Hodgkin's Lymphoma in Adolescents and Young Adults

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Abstract

Adolescents and young adults (AYAs) are defined as those individuals between the ages of 15 and 39 years. Hodgkin's lymphoma (HL) is the most common cancer observed in AYAs. Over the last two decades, significant improvements in both survival from HL and the reduction of therapy-related late effects have resulted from the work of collaborative study groups in pediatric and adult domains. The adolescent and young adult (AYA) population falls between these domains. AYA patients are in a critical developmental transition, with significant psychosocial challenges that may impact on the outcome of the primary treatment as well as on the medical care and surveillance of long-term sequelae in survivors. This article will examine available literature regarding outcomes for HL in the AYA population, identifying issues unique to this group, therapeutic options, and specific concerns in follow-up.

Keywords

Hodgkin's lymphoma, therapy, late effects, adolescents and young adults, second malignancies

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Adolescents and young adults (AYAs) are defined as those individuals between the ages of 15 and 39 years.[1] AYAs with cancer are considered a vulnerable group, in large part due to psychosocial challenges in this population, including lack of insurance, low rates of clinical trial enrollment, issues pertaining to independence, and concerns about body image and fertility. The resulting delays in seeking appropriate medical care, delays in diagnosis, and subsequent compliance issues during treatment complicate medical management of cancer among AYAs.[2–5] The most recent US Surveillance, Epidemiology, and End Results data indicate less survival improvement in AYAs with cancer compared with children and older adults.[6]

Hodgkin's lymphoma (HL) is the most common cancer observed among AYAs.[6] There is a slight overall male predominance in this age group, with a male:female ratio of 1.2.[6–9] Prior history of infection with Epstein–Barr virus (EBV) has been associated with an increased risk of HL.[10] Among AYAs, however, molecular studies show that EBV is related to HL in only a minority of cases and that it is unlikely to play a major etiologic role.[11,12] The most common histological subtype of HL among the adolescent and young adult (AYA) population is nodular sclerosing classical HL, occurring in 50–80 % of patients.[7–9,13,14] Over the past decades, the prognosis of HL has dramatically improved,[15] but the optimal treatment of AYA patients remains undefined and patients continue to be treated on many different regimens with either pediatric or adult protocols. We will examine available literature regarding outcomes for the AYA population and discuss the therapy-related long-term sequelae.

Studies Examining Adolescent and Young Adult Outcomes

Studies focusing specifically on AYAs diagnosed with HL are scarce. Reviewing the literature, we found eight studies, and their main characteristics are summarized in *Table 1*. A UK study analyzed adolescents diagnosed with HL between 1970 and 1997 who received treatment with adult-type protocols.[16] The OS at 5 and 20 years was 90% and 84% for stage I-IIA HL and 72% and 54% respectively for more advanced disease. However, the event-free survival (EFS) at five and 20 years was 59 % and 52 % in stage I–IIA disease, falling to 41 % and 31% in more advanced disease. The authors highlight that EFS is a more reliable measure of treatment efficacy than OS.

Herbertson et al. compared adolescent patients aged 15–19 years and young adult patients aged 20–25 years diagnosed with HL between 1969 and 1998.[17] There was no significant difference in EFS and OS between the two age groups in patients with low and intermediate risk. However, high-risk adolescent patients had a significantly worse disease outcome compared with high-risk young adults, with an EFS at five years of 43.6 % compared with 58.7 % in young adults (p=0.03) and an OS at five years of 66.7 % compared to 84.4 % in young adults (p=0.04).

The results of these studies should be interpreted with caution, however, as historical practices no longer considered appropriate, such as staging laparotomy and splenectomy, were employed, as well as older chemotherapy and radiotherapy protocols.

Table 1: Studies of Adolescent and Adult Outcomes

Author	Number of Patients	Age Range	Stages	Median FU (years)	Backbone Treatment	OS (%)	EFS (%)
Yung et al., 2004[16]	209	15–17	All	16.6	CT and/or RT MOPP-like LOPP/EVAP ChLVPP/PABlOE PABlOE	81.0 (5 yrs) 68.0 (20 yrs)	50.0 (5 yrs) 41.0 (20 yrs)
Foltz et al., 2006[7]	1,149	16–45	All	Adolescents: 8.5 Young adults: 7.8	CT and/or RT ABVD MOPP/ABV hybrid	Adolescents: 91.0 Young adults: 89.0 (10 yrs)	PFS: Adolescents: 77.0 Young adults: 80.0 (10 yrs)
Jones et al., 2007[18]	48	13–19	All	8.9	CT and/or RT PVACE BOP ABVD	93.0 (5 yrs) 86.0 (10 yrs)	NS
Koumarianou et al., 2007[9]	55	16–23	All	11.5	MOPP MOPP/ABVD ABVD BEACOPP with or without RT	From 1978–87: 65.0 From 1988–93: 80.0 From 1994–2003: 100 (5 yrs)	From 1978–87: 53.0 From 1988–93: 65.0 From 1994–2003: 88.5 (5 yrs)
Herbertson et al., 2008[17]	145	15–25	All	Adolescents: 14.3 Young adults: 15.5	ABVD ChlVPP ChlVPP/PABlOE LOPP LOPP/EVAP MOPP MOPP/ABV PABlOE VAPEC-B with or without RT	Adolescents: 85.4 (5 yrs) 76.3 (20 yrs) Young adults: 91.4 (5 yrs) 86.9 (20 yrs)	Adolescents: 59.9 (5 yrs) 56.1 (20 yrs) Young adults: 69.7 (5 yrs) 54.6 (20 yrs)
Eichenhauer et al., 2009[8]	3,785	15–45	All	7	CT and/or RT ABVD COPP/ABVD BEACOPP COPP/ABV/IMEP	Adolescents: 93.6 Young adults: 90.9 (6 yrs)	FFTF: Adolescents: 80.2 Young adults: 79.7 (6 yrs)
Canellos et al., 2010[19]	75	17–44	I–II no bulky	5	ABVD	100 (5 yrs)	PFS 92 (5 yrs)
Müller et al., 2011[14]	245	14–21	All	NS	Group A: ABVD Group P: OPPA/OEPA ± COPP with or without RT	Group A: 90.4 (5 yrs) 87.9 (10 yrs) Group P: 93.0 (5 yrs) 90.03 (10 yrs)	Group A: 78.1 (5 yrs) 73.8 (10 yrs) Group P: 83.0 (5 and 10 yrs)

CT = chemotherapy; EFS = event-free survival; FFTF = freedom from treatment failure; FU = follow-up; NS = not specified; OS = overall survival; PFS = progression-free survival; RT = radiotherapy. ABV = doxorubicin, bleomycin, and vinblastine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine; ChLVPP = chlorambucil, vinblastine, procarbazine, and prednisolone; COPP = cyclophosphamide, vincristine, prednisone, and procarbazine; EVAP = etoposide, vinblastine, adriamycin, and prednisolone; IMEP = ifosfamide, methotrexate, etoposide, and prednisone; LOPP = chlorambucil, oncovin, procarbazine, and prednisolone; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; OEPA = vincristine, etoposide, prednisone, and doxorubicin; OPPA = vincristine, prednisone, procarbazine, and doxorubicin; PABlOE = prednisolone, adriamycin, bleomycin, vincristine, and etoposide; PVACE BOP = procarbazine, vinblastine, doxorubicin, chlorambucil, etoposide, bleomycin, vincristine, and prednisolone; VAPEC-B = vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin;

A population-based UK study of adolescents with HL diagnosed from January 19981 to December 2000 found a 5 and 10 year OS of 93 and 86 % respectively for the cohort, with an OS for early stage disease of 100 and 91 % respectively.[18] Another study from British Columbia compared the outcomes of adolescents aged 16 to 21 with those of young adults aged 22–45, both age groups having received first-line doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)-based treatment between 1981 and 2004.[7] There were no significant differences in progression-free survival (PFS) and OS between the two groups, even in advanced-stage disease (10-year PFS and OS of 71 and 88 %, respectively, for advanced-stage adolescents compared to 75 and 86 % for young adults). Among the adolescents, there were no differences in outcomes between those aged 16–18 years and those 19–21 years (PFS, p= 0.25; OS, p=0.44). The authors discuss the possible bias of a greater number of young patients and those with poor prognostic features entering trials compared to older patients and those with lower risk disease. Indeed many clinical trials focus on those patients with poorer-risk disease.[18]

A retrospective study from Athens reported the outcomes of 55 patients diagnosed with HL and aged 16–23 years.[9] Patients were treated with the

regimens available at each time period, i.e., mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) (group A, 1978–87); MOPP/ABVD (group B, 1988–93); and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine (BEACOPP) or ABVD (group C, 1994–2003). Eligible patients received radiotherapy (RT). Improvements over time in OS (group A, 65 %; group B, 80 %; group C, 100 %) and EFS (group A, 53 %; group B, 65 %; group C, 88.5 %) were statistically significant (p=0.04 and p=0.005, respectively).

Eichenauer et al. analyzed the outcomes of 557 adolescents aged 15–20 years and 3,228 young adults aged 21–45 years treated between 1988 and 1998 within the German Hodgkin Study Group (GHSG) studies HD4 to HD9.[8] Treatment outcomes were comparable between age groups. At six years, the freedom from treatment failure (FFTF) was 80.2 % and 79.7 % and the OS 93.6 % and 90.9 % in adolescents and young adults, respectively. However, the 10-year estimates revealed a small but significant survival advantage for the adolescent group (92.3 % in adolescents versus 87.1 % in young adults).

A study from the Dana-Farber Cancer Institute of 75 patients aged 17–44 years was the only study limited to favorable early-stage HL and without RT.[19] After a median follow-up of five years, the PFS was 92 % and the OS was 100 %.

The most recent study is from Hungary, with patients aged 14–21 years diagnosed with HL between 1990 to 2004 and treated in pediatric and adult institutes.[14] There were no differences in outcome (OS and EFS) at five and 10 years comparing patients treated on adult and pediatric protocols. A subgroup analysis of patients younger than 18 years of age showed an OS of 89.4 ± 4 % at five years and 83.1 ± 6 % at 10 years following adult group therapy, compared with 92.8 ± 3 % and 89.6 ± 3 % following pediatric group therapy (p=0.2822). However, the five-year and 10-year EFS of children younger than 18 years were 69.6 ± 7 % and 59.1 ± 8 %, treated with adult group therapy, compared to 82.4 ± 4 % following pediatric group treatment (p=0.0157). Based on these data, the authors suggest the administration of pediatric protocols in patients younger than 18.

Pooling together the data from the studies that show specific patients' baseline characteristics (histological subtypes, gender, stages, B-symptoms and bulky disease), there were no differences between adolescents and young adults with HL, which strongly suggests similar disease biology in adolescent and young adult patients.[7,8,14]

Second malignancies (SMs) are considered events in determining EFS. Only Foltz et al. described the specific types and numbers of solid tumors (STs) among survivors of the study cohort.[7] Breast carcinoma (BC) represented 45 % of the malignancies in adolescents, but only 14 % in adults. The authors emphasize that observations should be interpreted with caution because the duration of follow-up—although quite sufficient to allow confident projection of likelihood of cure of the HL and risk of development of acute myeloid leukemia/myelodysplasia (AML/MDS) and non-Hodgkin's lymphoma (NHL)—remains too short to allow accurate prediction of the probability of developing secondary STs. Pooling the data of the three studies that report specific types and numbers of AML/MDS and NHL, 0.62 % of the patients developed AML/MDS and 0.9 % developed NHL as an SM.[7–9]

Adult Studies Including Adolescents and Young Adults

There are established standards of care for the treatment of HL in adults according to their risk groups.[20] Two cycles of ABVD followed by 20 Gy involved field radiotherapy (IF-RT) became the standard of care for early favorable HL after the results of the GHSG HD10 study were published. This study included patients aged 16–75 years and reported an FFTF of 92.0 % and an OS of 96.8 % at five years.[21]

More recently, Meyer et al. reported excellent results in patients with stages IA or IIA non-bulky HL treated with ABVD alone, with an OS of 94 % and freedom from disease progression of 87 % at 12 years.[22]

The GHSG HD14 study analyzed patients aged 18–60 years with newly diagnosed early-unfavorable HL who were randomly assigned to either four cycles of ABVD, or an intensified treatment consisting of two cycles of BEACOPP-escalated followed by two cycles of ABVD. Chemotherapy was followed by 30 Gy IF-RT in both arms. The BEACOPP arm demonstrated superior FFTF compared with ABVD (p=0.001), with a difference of 7.2 % at five years, making this regimen the standard of treatment for early-unfavorable HL.[23]

In the multicenter GHSG HD15-trial, patients with newly diagnosed advanced-stage HL aged 18–60 years were randomly assigned to receive either eight cycles of BEACOPP-escalated, six cycles of BEACOPP-escalated, or eight cycles of BEACOPP. RT was given only to patients with a persistent mass measuring 2.5 cm or more and positive on positron emission tomography (PET) after chemotherapy. FFTF was 84.4 %, 89.3 %, and 85.4 % and OS was 91.9 %, 95.3 %, and 94.5 % in each treatment group, respectively. Following these results, six cycles of BEACOPP-escalated followed by PET-guided radiotherapy to residual disease is recommended as the standard of care for advanced-stage HL. However, there is no reported specific subanalysis of the outcomes of AYAs.[24]

North American guidelines differ, as they recommend the use of ABVD for all stages of adult HL, balancing the risks of toxicity with BEACOPP versus the risk of relapse with ABVD and the similar OS results between the chemotherapy (CT) backbones.[25]

Three studies reported the specific number of AML/MDS, NHL, and STs. Combining these data, these SMs occur in 0.65 %, 0.95 %, and 1.55 % of HL survivors, respectively, with an approximate median follow-up of five years.[21,23,24] Meyer et al. did not report specific types of SMs; however, as expected considering the longer median follow-up in their study (11.3 years), the proportion of SMs was 8.2 %.[22]

Pediatric Studies Including Adolescents and Young Adults

There are few studies comparing the outcomes between children and adolescents (see *Table 2*). Excellent results for adolescents have been reported with the OPPA-OEPA/COPP protocols (the agents used in these drug combinations are listed in the note at the bottom of *Table 2*). The DAL-HD-90 trial reported no difference in OS or EFSamong age groups 15–18 years old versus children younger than 16 years old.[26] In the GPOH-HD-2002 trial, the boys' treatment was changed, with an increment

Table 2: Studies of Adolescent and Adult Outcomes with Pediatric Regimens

Author	Number of patients (A)	Range of age (A)	Stages	Median FU (years)	Backbone Treatment	OS in A (%)	EFS in A (%)
Cramer et al., 1985[70]	72 (40)	5–19 (15–19)	IA–IIB	6.8	MOPP/RT CVPP/RT	92.4 (12 yrs)	FFR 88 (12 yrs)
Weiner et al., et al., 1997[71]	179 (103)	4–20 (13–20)	IIB–IV	NS	MOPP/ABVD with or without RT	NS	72 (5 yrs)
Schellong et al., 1999[26]	578 (136)	2–18 (15–18)	All	5.1	OEPA+RT OPPA+RT OEPA/COPP+RT OPPA/COPP+RT	97 (5 yrs)	92 (5 yrs)
Hudson et al., 2004[72]	159 (105)	2.8–19 (14–19)	Bulky and/or IB, IIB, III, IV	5.8	VAMP/COP+RT	NS	74.8 (5 yrs)
Büyükpamukçu et al., 2009[73]	614 (48)	2–21 (15–21)	All	9.9	COPP+RT ABVD+RT COPP/ABVD+RT	70 (20 yrs)	NS
Mauz-Korholz et al., 2010[27]	573 (404)	2–18 (13–18)	All	5	OEPA/COPDAC OPPA/COPP with or without RT	97 (5 yrs)	86.9 (5 yrs)

A = adolescents; EFS = event-free survival; FFR = freedom from relapse; FU = follow-up; NS = not specified; OS = overall survival; RT = radiotherapy.
ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; COPDAC = cyclophosphamide, vincristine, prednisone, and dacarbazine; COPP = cyclophosphamide, vincristine, prednisone, and procarbazine; CVPP = lomustine, vinblastine, procarbazine, and prednisone; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; OEPA = vincristine, etoposide, prednisone, and doxorubicin; OPPA = vincristine, prednisone, procarbazine, and doxorubicin; VAMP = vincristine, doxorubicin, methotrexate, and prednisone;

of the total dose of etoposide from 1,000 to 1,250 mg/m^2 and a replacement of procarbazine by dacarbazine in order to avoid the gonadotoxicity associated with the former. A total of 573 children were enrolled. A subgroup analysis comparing those younger and those older than 13 years demonstrated that OS at five years was nearly identical in both groups, with rates of 98.2 % and 97.0 %, respectively, but that PFS and EFS tended to be more favorable in the younger age group (PFS: 94.6 % versus 89.0 %, p=0.085; EFS: 93.9 % versus 86.9 %, p=0.036).[27]

The Pediatric Oncology Group (POG) conducted a study of patients with intermediate- or high-risk HL from 1997 to 2001, which included 216 patients (31 % were 16–21 years old).[28] Rapid-early responders (RERs) to three cycles of doxorubicin, bleomycin, vinblastine, etoposide, prednisone and cyclophosphamide (ABVE-PC) received 21 Gy radiation to involved regions. Slow-early responders (SERs) received two additional ABVE-PC cycles before 21 Gy radiation. The EFS and OS at five years were 84 % and 95 %, respectively.

Kelly et al., in a study by the Children's Oncology Group (COG) reported the results of 98 patients aged four to 21 years (48 % were 15–21 years) diagnosed with high-risk HL from 1999 to 2002.[29] All patients initially received four cycles of BEACOPP-escalated. Those patients with rapid early response continued treatment with less intensive protocols. Girls received four cycles of COPP/ABV (doxorubicin, bleomycin, vinblastine) with no consolidating RT to reduce the risk of secondary BC, and boys received two cycles of ABVD followed by IF-RT. Those patients of either gender with slow early response received four additional cycles of BEACOPP-escalated followed by IF-RT. EFS and OS at five years were 94 % and 97 %, respectively. Despite this excellent outcome, the COG committee has reduced intensity of therapy in subsequent studies in an attempt to reduce long term toxicities.

In OPPA-OEPA/COPP protocols, there are no reports of BCs as SMs, but the median follow-up (five years) is short for a proper evaluation. The proportion of other STs was 0.69 % and the proportions of NHL, AML, and acute lymphoblastic leukemia were 0.9 % for each.[26,27] In the POG study, with a median follow-up of 5.2 years, three patients developed AML and one osteosarcoma.[28] In the COG study, with a median follow-up of 6.3 years, two patients developed AML.[29]

Long-term Sequelae

Second Malignancies

The most important late treatment effect among female AYA survivors of HL is BC, which accounts for almost 40 % of diagnosed SMs in this population.[30,31] Among women treated for HL before the age of 30, the risk of developing BC is six times greater than in the general population, with an absolute excess risk of 20–40 occurrences per 10,000 annually.[32] Particularly, mantle RT at doses of 35–45 Gy is associated with a two- to 20-fold increased relative risk of BC, depending on the age at treatment. Studies of survivors treated with these doses have reported a 30-year cumulative incidence of BC of approximately 20–30 % among females treated before the age of 30.[33] De Bruin et al. did not find an increased risk of BC in women treated between the ages of 41 and 50.[34]

Comparing BC after HL with *de novo* BC, the following relevant characteristics in HL survivors are:

- earlier stage at diagnosis, possibly due to recommended screening guidelines for HL survivors;
- increased risk of synchronous or metachronous bilateral BC, secondary to often bilateral radiation exposure, limiting opportunities of breast conserving therapy;
- younger age at diagnosis, thus likely to display a more aggressive phenotype and to be hormone receptor-negative;
- evidence of increased genetic instability in the tumor; and
- increased risk of death from causes other than BC, including a seven-fold increased risk of death from other cancers and a two- to four-fold increased risk of cardiac death.[32,35,36]

Elkin et al. found that the rates of local failure and metastatic failure were similar in the two groups (BC in HL survivors and *de novo* BC), and that the BC-specific mortality was elevated in the HL survivors group—but the difference was not statistically significant.[32] Close surveillance of the contralateral breast is recommended for HL survivors who develop unilateral BC.

Studies related to late effects of mantle/extended-field RT have helped to identify groups of survivors who may benefit from early cancer screening or enhanced cardiac surveillance, and have driven the development of better treatment protocols that are less reliant on the use of RT and alkylating agents. Contemporary IF-RT treats only initially involved lymph node regions (RT doses are typically 30 Gy for adults and 21 Gy for children) and early clinical studies have shown a clinically significant reduction in the risk of SM.[33] In keeping with this, the evidence indicates that reducing the proportion of breast tissue exposed to radiation with the use of IF-RT will indeed decrease the future risk of BC.[34] Mantle RT was associated with an approximately three-fold increased risk of BC compared with IF-RT of comparable prescription dose (36–44 Gy).[34,37] Moreover, a study comparing IF-RT and involved nodal radiation therapy (IN-RT) found that the latter produced an average reduction in mean heart dose of 50 % and in breast dose of 42 %.[38] Studies examining the dose–risk relationship for STs suggest a decrease in risk parallel to a dose reduction to less than 40 Gy.[34,39–41] It will take at least another decade to study the BC risk associated with contemporary HL treatments, so it may be inappropriate to alarm patients who are scheduled for conformal dose-reduced RT by relating the experience from radical RT given between three and five decades ago. Regardless, it is important to counsel patients on preventive measures, such as smoking cessation and healthy lifestyle modifications.[32,34,42]

The risk of secondary AML/MDS syndrome is clearly related to the primary CT and is dependent on dose and type of drug.[43–46] However, a meta-analysis showed increased risk after CT+RT compared with CT only for advanced-stage disease.[47] In a study of eight randomized trials of the GHSG from 1978 to 1998 (HD1 to HD9), Scholz et al. found using intermediate- and advanced-stage CT, the cumulative risk of AML/MDS is 1.5 %, while the risk of AML/MDS after BEACOPP-escalated is 4.4 % (p=0.004) and comparable with that after relapse therapy (4.5 %).[48] For secondary NHL, there are no differences in cumulative risk between the primary therapies (2.9 %), while the risk after relapse therapy is increased (6.6 %, p=0.002). The authors concluded that recently published long-term follow-up data revealed that the gain in OS obtained with BEACOPP-escalated for advanced-stage disease clearly outweighs the increased incidence of leukemia. In addition, the results of the HD15-trial favors the reduction from eight to six cycles of BEACOPP-escalated, with a resultant decrease in cumulative doses of CT and decreased incidence of AML/MDS (p=0.0001).

Cardiac and Pulmonary Toxicity

The effects of thoracic RT on cardiac risk are difficult to separate from those of anthracyclines because few patients undergo RT without the use of anthracyclines. The pathogenesis of injury differs: radiation primarily affects the fine vasculature of the heart and anthracyclines produce direct damage to the myocytes.[49] The use of IF-RT or IN-RT may reduce the morbidity caused by damage to the valves and the microvasculature within the myocardium, but it is not clear that the risk of coronary artery disease will be substantially reduced among patients receiving mediastinal treatment.[33] Increased risk of anthracycline-related cardiomyopathy is associated with female sex, cumulative doses higher than 200–300 mg/m^2, younger age at time of exposure, and increased time from exposure.[50–52] Given that the use of anthracyclines is part of all contemporary protocols, it is plausible that cardiac morbidity may surpass SM as the dominant long-term sequelae among survivors of contemporary HL therapy.[33]

Thyroid Abnormalities

Abnormalities of the thyroid are extremely common in young adult survivors of childhood HL, particularly among females treated with high doses of radiation to the neck. The Childhood Cancer Survivor Study included 1,791 survivors of childhood and adolescent HL diagnosed between 1970 and 1986.[53] At 20 years from diagnosis, hypothyroidism occurred in 7.6 % of patients who had not received RT, 30 % of those who had received less than 35 Gy and 50 % of those who had received more than 35 Gy. Although no thyroid cancers were noted in patients who had received less than 25 Gy, overall, there was an 18-fold increased risk of thyroid cancer in survivors of pediatric HL.

Gonadal Toxicity

Gonadal toxicity may manifest as infertility, lack of sexual development, and sexual dysfunction. Infertility caused by azoospermia is the most common manifestation of gonadal toxicity. Some pubertal male patients will have impaired spermatogenesis before they begin therapy.[54] Alkylator CT, especially if containing procarbazine and/or cyclophosphamide, is most harmful to gonadal functioning. At higher cumulative doses, alkylator containing regimens may cause prolonged azoospermia in 90–100 % of men.[55] A few studies have evaluated male fertility following cyclophosphamide-containing regimens given to children and young adults with sarcomas and other cancers[56–58] and suggest that the incidence of sterility will be low if the cyclophosphamide dose is less than 7.5 g/m^2. Data concerning ovarian function following CT for female children and young adults with HL suggest that the ovaries of children and adolescents are less sensitive to the effects of alkylating agents than the ovaries of older women; females over 30 years have a much higher risk of acute ovarian failure. However, with long-term follow-up, the cumulative risk of menopause before the age of 40 becomes the same irrespective of treatment age, and the incidence of early menopause in young female survivors may be as high as 37 %.[55,59,60]

Options for fertility preservation in women receiving cytotoxic therapies are available in some jurisdictions (see, for example, recommendations from the network FertiPROTEKT [available at: www.fertiprotect.eu]).[61] Balanced and realistic counseling about fertility prior to the start of therapy is essential. Semen cryopreservation before treatment is started should be offered to all post-pubertal males.[55]

Reducing Treatment Toxicity

Response-adapted therapy is an emerging concept in which treatment is decided according to early response to initial CT, usually after two cycles. Response is defined by anatomical (computed tomography) and, more recently, functional (positron emission tomography [PET]) imaging.[24] The GHSG HD18-trial stratifies according to PET scans

performed after two cycles of BEACOPP-escalated. The major goal of this currently ongoing study is to show whether the total number of cycles can be reduced from eight to four in patients with negative early interim PET.[62] Similarly, the EuroNet-PHL-C1 trial for children and adolescents with HL is comparing the five-year EFS rate in patients with an adequate response determined by PET after two courses of vincristine, etoposide, prednisone, and doxorubicin (OEPA) who do not receive RT with those patients whose response is such that RT is required. The estimaged target EFS is 90 %.[63] In addition to decreasing the number of patients receiving RT, efforts are aimed at reducing RT fields from currently accepted IF-RT to more recently proposed IN-RT. However, it will be many years before an associated reduction in late toxicity will be clinically demonstrable.[33]

Follow-up for Survivors

In order to reduce the morbidity associated with long-term sequelae, early initiation of screening is recommended for survivors. The COG has developed *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*[64] and some pediatric academic institutions have successfully developed formal programs for young adult survivors in partnership with neighboring adult institutions.

Psychosocial Problems and Interventions

Young adult survivors of childhood and adolescent cancer are a growing population many of whom remain at lifelong risk of potentially serious complications of their cancer therapy. Management of this unique group requires a broad-based interdisciplinary clinical team, which should include physical and occupational therapy, palliative care, psychology, social work, oncology, and nursing representatives. However, research shows that many of these survivors have deficient health-related knowledge and are not engaging in the recommended health promotion and screening practices that could improve their long-term outcomes.[65]

In a population-based study of AYA survivors, Keegan et al. found that this group of patients has substantial unmet information needs varying according to demographic and health-related factors.[66] More than half of all AYAs had unmet information needs relating to their cancer returning and cancer treatments. They must also contend with a lack of services, either due to financial constraints or inadequate resources from the medical team. The majority of AYAs who needed a pain management expert, a physical and occupational therapist, a mental health worker, or financial advice on how to pay for healthcare did not receive those services. Some AYA patients and survivors are unemployed due to their condition, with the subsequent lack of health insurance and access to appropriate long-term follow-up care. In a study of young adult cancer survivors, 20 % reported not having visited a cancer center in the past two years.[67] Systematic healthcare transition constitutes the standard of care for AYA survivors of childhood cancer. In developing a transitional care program, it is necessary to consider the scope of services to be provided, the available resources, and other local exigencies that help determine the optimal model for use.[65]

Zebrack and Isaacson described the psychosocial interventions likely to reduce distress and promote individuals' ability to cope with stressful conditions – these interventions are detailed below.[68]

- Peer support programs offer AYAs opportunities to build interpersonal and problem solving skills, create a sense of community among support group members, and address areas of concern (such as coping with uncertainty about the future, establishing autonomy while dealing with forced dependence on family and friends, social exclusion, body image, sex and sexuality, and infertility). There are reports showing improvements in psychological wellbeing as well as in knowledge, confidence, ability to cope, self-efficacy, and effective interpersonal interactions from group participation.
- Technology-based interventions satisfy AYAs' needs for information and support and have been associated with increased self-efficacy, improved knowledge and enhanced treatment adherence. However, the vast amount of information available on the Internet may cause confusion and AYAs need guidance in how to seek, sift through, and understand this information.
- Skill-based interventions—including problem-solving interventions and cognitive behavioral therapies—teach new skills or induce new ways of thinking, to promote change in one's conditions or circumstances.

The ability to engender trust and to be flexible are key requirements of caregivers who deal with AYA patients. The ability to relate to others is important in winning the trust and respect of the AYA population in particular. Transition times are often unpredictable and thus challenging, but replete with possibility,[69] and the quality of survivorship is critical to any assessment of the quality of treatment.

Conclusions

There is clear evidence to support the treatment of patients aged 16–18 years with pediatric regimens. For HL patients aged 18-21 years the published results are not clearly different and the result of the recently closed pediatric COG protocols in which this patient group is included will be of interest. In general, however, contemporary adult and pediatric treatment regimens have shown excellent survival results with overall reduction of therapy intensity. It is expected that these protocols will result in very different long term toxicity profiles from those described in published studies to date.

In the future, increasingly sophisticated studies will be required to define patients whose therapy can be further reduced without compromising cure rates. Clearly this should only be done in the context of clinical trials. Current therapeutic programs may be enhanced with attention to the psychosocial needs of the AYA population during and following therapy, and determining best practices for long term follow up. ■

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