ABSTRACT

Objective: The objective of this study is to maximize the chance of cure while minimizing surgery, radiotherapy and chemotherapy as much as possible to avoid late effects and toxicity of combined modality treatment in children with Hodgkin’s disease.

Patients and Methods: One hundred twenty-one (121) children under the age of 18 years with a histopathologic diagnosis of Hodgkin’s disease were enrolled into this study. Patients were stratified according to stage into 3 risk groups: low (Stages: I, II A), intermediate (Stages: II B, III A) and high risk group (Stages: III B, IV). Oral Etoposide was used in this study instead of procarbazine in the management of boys with HD to reduce the gonadotoxic effects of procarbazine. Two cycles of OPPA for females and E-OPA for males were effective induction treatment for children with all stages of HD and stage-tailored chemotherapy (2, 4, 6 cycles of OPPA, E-OPA/COPP) was sufficient to eradicate occult microfoci. Involving field radiotherapy was given in doses of 30, 25, 20 Gy, depending on the extent of initial chemotherapy and risk status. Staging laparotomy was performed in 30 patients out of the 121 patients, 24 of them underwent splenectomy. Patients who received whole neck radiotherapy were submitted to thyroid U/S and thyroid hormonal profile. Only 3 adolescent patients did semen analysis.

Results: The overall and disease-free survival rates at 6 years were 95.3% and 86.1% (95% CI), respectively (entire group), 96.1%, 92.3% (95% CI) for low risk, 96.1%, 80.7% (95% CI) for intermediate risk and 93.3%, 80% (95% CI) for high risk patients. During the follow-up period all patients had normal thyroid functions.

Conclusions: In children with HD, only low dose involved field radiotherapy with reduced doses is needed, if a risk-dependent chemotherapy is given. In this series the strategy of selective laparotomy and restrictive splenectomy is very useful in the context of combined modality treatment, in which laparotomy omitted if both abdominal U/S and CT were negative.

Key Words: Hodgkin’s disease – Pediatric – Risk-adapted chemotherapy – Involved field radiotherapy.

INTRODUCTION

Hodgkin’s disease (HD) is a neoplasm in which survival and cure has improved dramatically over the 50 years with survival rate reaching 94% [1-3]. This high cure rate is blemished somewhat by the consequences of surgical staging, growth retardation in the irradiated tissues, the occurrence of second malignancies and gonadal toxicity following intensive therapy with radiation and chemotherapy [4,5]. These adverse effects are of great concern to both chemotherapists and radiotherapists and have resulted in more selective use of the staging laparotomy, reduction in the intensity of radiotherapy and use of less toxic chemotherapy regimens [4,6]. When combined modality programs were used, lower irradiation doses were successful with a local control rate of 97% [7]. On the basis of these data, current pediatric protocols now use low-dose involved field (I.F.) radiation with combination chemotherapy.

Chemotherapy for HD causes a high and apparently dose-related incidence of testicular dysfunction in pre-pubertal, as well as in pubertal boys affecting Leydig cell function as well as spermatogenesis [6,8]. Circumstantial evidence indicated that procarbazine was the major gonadotoxic agent involved. It was demonstrated...
that testicular function was not severely affected when patients were treated for HD without procarbazine even if cyclophosphamide was given in cumulative doses below 3800mg/m$^2$ [6]. Over the past decade, etoposide has found an established role in the management of several childhood cancers, especially lymphoma. Moreover, a pilot study showed that oral etoposide (100mg/m$^2$/d) for 4-5 days was feasible in the majority of children [9].

**Study objective:**

NCI, HD III and our previous two studies NCI HD I and NCI HD II were carried out to maximize the chance of cure while minimizing surgery, radiotherapy and chemotherapy as much as possible to avoid late effects and toxicity of combined modality treatment. Radiotherapy was limited to the involved site(s) using the lowest dose necessary, with the rationale that poly chemotherapy would be sufficient to eradicate occult microfoci in adjacent lymphatic areas. The number of poly-chemotherapy cycles and the exposure to alkylating agents and procarbazine (the two agents incriminated for gonadotoxicity and secondary malignancy) was limited and stage-dependent. Furthermore, this study continued to support the policy of selective staging adopted in the second study (NCI-HD II). Splenectomy was to be done in those patients with high probability of splenic involvement. Also, the purpose of this study was to evaluate the efficacy of oral etoposide (instead of procarbazine) in the management of pediatric Hodgkin’s disease in boys aiming to reduce the gonadotoxic effects of procarbazine.

**PATIENTS AND METHODS**

All patients, 18 years old or less presenting to the pediatric clinic of the NCI, Cairo University with pathologically proven diagnosis of HD and previously untreated with chemotherapy or radiotherapy, were eligible for entry into this study.

The diagnosis of HD was established by biopsy of lymph node or other suspicious tissue. Rye classification was used for histological diagnosis and subtyping [10].

All children underwent uniform clinical staging including history and physical examination. Routine laboratory studies including complete blood count, erythrocyte sedimentation rate (ESR), renal and liver function tests were also performed.

All children underwent posteroanterior and lateral chest X-rays and thoracic computed tomography. Abdomino-pelvic computed tomography scanning was performed in addition to abdomino-pelvic sonography (US) to assess the subdiaphragmatic regions.

Bone marrow aspiration and/or biopsy was performed in all children; however skeletal survey and bone scan were optional. Staging laparotomy was selective for this study, performed only in patients with a high probability of abdominal involvement, if both abdomino-pelvic US and/or computed tomography were positive. At laparotomy, splenectomy was omitted if there was no splenic surface nodularity, splenic hilar lymph node (LN), or pancreatic LN enlargement. Prophylactic long acting penicillin was administered to all asplenic children.

Initially, patients were staged according to the Ann Arbor staging system [11] and then were categorized into three risk groups:

1. Low risk = stages I & IIA
2. Intermediate risk = stages IIB & IIIA
3. High risk group = stages IIIB & IV.

**Study design:**

**Chemotherapy:** In the present study, a hybrid chemotherapy regimen based on MOPP was utilized (Tables 1,2) aiming to decrease the incidence of secondary malignancy and sterility reported after MOPP combination chemotherapy.

- In the OPPA/E-OPA regimen nitrogen mustard was replaced by adriamycin and by cyclophosphamide in the latter cycles of COPP, while procarbazine was replaced by oral etoposide in the EOPA regimen given to males.

- The total cumulative dose of adriamycin in the 2 cycles of OPPA/E-OPA is 160mg/m$^2$ which corresponds to the cumulative dose of 3 cycles of ABVD.

- The dose intensity of vincristine and prednisone is relatively high with the total cumulative doses of the two drugs equivalent to 3 MOPP cycles.
All patients received risk-adapted chemotherapy:
- Low-risk group patients received 2 courses of OPPA for females and E-OPA for males.
- Intermediate risk group patients received 2 courses of OPPA/E-OPA followed by 2 courses of COPP.
- High-risk group patients received 2 courses of OPPA/E-OPA followed by 4 courses of COPP.

Radiotherapy was initiated 2 weeks following the last chemotherapy treatment, and strictly limited to the initially involved sites. The standard dose of radiotherapy (RT) was reduced. It was calculated guided by the previous polychemotherapy cycles given to the patients, 30Gy, 25Gy or 20Gy for low, intermediate and high-risk groups, respectively.

Evaluation of remission:
A remission evaluation was performed twice; the first one at the end of chemotherapy and the second at the end of radiotherapy. Regarding the evaluation performed at the end of chemotherapy, good response was defined as complete clinical and/or radiological disappearance of all tumors (complete remission, CR) or as a tumor volume reduction of 75% or more (good partial remission, PR). Poor response or failure was defined as either a less than 75% shrinkage of the tumor mass or early progression of the mass before radiotherapy was started [9].

Statistical analysis:
Analysis of overall survival and event free survival were calculated using the Kaplan-Meier method [12]. The log-rank test was used to compare two or more survival curves in an explorative data analysis [12]. Cox-regression analysis was performed to determine the independent risk factors influencing prognosis [13].

RESULTS
Between January 1999 and June 2001, 121 children referred to the National Cancer Institute, Cairo University, with previously untreated biopsy-proven Hodgkin's disease, were enrolled into this study.

Epidemiological results:
The mean age at presentation was 9.6±4 years (range 3-18 years). Among 121 patients, 89 (73.6%) were males and 32 (26.4%) were females with a male to female ratio of 2.8:1. All patients had biopsy-proven Hodgkin's disease (HD) and the pathological material was reviewed using the Rye classification [10]. Fifty-four percent had mixed cellularity, 23% had nodular sclerosing and 15% had lymphocytic predominance. Six cases had lymphocytic depletion and only two cases were categorized as lymphocytic rich.

Cervical nodal enlargement was by far the most common presentation in this study. Out of 121 patients, one hundred cases (82.6%) presented with cervical lymphadenopathy. Respiratory symptoms were the presenting symptom in 4 patients (3.3%) due to huge mediastinal involvement. Splenomegaly was clinically present in 18 patients (14.9%) while hepatomegaly was seen in 16 patients (13.2%). Among 121 patients, 76 patients (62.8%) had constitutional symptoms (B) in the form of unexplained fever and/or night sweats, and/or loss of weight more than 10% in the preceding 6 months, while 45 patients (37.2%) did not suffer from these symptoms (A).

Bulky disease was present in 56/121 (46.3%) of patients. It was defined as the presence of peripheral lymphadenopathy ≥5cm in diameter or the presence of mediastinal lymph nodes of >1/3 of the transthoracic diameter.The ESR was performed in 85 patients only. Sixty seven patients (78.8%) had an ESR with 2nd hour value <100 while 18 patients (21.2%) had a 2nd hour value ≥100. Mediastinal lymph node enlargement was found in 54 patients (44.6%). Hilar lymphadenopathy was found in 32 patients (26.4%), while lung involvement was found in 4 patients (3.3%) and pleural effusion in 5 patients (4.1%). Abdominal ultrasonography (U/S) and CT were mandatory for all study patients. Seventy-four patients (61.2%) had a pathological U/S, while 60 patients (49.6%) were found to have a pathological CT abdomen.

Staging laparotomy:
In our series of 121 patients, only 30 patients (24.7%) had a staging laparotomy. Twenty-four of them (80%) had a splenectomy while 6 patients (20%) did not. As a rule in this study, staging laparotomy was only done if abdominal U/S and CT abdomen were positive for enlarged lymph nodes or splenic focal lesions. As for cases presenting clinically with stage I or II, no
staging laparotomy was performed. This is based on the fact that a multidrug chemotherapy regimen is capable of eradicating microscopic abdominal disease, proved by the low risk of abdominal relapse in cases with stage I or II supradiaphragmatic disease [14].

Among the thirty patients who had staging laparotomy, 24 patients (80%) had the same pathological stage as the clinical, while 3 patients (10%) were downstaged due to negative results of abdominal lymph nodes for Hodgkin’s disease. Three patients (10%) were upstaged to stage IV due to involvement of the liver as proved by liver biopsy.

Response to chemotherapy:

Of 412 cycles administered, 294 cycles (71.3%) were administered as scheduled, while there were delays in 118 cycles (28.7%). The delay ranged from 4 to 14 days in 70 patients. Neutropenia was by far the most common cause for delay, which was found in 40/70 patients (57.1%). The next common cause was the presence of infection, which was found in 14/70 patients (20%), followed by social reasons in 12/70 patients (17.1%).

At the end of chemotherapy, there were 101 patients evaluable to response to therapy. Nine patients disappeared during treatment and did not continue the scheduled chemotherapy. Three patients were treated outside the protocol (2 received radiotherapy before chemotherapy, because of the presence of paraverterbral mass with intraspinal extension in one and a mediastinal syndrome in the other, while the 3rd patient had rheumatic heart disease and did not receive Adriamycin, but received 6 cycles of COPP). Response to initial chemotherapy was not evaluable in 8 patients due to total excision of the peripheral lymph nodes before the start of chemotherapy. Seventy-seven patients (76.2%) were in complete remission, while 22 patients (21%) were in partial remission. Two patients (1%) had disease progression.

Response to radiotherapy:

There were 96 evaluable patients post-radiotherapy. Ninety-one patients (94.8%) were in complete remission, while 4 patients (4.2%) had residual disease (P.R.). Three of them had mediastinal disease which had slow regression and later were negative on Gallium scan. The fourth one died from progressive disease after salvage chemotherapy. Only one showed increasing disease at the end of radiotherapy.

Five patients were evaluable at the end of chemotherapy, but not at the end of radiotherapy. Two of them had progressive disease and needed further aggressive chemotherapy before radiotherapy. The other 3 patients did not receive their radiotherapy as scheduled.

Delay in the schedule of radiotherapy was encountered in 34 patients (28%). The major causes of delay was neutropenia and infection which were present in 24 patients (70.6%). Machine breakdown was the cause in 5 patients, while social problems were the cause in the last 5 patients.

Risk group response:

When the relation between the different risk groups of the disease and the response to treatment was analysed, it was found to be statistically insignificant \((p=0.08)\). For the low risk group, 1B and IIA, all the patients (100%) were in CR at the end of treatment. For the intermediate risk group, 89.3% were in CR, 7.1% in PR and one patient (3.6%) showed progression of the disease. For the high risk group, 92% were in CR while 8% were in PR.

Toxicity:

A- Chemotherapy and radiotherapy toxicity:

Bone marrow suppression grade 3 was recorded in 21 patients (17.9%), 6 patients suffered from grade 4 toxicity. Chest infection was by far the most common type of infection, followed by otitis media and skin infection. Oral antibiotics were used successfully for the majority of patients and only 10 patients needed hospitalization for intravenous antibiotics. No one suffered from grade 4 infection, i.e. septic shock.

During the whole period of chemotherapy, only one patient suffered from Herpes Zoster (HZ) infection, while during radiotherapy 3 patients developed HZ with one severe case affecting the face, eyes and ears.

No single case of cardiotoxicity was documented as a side effect of using doxorubicin. Peripheral neurotoxicity due to the use of vincristine was recorded in 7 patients. Only one patient suffered from foot drop that necessitated replacing vincristine with vinblastine. Cystitis in the form of burning micturition and frequency
was recorded in 4 patients during the COPP regimen of chemotherapy and was controlled by increasing oral fluid intake.

B- Complications of staging laparotomy:

There were 4 patients (13.3%) who developed unexplained postoperative fever. Two patients had recurrent attacks of intestinal obstruction requiring admission with supportive measures sufficient to relieve the obstruction. One case had a large hematoma in the splenic bed that transformed to a subphrenic abscess resolving after more than 6 months with conservative measures. Three patients (10%) suffered from wound infection. Two patients (6.6%) developed chest infection. One patient (3.3%) developed an incisional hernia but no surgical intervention was done.

Survival:

Overall survival (OS) and disease-free survival (DFS) for the whole cohort at 6 years were 95.3% and 86.1% (95% CI), respectively (Figs. 1,3). As of December 2005, the median follow-up period was 57 months (range 6 to 79 months). Life table analysis showed that the OS and DFS at 6-years were 96.1% and 92.3%, respectively, with a confidence interval (CI) of 95% for the low-risk group; OS was 96.1%, DFS 80.7% (95% CI) for the intermediate risk group; OS 93.3%, DFS 80% (95% CI) for the high-risk group (Figs. 2,4).

The only statistically significant prognostic indicator for overall and disease-free survival in our study was the relation between the DFS and the initial response to chemotherapy, with a *p*-value of 0.03, indicating that those who were initially good responders usually continued in complete remission. The DFS was 96% in cases of CR, 62% in PR and 50% in cases of progression of the disease.

The DFS in laparotomized patients was found to be 75% while in non laparotomized 87% with a *p*-value=0.46, which means that staging laparotomy did not affect the DFS. The DFS in relation to different stages of the disease was insignificant, *p*-value=0.64. The DFS in males was found to be 80%, while in females 73%, with a *p*-value=0.37 which means that sex did not affect the DFS. The DFS in relation to bulky tumors was found to be 70%, while in non bulky tumors, the DFS was 87% with a *p*-value=0.98. Furthermore the DFS was studied in relation to histology. It was found to be 92% in case of M.C. subtype, 35% in N.S., 68% in L.D. and 100% in L.P. and L.R. with *p*-value= 0.3. The DFS in relation to ESR was not significant, *p*-value=0.4. The overall survival and DFS in relation to different risk groups is shown in Figs. (2,4) with *p*-values=0.7, 0.2, respectively.

Treatment failure:

There were 14 treatment failures, either initial (n=3), or relapse (n=11).

Initial treatment failure correlated strongly with response to primary chemotherapy. The three patients who had initial treatment failure were poor chemotherapy responders. The first case was stage IIIB and showed increasing disease after 2 E-OPA. He continued 4 COPP with partial remission, but developed new lesions before radiotherapy. The second patient was clinically staged IIISB. He received his 6 scheduled courses of chemotherapy with poor tolerance and frequent delays and then he received involved field radiotherapy. Disease progression was manifested with residual hilar lymphadenopathy followed by development of increasing abdominal disease. The third case was stage IIB and showed disease progression after radiotherapy.

Relapses:

Eleven patients relapsed. Six relapses occurred within the irradiated field, and five occurred outside the irradiated field, with or without involvement of one or more of the following: bone, lung, liver, and bone marrow. All of them were salvaged by chemotherapy (8/11) or by chemotherapy followed by autologous bone marrow transplant (3/11). Out of the 11 relapsed patients, 6 patients went into second remission, one patient is alive in PR. Four patients had progressive disease after salvage chemotherapy, two of them are still alive on palliative treatment, one died from progressive disease, while the fourth patient died from toxicity after salvage chemotherapy.

Deaths:

Four patients died during this study. The first one was a male patient, 15 years old, clinically staged as IIISB. No staging laparotomy was done due to massive mediastinal lymphadenopathy. After 2 E-OPA, there was a newly developed lesion at the cardiophrenic region.
He continued 4 COPP courses with partial remission, but before starting radiotherapy he developed acute hepatitis B, increasing disease, pancytopenia and died from hepatorenal failure.

The second case was a male patient, 12 years old, clinical stage I. He presented with bulky right cervical lymphadenopathy and initial ESR 70/100. He received 2 E-OPA and attained complete remission, followed by involved field radiotherapy. Three months later, he relapsed in the subdiaphragmatic region as documented by abdominal ultrasound which showed splenomegaly and evident focal lesions. He received one course of ifosfamide/etoposide, but before the second course, he was admitted as an emergency because of diarrhea and dehydration which rapidly progressed to septic shock and death.

The third patient was a 13-year old male, clinical stage IIISB. He received his 6 scheduled courses of chemotherapy with poor tolerance and frequent delays. He then received involved field radiotherapy and was in partial remission with residual hilar lymphadenopathy. Five months later, he developed new lesions in the abdomen and mediastinal lymphadenopathy, and received 6 courses of MINE (methotrexate, ifosfamide, novantrone, etoposide). He showed good response, but after the last course, he developed jaundice, pancytopenia and pneumonia. He died from septic shock.

The fourth patient, a 16-year old female, presented with a huge mediastinal mass and supraclavicular lymphadenopathy. She was stage II B, received 2 courses of OPPA followed by involved field radiotherapy. The mediastinal mass continued to increase in size with a newly developed pulmonary lesion. She received 6 cycles of ABVD outside NCI with no response, then 2 cycles of MINE as preparation for BMT but died from progressive disease.

### Table (1): Application and dosage of EOPA.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin i.v.</td>
<td>1,15</td>
<td>40mg/m²/dose as a 30min. continous infusion +cardioxan</td>
</tr>
<tr>
<td>Vincristine i.v.</td>
<td>1,8,15</td>
<td>1.5mg/m²/dose: (maximum single dose = 2.0mg)</td>
</tr>
<tr>
<td>Etoposide p.o.</td>
<td>1 to 15</td>
<td>50mg/m²/day</td>
</tr>
<tr>
<td>Prednisone p.o.</td>
<td>1 to 15</td>
<td>60mg/m²/day in 3 divided doses</td>
</tr>
</tbody>
</table>

### Table (2): Application and dosage of COPP.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide i.v.</td>
<td>1.8</td>
<td>500mg/m²/dose. +Uromitoxane</td>
</tr>
<tr>
<td>Vincristine i.v.</td>
<td>1.8</td>
<td>1.5mg/m²/dose: (maximum single dose = 2.0 mg)</td>
</tr>
<tr>
<td>Procarbazine p.o.</td>
<td>1 to 15</td>
<td>100mg/m²/day</td>
</tr>
<tr>
<td>Prednisone p.o.</td>
<td>1 to 15</td>
<td>40mg/m²/day in 3 divided doses</td>
</tr>
</tbody>
</table>

### Figure (1): Overall survival among the whole group (95.3%, 95% CI).

### Figure (2): Overall survival of 121 patients with HD classified by risk group (Low risk 96.1%, Intermediate risk 96.1%, High risk 93.3%, 95% CI).
DISCUSSION

The vast majority of children with Hodgkin’s disease are cured by combined modality treatment (94%) [8,15,16]. However, the use of polytherapy and radiotherapy broadens the spectrum of potential toxicities particularly long-term side effects including second malignancies, gonadotoxicity, musculoskeletal development, and thyroid malfunction. Current approaches use chemotherapy alone with or without low-dose involved-field radiation therapy [6,8,14,17]. The volume of radiation and the intensity/duration of chemotherapy are determined by prognostic factors at presentation, including presence of constitutional symptoms, disease stage, and bulk disease.

As a result of the high rate of cure, there are now thousands of long-term survivors of childhood Hodgkin’s disease who are at risk for late effects of therapy [8,18-21].

With the trend to reduce therapy as much as possible, staging of the disease is a critical determinant in treatment. The purpose of staging laparotomies was for the detection of occult disease in the abdomen. If there were positive findings, either radiotherapy fields were enlarged and/or chemotherapy was added to the treatment program. Approximately 25-30% of patients who were Stage I or IIA after complete clinical staging with laparotomy had abdominal disease primarily in the spleen which was the primary rationale for this procedure for several years. However, several factors have led to the decline in the use of laparotomies: the increasing confidence in the ability of chemotherapy to eradicate occult abdominal disease and to salvage relapsing patients, the probability that low dose involved field radiation encompassing the spleen and para-aortic lymph nodes as well as the mantle field would eradicate occult disease in the spleen and upper abdominal nodes and finally the morbidity and mortality of staging laparotomy, and splenectomy [1,22,23].

In our series, 30/121 patients underwent staging laparotomy. It was not mandatory for all patients. It was done only for those patients with abdominal enlarged lymph nodes and/or splenic focal lesions confirmed by abdominal ultrasound and CT. Those with a free U/S and CT abdomen were clinically staged and started chemotherapy immediately. This was based on the evidence that multidrug chemotherapy regimens are capable of eradicating any microscopic abdominal disease, as proved by the low risk of abdominal relapse in cases of clinical stage I and II supradiaphragmatic disease [14].

Among the thirty patients who did perform staging laparotomy, 6 patients (20%) had altered
clinical stage. Three of them (10%) were upstaged while the other 3 patients (10%) were downstaged. Schellong et al. [24] reported that 1/3 of their patients' stage had been altered after laparotomy, 23% were upstaged, while 11% were downstaged.

Laparotomy also altered the clinical stage of 37% of children as reported by Barker and colleagues, [25]. The previous two experiences at the same institute (NCI, Cairo University) were reported. The first was that of Gad El-Mawla et al. [26] who reported 45.3% change of stage after laparotomy. The second report by Aboulnaga [5] was almost 46% change of stage after laparotomy. The small percentage of change in clinical stage after laparotomy (20%) reported in this study may be due to the small number of patients who performed laparotomy and the selection of clinical stage III patients to undergo the surgical procedure. It may also be due to increased experience and availability of prestaging diagnostic techniques.

There is accumulating data that with advances in abdominal U/S, CT scan, and 18 F-fluorodeoxyglucose- positron emission tomography, and with better interpretation of the images, and the use of combined modality treatment, the need for staging laparotomy will gradually decrease [1,22,23].

Our chemotherapy regimen was tolerable, cost effective and easy to administer on an outpatient basis. Scheduling of chemotherapy was good, 294/412 cycles (71.4%) were received on time and full doses, while 118/412 (28.6%) of cycles were delayed. The most common cause of delay was neutropenia which was found in 40/70 (57.1%) of patients with delayed cycles. Infection was the next common cause (20%), while social reasons were to be blamed in 17.1% of patients. Six patients needed hospital admission for supportive care.

In this series, 104 patients were evaluable for the induction chemotherapy with 2 cycles of E-OPA in boys and OPPA in girls. Fifty-four patients (51.9%) were in complete remission (CR), while 45 (43.3%) showed regression more than 75% i.e. partial remission (P.R.). These figures are much lower than that reported by Aboulnaga [5] who found 63.7% in CR.

Schellong et al. [24] reported 71.2% of their total study patients in CR after induction with 2 cycles of OPPA. When procarbazine in OPPA was replaced by etoposide (E-OPA) for boys in the study (DAL,-HD-90), initial response to OPPA or E-OPA induction was virtually identical and almost 70% [27].

One hundred and one patients (101) were evaluable at the end of chemotherapy, 99 patients (98%) were considered good responders: 77 (76.2%) were in CR, while 22 (21.8%) were in PR. This response to primary chemotherapy was comparable to that of the French National Study, as reported by Oberlin et al. [9].

The actuarial 6 year-overall survival was 95.3% (95% CI), with a mean time of 76.4 months and DFS 86.1% (CI 95%) for the whole study group. There was no significant influence of staging laparotomy, sex, ESR, histology or bulky disease on DFS. In comparison to the German-Austrian study which included 578 patients, the probability of 5-year event-free survival and overall survival was 91% and 98% in the total group [27].

With OPPA, the O.S. and EFS were 97% and 94%, respectively, while with E-OPA induction therapy, results were 98% and 89% [27]. These results are very promising but although we are applying the same regimen, our results were less than Schellong et al. [27]. In a 2003 study, reported by Smith et al. in Stanford [28], which attempted to identify children at high risk for relapse after combined modality, they found that male sex, stage (IIB, IIIB or IV disease), bulky mediastinal disease, WBC more than 13.5x10^3/mm^3, and hemoglobin less than 11.0 g/dL greatly affected DFS and OS with an evaluation score of 4 or 5. This type of prognostic index may be useful in assigning risk-adapted therapy.

Similar results to our study, at 3 years follow-up, were obtained by POG. Patients were treated with 8 cycles of chemotherapy: 4 MOPP alternating with 4 ABVD followed by low-dose radiotherapy (20Gy). The O.S. was 91% and the EFS was 77% with a median follow-up of 35 months [29]. In Egypt, Aboulnaga [5] reported a 4 year EFS of 87.8%.

Higher results were obtained at the St. Jude Children's Research Hospital. Eighty-five patients were enrolled in the study. They were given 5 cycles of COP alternated with 4 cycles
of ABVD and low dose regional radiotherapy (20Gy). Vincristine and cyclophosphamide were administered during irradiation and during the 2-4 week-rest period between radiation volumes. With a median period of follow-up of 4.1 years, the D.F.S. of all patients was 93%. Abnormalities in pulmonary function tests were found in 25% of patients, one patient developed pulmonary fibrosis and another had congestive heart failure 19 months post treatment. Thyroid abnormalities occurred in 27% of patients, but no information was available on male fertility [30].

In our study, 96 patients were evaluable at the end of radiotherapy, 95 (99%) were considered good responders, 91 (94.8%) were in CR, while 4 (4.2%) were in PR, 3 of them had a residual mediastinal mass which showed slow regression and a negative Gallium scan.

Aboulnaga [5] reported 100% complete response using procarbazine for boys and girls at the end of treatment. The high cure rate following local therapy confirms the value of combined modality treatment in our patients. The poor response to initial induction chemotherapy (47.8%), as compared to a similar study carried by the German Austrian Pediatric H.D. Study Group in 1996 [31], may indicate a difference in tumor biology making it more responsive to procarbazine rather than etoposide. The initial poor response may be also due to high incidence of bulky disease and mixed cellularity subtype.

Of the 11 relapsed patients, 6 relapsed in sites previously irradiated while 2 had additional relapse sites in the form of hepatic focal lesions and bone lesions. The 6 patients were stage IIIS who received 6 courses of chemotherapy and 20Gy involved-field radiotherapy. This may be indicative that the reduction of the radiation dose may impair the results of disease free survival in our patients. In the German Austrian study HD 90 [32] reported by Dieckmann et al, it was determined that treatment strategies had an impact on different risk factors. Bulky disease and/or number of involved lymph nodes might require higher doses of radiation only in insufficient remission, while B symptoms had major impact on outcome. Further randomized studies are needed to assess whether reduction of radiation dose will compromise cure or not as most studies concluded that low-dose radiotherapy does not impair the results after combined modality treatment [16,24,27,30,31,33].

During this study, all patients who received whole neck radiotherapy were submitted to thyroid ultrasound and thyroid hormonal profile consisting of T3, T4 and TSH after one year from completion of radiotherapy. All of the 25 patients who underwent thyroid U/S showed normal echo patterns. Fifteen of them showed normal hormonal profiles.

Testosterone, FSH and LH performed on 3 adolescent male patients showed normal values. Two of them had a completely normal semen analysis and the third one showed asthenospermia. These preliminary results of testicular function indicate a lower risk of germ cell damage than previously documented with OPA. The same results were obtained by Gerres et al., [34] and Schellong et al., [27] who adopted the same protocol of treatment. Testicular function was found to be normal in their patients with stages I, IIA when etoposide was used (2 cycles of E-OPA). Additional chemotherapy with cyclophosphamide and procarbazine (2 cycles of E-OPA and 2 or 4 cycles of COPP) negatively affected spermatogenesis in a considerable number of patients.

Response to primary chemotherapy seemed to be the most important prognostic factor in terms of overall survival and EFS. Treatment failure in children and adolescents with Hodgkin’s lymphoma can be divided into 3 groups [8,28,35], primary progressive disease, relapse limited to the site (s) of initial involvement (in patients treated with chemotherapy alone) or relapse in other sites.

The presence of “B” symptoms and extranodal disease at the time of relapse are adverse prognostic features [36]. In the German Pediatric Oncology and Hematology Group (GPOH) and the Children’s Oncology Group (COG) Hodgkin’s lymphoma trials, most relapses occurred in patients who received chemotherapy alone as primary treatment, and most of the relapses were confined to sites of initial involvement [16,37]. Patients with favorable disease at diagnosis (i.e., stage IA or stage IIA, no bulky tumor, no “B” symptoms), with relapse confined to an area of initial involvement after chemotherapy and no radiation, can usually be salvaged with further chemotherapy and LD-IFRT. For some post-pubertal patients, standard-dose radiation may be an option [38]. For all other patients, treatment of relapse/progression in-
cludes induction chemotherapy, [39-42] high-dose chemotherapy with peripheral blood stem cell rescue [43-47]. In our study, out of the eleven relapsed patients 3 had received high-dose chemotherapy with peripheral blood stem cell rescue.

In conclusion, the present study demonstrates that the chosen risk-adapted chemotherapy enables a considerable reduction of radiotherapy concerning both fields and dosage without jeopardizing both local control and disease-free survival. Also, minimizing invasive staging procedures does not affect the treatment results under the conditions of combined modality therapy. From the available data, it could be concluded that occult microfoci are sufficiently eradicated everywhere by the risk-adapted chemotherapy combinations of OPPA/E-OPA and COPP and that it is not necessary to identify regions with solely microscopic evidence of involvement if an effective chemotherapy is given.

The use of oral etoposide is as effective as the use of procarbazine in treating children with H.D., with less gonadotoxicity, that needs longer duration of follow-up to be confirmed. Current efforts are directed for further decrease of the burden of therapy in low and intermediate risk patients by investigating new drugs with less toxicity than procarbazine, cyclophosphamide, Adriamycin, and etoposide. However, treatment strategies must be carefully chosen to ensure a reasonable chance of success and, ultimately, cure. Lower doses of radiotherapy allow not only good local control of the disease, but also less affection to soft tissue and skeletal growth with less disfigurement.

Long-term follow-up among the pediatric population is mandatory. This is particularly important to assess the disease status as well as late effects of treatment. Particular areas of concern with respect to the children are assessment of those organs and tissues that are more sensitive to treatment because of a child’s age and growth status. Thyroid gland and gonads are of particular interest. The appropriate studies to perform and the intervals for visits may vary, but all agree that careful follow-up is essential as the late effects of treatment may not appear for many years.

REFERENCES

5- Aboulnaga S. Pediatric Hodgkin’s Disease, the response to a combined modality treatment. MD thesis, National Cancer Institute, Cairo University, 1994.


