ul style="list-style-type: none"> Abdomen CT scan Liver biopsy, if elevated alkaline phosphatase or any other clinical suspicion Bone marrow biopsy 	<ul style="list-style-type: none"> Complete hemogram ESR, LDH, albumin, BUN, creatinine Chest X-ray CT scan of thorax abdomen, and pelvis Whole body FDG-PET scan Bone marrow biopsy in stages IB, IIB, III, and IV Pregnancy test <p><i>In selected cases:</i></p> <ul style="list-style-type: none"> Neck CT scan HIV serology Left ventricular ejection fraction 	<ul style="list-style-type: none"> Complete hemogram, Liver and renal function tests LDH, albumin ESR Chest X-ray CT scan of the neck, thorax, abdomen and pelvis Left ventricular ejection fraction Bone marrow biopsy in patients with systemic symptoms or abnormal hemogram Baseline FDG-PET or CT-PET recommended, although not mandatory Thyroid function tests and dental care in candidates to neck irradiation Pregnancy test Fertility counseling
First-line therapy			
Favorable early disease	<p>< 3 nodal areas, no bulk, no symptoms</p> <ul style="list-style-type: none"> ABVD × 2 courses + IF-RT (30 Gy) 	<p>Stage IA-IIA non bulky</p> <ul style="list-style-type: none"> ABVD × 2 to 4 courses + IF-RT (30 Gy) or Stanford V × 8 weeks + IF-RT (30 Gy) 	<p>EORTC criteria</p> <ul style="list-style-type: none"> ABVD × 3 to 4 courses + IF-RT (30 Gy) ABVD × 2 courses + IF-RT (20 Gy) only in controlled clinical trials
Unfavorable early disease	<p>≥ 3 nodal areas, no</p> <ul style="list-style-type: none"> ABVD × 4 courses + IF-RT (30 Gy) 	<p>Stage IA-IIA with bulk</p> <ul style="list-style-type: none"> ABVD × 4 to 6 courses + IF-RT (30 Gy) or Stanford V × 12 weeks + RT (30 Gy) on initial bulk or on residual FDG-PET positive sites after CT <p>Stage IB-IIB, no bulk</p> <ul style="list-style-type: none"> ABVD × 6 courses + IF-RT (30-36 Gy) on initial bulk, or Stanford V × 12 weeks + RT (36 Gy) on initial sites > 5 cm or on residual FDG-PET-positive sites after CT 	<p>EORTC criteria</p> <ul style="list-style-type: none"> ABVD × 4 to 6 courses + IF-RT (30 Gy)
First-line therapy for advanced disease			
	<p>Patients ≤ 60 years</p> <ul style="list-style-type: none"> BEACOPP escalated × 8 courses + RT (30 Gy) on PET-positive residual disease <p>Patients > 60 years</p> <ul style="list-style-type: none"> ABVD × 6-8 courses + RT (30 Gy) on PET-positive residual disease 	<p>Patients ≤ 60 years</p> <ul style="list-style-type: none"> ABVD × 6 courses or Stanford V × 12 weeks + RT (36 Gy) on initial sites > 5 cm or on PET-positive residual disease Escalated BEACOPP (if IPS ≥ 4) × 4 courses, followed by baseline BEACOPP × 4 + RT to initial sites > 5 cm, if CR at restaging with PET-CT after 4 courses Escalated BEACOPP × 8 courses + RT to initial sites > 5 cm, if PR at restaging with PET-CT after 4 courses 	<p>Patients ≤ 70 years</p> <ul style="list-style-type: none"> ABVD × 6 to 8 courses First-line baseline or escalated BEACOPP is not recommended outside clinical trials Baseline and escalated BEACOPP should not be used in patients older than 65 years for toxicity

continuing to next page.

cardiac co-morbidity or toxicity. As far as FDG-PET is concerned, this technology may play a role in the staging of Hodgkin's lymphoma and could have an impact on the initial treatment choice. The NCCN (National Comprehensive Cancer Network) guidelines¹⁰ recommend the use of whole body FDG-PET scan in the initial work-up of patients with Hodgkin's lymphoma to define the extent of disease, especially if CT scan is equivocal. On the other hand, the ESMO (European Society of Medical Oncology) guidelines¹¹ do not recommend FDG-PET scan among the initial staging procedures. The present SIE-SIES-GITMO guidelines indicate that baseline FDG-PET scan is

recommended, even though not mandatory, and emphasize the utility of early FDG-PET re-evaluation after a short ABVD chemotherapy to prospectively discriminate patients responsive to therapy and expected to have a durable remission.

As far as early stage therapy is concerned, all the available guidelines agree on recommending a combined modality approach with a short ABVD chemotherapy, followed by radiotherapy on involved nodal areas (Table 7). Based on the EORTC and GHSG trials, the number of cycles of ABVD is defined according to risk factors and the irradiation dose ranges between 20 and 30 Gy (with a pos-

Table 7. A comparison between recommendations of the different available guidelines (second part).

Guidelines	ESMO 2008	NCCN 2008	SIE-SIES-GITMO
Evaluation of response and monitoring			
	<ul style="list-style-type: none"> • At the end of treatment with physical examination, lab tests and CT scan of all initially involved areas • FDG-PET scan capacity to distinguish between active or non active tissue requires further confirmation in prospective trials • Physical examination and lab tests should be performed every 3 months for the first year, every 6 months in the 2nd and 3rd years and once a year, thereafter. • CT scan is mandatory to confirm a complete remission • After RT involving breast tissue, women should be screened for secondary breast cancer clinically and by mammography (from the age of 40 years, onwards) 	<ul style="list-style-type: none"> • At the end of treatment, with physical examination, every 2 to 4 months for 1-2 years, then every 3 to 6 months for the next 3-5 years • Complete hemogram ESR (if elevated at diagnosis), chemistry profile every 2 to 4 months for 1-2 years, then every 3 to 6 months for the next 3-5 years • TSH at least annually if RT to neck was given • Chest X-ray or CT scan every 6 to 12 months during first 2-5 years. • Abdominal and pelvic CT scan every 6 to 12 months for first 2-5 years • Cardiovascular survey, breast self exam, and skin cancer survey • No routinely FDG-PET surveillance • Fertility counseling • Monitoring during the first 5 years after therapy to detect recurrences, then annually for the risk of late complications 	<ul style="list-style-type: none"> • Neck, chest, abdomen and pelvis CT and FDG-PET scan at the end of treatment • Early evaluation of response with FDG-PET after 2 courses of ABVD is suggested • Neck, chest, abdomen and pelvis CT scan (or total body CT-PET, if available) every 6 months for 2 years, then annually up to 5 years after the end of treatment, or depending on clinical circumstances • Complete hemogram and physical examination every 3 to 4 months for the first 2 years, every 6 months for the next 3 years and every 12 months until the 10th year of follow-up • Annual breast cancer screening is recommended in patients older than 35 years who were given RT involving breast tissue • Cardiovascular monitoring • Thyroid monitoring is recommended in patients who were given neck irradiation • Reproductive counseling
Salvage therapy			
	<p>Relapses</p> <ul style="list-style-type: none"> • High-dose chemotherapy and ASCT in young patients • Gemcitabine alone or in combination in patients relapsing after ASCT • Allogeneic SCT in chemosensitive young patients with suitable donor (only in a controlled trial setting) 	<p>After CT or CT+RT</p> <ul style="list-style-type: none"> • Non cross-resistant chemotherapy • HDCT +ASCT • RT, in particular cases <p>After RT alone</p> <ul style="list-style-type: none"> • Chemotherapy, as in advanced stage disease 	<p>Relapses within 3 years from CR or refractory</p> <ul style="list-style-type: none"> • Debulking with a second-line non cross-resistant chemotherapy, followed, by high-dose chemotherapy and ASCT in chemosensitive patients, <p>Relapses after 3 years from CR and fit elderly</p> <ul style="list-style-type: none"> • Standard-dose non cross resistant chemotherapy (even with the same regimen that produced first remission) <p>Relapses after ASCT</p> <ul style="list-style-type: none"> • Allogeneic stem cell transplant after reduced intensity conditioning • Myeloablative allogeneic stem cell transplant in selected cases only

ASCT: autologous stem cell transplant; CR: complete remission; HDCT: high-dose chemotherapy; RT: radiotherapy.

sible 6 Gy boost on prior bulk). In the favorable group, the number of courses of ABVD varies from two (ESMO guidelines) to four (NCCN and SIE-SIES-GITMO guidelines), with 30 Gy IF-RT. In the NCCN guidelines, the Stanford V program, in its 8-week version, is indicated as an alternative option. In the unfavorable group, four courses of ABVD are recommended by the ESMO and six by the NCCN and the SIE-SIES-GITMO guidelines, with the 12-week Stanford V + RT on bulk or on FDG-PET positive residual disease as an alternative option. The definition of the unfavorable group, however, is not uniform between the different guidelines and includes more than two nodal sites and bulk in the ESMO, bulk and/or systemic symptoms in the NCCN and the EORTC criteria in the present guidelines.

Different recommendations have been devised in the different guidelines as to the use of escalated BEACOPP chemotherapy in advanced stage disease. According to the ESMO guidelines, the evidence accumulated so far is sufficient to recommend this therapy as a standard in patients

less than 60 years of age; indeed, escalated BEACOPP chemotherapy has resulted in a higher overall response rate, and a longer disease-free and overall survival compared to the alternating COPP-ABVD⁴³ and the baseline BEACOPP.⁴³ In a direct comparison with ABVD, however, a superiority in terms of overall survival for BEACOPP has not yet emerged.^{47,48} At variance with the ESMO, the NCCN guidelines recommend escalated BEACOPP only for high-risk patients with an IPS score ≥ 4 and the SIE-SIES-GITMO guidelines conclude that, based on the currently available evidence, first-line escalated BEACOPP therapy cannot be recommended as a standard, but only evaluated in controlled clinical trials. These discrepancies document that, despite the evidence-based nature of recommendations, there are intrinsic limitations in the process of translating the evidence into practice recommendations. In particular, the trade-offs between toxicity and benefit or between quality of life and survival prolongation, are subjective in nature and may change from one panel to another. Recommendations on response evalua-

tion, monitoring and duration of follow-up are consistent among the different guidelines and indicate the need for a prolonged surveillance to monitor for late complications. As far as FDG-PET scan is concerned, the ESMO guidelines suggest that the capacity of this technology in the response evaluation (distinguishing between active and non-active residuals) requires prospective confirmation. The NCCN guidelines discourage the use of FDG-PET in routine clinical surveillance, and a consensus was not reached in the SIE-SIES-GITMO guidelines on the utility of FDG-PET in the follow-up because of the possibility of false positivity.

The need for reproductive counseling is emphasized in the NCCN guidelines, but only the SIE-SIES-GITMO guidelines provide extensive recommendations to prospectively limit the risk of therapy-related gonadic damage and to preserve fertility.

We believe that the therapeutic recommendations issued in these guidelines could be greatly influenced by the clin-

ical trials that will be concluded in 2009 and 2010. Therefore, the present guidelines are due to be up-dated by the end of 2010.

Authorship and Disclosures

All the Authors contributed to the discussion and formulation of the recommendations as Members of the Expert Panel. EB wrote the paper, with the contribution of AB for the allogeneic stem cell transplant, of AL for the treatment of elderly patients and of GBa for the discussion. MM contributed to literature searching, GBa co-ordinated the Consensus Meetings and ST conceived the study and coordinated the guidelines production process. All the Authors have reviewed and approved the paper and do not have conflicts of interest to declare.

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