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Toxic Effects of Hodgkin Lymphoma Treatment

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1. Introduction

In Hodgkin Lymphoma therapy chemotherapy and radiotherapy are applied, and both of them can cause early or late toxicity. Optimal treatment of Hodgkin Lymphoma understands applying "enough therapy, not too few or too much". Early and late toxicities, caused by applying chemotherapy and radiotherapy, will be analyzed with respect to system toxicity (haematological, gastrointestinal, cardiopulmonary toxicity, neurological, etc).

All anti tumour drugs that are used in treatment of this disease will be individually analyzed. These drugs are recommended by protocols suggested in the up to date guidelines. Also early and late toxicity of earlier applied types of radio therapy and Involved field (IF) irradiation will be observed. Late toxicity and development of secondary malignancy and sterility will be discussed separately. This will stress importance of applying special steps that will provide possibility of having offspring even in population of diseased and treated HL patients.

World-wide studies that confirmed toxicity of earlier applied protocols and irradiation treatments (total nodal, subtotal nodal and extended field) will also be discussed. These findings influenced new views of treating HL that understand applying chemotherapy in all clinical stages with or without IF irradiation.

Personal experiences will also be listed based on a studies of patients diagnosed with HL and treated at Haematology Clinic at Clinical Centre University Sarajevo. One such study had primary goal in determining secondary malignancies as a consequence of late toxicity in HL treatment. The study was conducted from 1992 – 2001. In the first group of patients in that study 10 patients (7.9%) were with secondary malignancy out of which one was with myelodysplasia, three with Non Hodgkin Lymphoma, six with solid carcinoma (Ca planocellulare papillae – one patient, Ca planocellulare laringys – one patient, Neo palatum molae – one patient and Ca mammae – three patients). In the same group, epidemiologically observed, the most patients ware aged from 14 to 24 years.

In our country, which is listed as undeveloped, first peak in age bimodal graph was shifted towards younger aged group (15-24 years). This indicates that even maximal success in HL treatment of these patients can, in 15-20 years after the treatment, question this success. This time span is cumulative period needed to develop malignant mutation. Second analyzed period is targeted towards analyzing patients with HL treated from 2002 – 2011 with applying chemotherapy using ABVD and BEACOPP protocol with or without IF irradiation.

To fully understand toxicity of the Hodgkin lymphoma therapy it is necessary to shortly review therapy applications. First therapy approaches in Hodgkin Lymphoma treatment appeared in period from 1932-1950 when treatment was conducted using herbs, X-rays and surgery. Vera Peters and her colleagues from Sanford University pioneered in the field of radiotherapy. They created high dose radiation therapy that was dominant from 1950 to 1970. (Peters M, 1950) Toxicities of such therapy approach were analyzed in the studies conducted in the upcoming years. Those studies changed further chemotherapy approaches from 1970 till 2008. (Kaplan HS, 1996)

Prior to the mid-1960s advanced-stage Hodgkin lymphoma was treated with single-agent chemotherapy. In 1964 Vincent DeVita and George Canellos at the National Cancer Institute (United States) developed the MOPP regimen. National Cancer Institute developed the first combination chemotherapy that cured a number of patients who relapsed after standard radiation therapy. (DeVita V. et al, 1970; De Vita V. et al, 1992.) ABVD was developed as a potentially less toxic end more effective alternative to MOPP. Initial results of ABVD regimen were published at Universita degli Studi di Milano in academic year 1974/1975 (thesis of a student led by Bonadonna Gianni) and these initial results were also published in 1975 by an Italian group led by Bonadonna. (Bonadonna G et al, 1975)

In 1994 German Hodgkin's Lymphoma study Group (GHSG), lead by Volker Dihel, developed a regimen BEACOPP in an attempt to improve the prospect for patients with advanced disease stages. Results were published subsequently for a large prospectively randomised trial HD9 in patients with previously untreated advanced Hodgkin lymphoma. (Diehl V. et al, 1998).

Further improvement of Hodgkin lymphoma treatment is introduction of high dose therapy followed by autologous stem cell transplantation (HDT-ASCT). New findings in the field of immunology and molecular biology, as well as many studies that analyzed response and toxicity of previous therapy options, influenced adoption of contemporary individual treatment approach with application of targeted immunotherapy. This does not conclude HL as there are large numbers of Hodgkin Lymphoma patients that do not achieve required response. Also different treatment complications require constant improvement of therapy approach. Contemporary approach is ever more directed towards researching targeted therapy using antibodies, immunomodulators, HDAC inhibitors and m-TOR inhibitors.

In Hodgkin Lymphoma therapy currently Chemotherapy and Radiotherapy are most often used.

1.1 Chemotherapy

Most often protocol is ABVD which gives 82% CR and 72% OS with follow up of 8 years. On the other side, BEACOPP gives 88% CR1 baseline (B) vs. 96% escalated (E), FFS 76%(B) and 87%(E) and OS of 88% (B) and 91% (E) and follow up of 5 years (Michael C. et al, 2008a; Griffin R. et al., 2010). Up to date treatment options (from 2011) are conducted using EORTC, NCCN and GHSG guidelines. These guidelines state that following protocols (along with ABVD and BEACOPP) are to be used: Stanford V, DHAP, ICE, ASHAP, MINE, Mini-BEAM, HDT+SCT; and rarely: VIM-D, MIME, GVD, GDP, GCD, GEM-P, IGEV, EPOCH, CVP, ABVD/MOPP, COPP/ABVD, COPP, CHLVPP, EVA.

1.2 Radiotherapy

Radiation volume in HL was used in three ways: mantle field, paraaortic region and pelvis. The *mantle field* region encompassed the cervical, supraclavicular, infraclavicular, axillary, mediastinal and hilar nodes. (Sandra J. Horning 2001) *Paraaortic* understands irradiation of spleen and pelvis area individually or in continuity when marked as inverse Y. If all stated areas are used, irradiation is marked as total nodal (TN). If mantle field and paraaortic area are used irradiation is named subtotal nodal (STNI), while only mantle field is marked as extended field (EFRT). There is also involved field (IF) that encompasses lymph node in question and complete lymph drain.(Griffin R. et al., 2010)

Optimal treatment of Hodgkin Lymphoma understands applying "enough therapy, not too few or too much". In creating HL treatment plan, it is very important to define illness and its risks, and fully review patient's condition. Meaning, early favourable and early unfavourable, as well as advanced stage with risk factors (IPS: age, gender, Hgb, albumin < 40g/l, advanced stage IV, white cell count > 15000/mm^2 absolute lymphocyte count) with respect to comorbidity. Pet CT gives significant data regarding disease stage and evaluation of disease location as well as its absence, and hence it gives possibility of optimal therapy dosage. Special attention is required when dealing with younger patients and females younger than 30 years as infertility and secondary malignancies can occur.

1.3 Toxic effects

In Hodgkin Lymphoma therapy, application of chemotherapy and radiotherapy has healing effect but also has different toxic side effects. These side effects can cause early and late toxicity (acute and chronic side effects) which can occur in different systems: haematological, cardiovascular, respiratory, gastrointestinal, renal, urogenital, neurological, reproduction system and skin. These toxicities affect pregnancy and can have carcinogenic effect. Early toxicities are relatively easy to overcome, while late toxicity occurs in the form of: sterility, cardiovascular disease, pulmotoxicity, neurotoxicity and secondary malignancy what poses significant complications. Quality of life and reduction of early and late toxicity represent significant goals in the Hodgkin Lymphoma treatment.

2. Toxicities according to affected system during HL treatment

By applying chemotherapy and radiotherapy different toxicities can occur. Most significant toxicities are named in the remaining of this section and for each of them most important characteristics are listed.

2.1 Hematotoxicity

This toxicity causes s*econdary leukaemia*, *hemolytic anemia* and *myelosuppression* which is most often followed by *neutropenia* which is further most often followed by sepsis. Most difficult cases are when sepsis is caused by gram-negative bacteria or respiratory infection with possibility of ARDS. *Thrombocytopenia* with grade 4 (according to WHO) can cause significant bleedings. A*nemia* can reduce working ability, tissue ischemia or worsened cardiovascular diseases.

2.2 Cardiotoxicity

Pericardium: acute pericarditis, Constrictive pericarditis from 1-6 months of radiotherapy
Myocardium: myocardial fibrosis, Progressive and restrictive cardiomyopathy
Blood vessels*: coronary arterial disease* (CAD) and structural changes in coronary arteries which are similar to atherosclerosis
Valvular disease: Predominantly affects mitral valve and aortic valve (both regurgitation and stenosis possible)
Conduction system: *arrhythmia* (persistent tachycardia) and complete or incomplete atrioventricular block. (Christopher F. 2010)

2.3 Pulmonary toxicity

Most often toxicities are lung fibrosis and pneumonitis.

2.4 Gastrointestinal complications of chemotherapy

Following gastrointestinal complications can occur: nausea, vomiting, emesis, diarrhea, ileus, mucositis, ventricular and colon neoplasm .
Hepatotoxicity: laesio hepatis.

2.5 Urogenital/Renal toxicity

Most often toxicities are cystitis and renal insufficiency.

2.6 Endocrine

Following can occur in the endocrine system: hypothyroidism, Grave′s disease, thyroiditis, thyrotoxicosis, thyroid nodule, thyroid malignancies.

2.7 Gonadal complications teratogenicity of cancer therapy

Infertility occurs in both genders. Azoospermia and hormonal elevation occur in male patients while amenorrhoea and FSH elevation occur in females.

2.8 Dermatologic toxicity

Alopecia, erythema and exanthema, striae, hyperpigmentation, oedema, hyperkeratosis, pruritus and nail changes are often dermatologic toxicities.
Local toxicity: Extravasation (necrotizing is possible)

2.9 Secondary malignancies after chemotherapy

Most difficult complications occur on lungs, breast, stomach, colon and thyroid gland. Also malignant melanoma, aggressive and indolent lymphoma and acute secondary leukaemia can occur as secondary malignancies.

2.10 Other

Hypersensitivity reactions are possible to occur.

3. Early and late toxicity of drugs used in HL treatment

When applying drugs it is extremely important to know the cumulative dosage that causes toxicity.

Drug	Cumulative dosage	Substance
Adriamycin / Doxorubicin	450-550 mg/m²	Anthracyclines
Bleomicin	Pulmotoxicity >300mg (age <15 and >65 years)	Antibiotic
Lomustin/CCNU	Cumulative dosage of nephrotoxicity >1200-1500mg/m²	Alkylating agent
Dacarbazin/DTIC	standard doze 200-375/m² /d i.v, during 3-4 weeks 750-850mg/m²//d i·v during 4 weeks	non classic Alkylating agent
Carmustin/BCNU	Pulmotoxicity >1000mg/m²	Alkylating agent
Prokarbazin	>/=4g/m²	non classic Alkylating agent
Vinkristin	neurotoxicity >20 mg cumulative dosage	Vinca alkaloids
Cisplatin	>100-200 mg/m²	Alkylating agent
Cyclophosphamide	>7,5g/m², Mega dose 16 -19 g/m²/ (application of these dosages only in specialized haematological and oncology centres)	Alkylating agent
Chlorambucil	Lung fibrosis >2000mg	Alkylating agent
Melphalan	>/=140 mg/m²	Alkylating agent
Carboplatin	</2g/m²	Alkylating agent
Rituximab/Mabthera*	standard dosage 375/ m²	monoclonal antibody

Table 1. Drugs used in HL treatment and their cumulative dosages (Berger D.P. et al, 2002).

3.1 Adriamycin/Doxorubicin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: acute (arrhythmia, ischemia, infarct) and chronic (dilatative cardiomyopathy) side effects. Risk groups: earlier cardiac illness, younger than 15 and older than 65 years, bolus injection, mediastinum irradiation, cumulative dosage larger than 450-550/mg/m²; *Gastrointestinal complications of Chemotherapy***:** nausea, vomiting, mucositis, stomatitis, diarrhea; *Dermatologic Toxicity:* exanthem, urticaria, alopecia, rarely hyperpigmentation.*Local toxicity*: extravasation; *Gonadal Complications*: infertility; *Second Malignancies after Chemotherapy:* potentially mutagenic, teratogenic and carcinogenic. (Berger D.P. et al, 2002)

3.2 Bleomycin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Pulmonary Toxicity*: interstitial pneumonitis and lung fibrosis; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, loss of appetite,

mucositis, diarrhea; *Dermatologic Toxicity*: alopecia, erythema, exanthem, striae, hyperpigmentation, oedema, hyperkeratosis, pruritus, nail changes; *Other*: fever, myalgia, shivering. (Berger D.P. et al, 2002)

3.3 Carboplatin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, loss of appetite, mucositis. Liver: transitory increase of transaminase; *Renal Toxicity*: rarely nephrotoxicity which appears upon inadequate rehydration; *Dermatologic Toxicity*: alopecia, erythema, dermatitis, allergies, pruritus; *Neurotoxicity*: rarely peripheral neurotoxicity, rarely hearing problems and optic neuritis; *Gonadal Complications*: infertility; *Other*: fever, shivering. (Berger D.P. et al, 2002)

3.4 Carmustin (BCNU)

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Pulmonary Toxicity*: interstitial pneumonitis, lung infiltrate and lung fibrosis upon administering cumulative dosage; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, mucositis, diarrhoea, rarely esophagitis, ulcer, gastrointestinal bleeding. Liver: transitory increase of transaminase, veno-occlusive-disease (VOD); *Renal toxicity*: renal insufficiency; *Dermatologic Toxicity*: alopecia, dermatitis, erythema, hyperpigmentation; *Neurotoxicity*: peripheral and central neurotoxicity, psychoorganic syndrome, neuroretinitis, optic neuritis, ataxia; *Gonadal Complications*: infertility, azoospermia, amenorrhoea. (Berger D.P. et al, 2002)

3.5 Chlorambucil

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Pulmotoxicity*: lung fibrosis, cumulative dosage larger than 2000mg; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, mucositis. Liver: transitory transaminase increase, rarely heavier liver toxicity; *Dermatologic Toxicity*: alopecia, erythema; *Neurotoxicity*: rarely peripheral and central neurotoxicity; *Gonadal Complications*: infertility (cumulative dose > 400mg) amenorrhoea and azoospermia; *Other*: fever, rarely cystitis; *Second Malignancies after Chemotherapy*: potentially mutagen, carcinogen and teratogenic. (Berger D.P. et al, 2002)

3.6 Cisplatin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: rarely rhythm disorders, cardiac insufficiency; *Gastrointestinal Complications of Chemotherapy*: nausea, emesis, loss of appetite, mucositis, diarrhoea, enteritis. Liver: transitory transaminase increase; *Renal toxicity*: electrolyte disbalance: decrease of level of Na, K, Ca and Mg. Cumulative dosage – nephrotoxicity followed with tubular insufficiency; *Dermatologic Toxicity*: alopecia, dermatitis, allergy reactions; *Neurotoxicity*: peripheral neurotoxicity, ototoxicity, when applying cumulative dosage > 100-200mg/m^2, dizziness, rarely focal encephalopathy, optic neuritis; *Gonadal Complications*: infertility; *Other*: Local toxicity: local phlebitis, possible necrotizing extravasation. (Berger D.P. et al, 2002)

3.7 Cyclophosphamide

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: high dosage – in 5-10% cases acute myopericarditis, cardio insufficiency, and hemorrhagic myocardium necrosis; *Pulmotoxicity*: high dosage – lung fibrosis, pneumonitis; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, mucositis, stomatitis, loss of appetite Liver: transitory transaminase increase, rarely cholestasis; *Urogenital Toxicity*: hemorrhagic cystitis when applying high therapy doses; *Renal toxicity:* renal insufficiency; *Dermatologic Toxicity*: alopecia, rarely hyperpigmentation, dermatitis, erythema; *Neurotoxicity*: when applying high dosages – acute encephalopathy; *Gonadal Complications*: infertility, azoospermia, amenorrhea; *Other*: fever, allergy reactions. (Berger D.P. et al, 2002)

3.8 Cytarabin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Pulmonary Toxicity*: when applying high dosages – pulmotoxicity, lung oedema, ARDS (acute respiratory distress syndrome); *Gastrointestinal Complications of Chemotherapy*: nausea, emesis, mucositis, diarrhoea, loss of appetite, when applying high dosages rarely pancreatitis, ulcer, esophagitis, colon necrosis Liver: transitory transaminase increase, cholestasis; *Dermatologic Toxicity*: dermatitis, erythema, exanthema, conjunctivitis, keratitis, alopecia; *Neurotoxicity*: peripheral and central neurotoxicity, cerebral and cerebellum disorders at patients > 60 years and high dose therapy (48 g/m2). After intrathecal application - acute arachnoiditis and leukoencephalopathy; *Other*: fever, myalgia, arthralgia, bone pain. (Berger D.P. et al, 2002)

3.9 Dacarbazine (DTIC)

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, rarely mucositis, diarrhoea, Liver: transitory transaminase increase, veno-occlusive-disease (VOD); *Renal toxicity*: Kidneys: rarely renal insufficiency; *Dermatologic Toxicity*: alopecia, erythema, exanthem, photosensitivity, allergy reactions; *Neurotoxicity*: rarely CNS disorders (headache, sight disorders, confusion, lethargy, spasms, paresthesia); *Other*: fever, myalgia, shivering. Local toxicity: extravasation, local thromboflebitis. (Berger D.P. et al, 2002)

3.10 Etopozid/VP-16

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: rarely arrhythmia, hypotonia at intravenous application, ischemia; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, rarely mucositis, dysphagia, diarrhea, constipation, Liver: transitory transaminase increase; *Dermatologic Toxicity*: alopecia, rarely erythema, hyperpigmentation, allergy reactions; *Neurotoxicity*: rarely peripheral neuropathy and CNS disorders (somnolence); *Gonadal Complications*: infertility. (Berger D.P. et al, 2002)

3.11 Gemcitabin

Application of this drug can cause following toxicities:

Hematotoxicity: myelosuppression; *Pulmonary Toxicity*: Lung oedema (rarely); *Gastrointestinal complications of Chemotherapy*: nausea, emesis, rarely mucositis, diarrhoea; *Renal toxicity*: proteinuria, hematuria, Liver: transitory transaminase increase; *Dermatologic Toxicity*: rarely erythema, pruritus, rarely alopecia, oedema; *Other*: peripheral oedema. (Berger D.P. et al, 2002)

3.12 Ifosfamid

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Gastrointestinal complications of Chemotherapy*: loss of appetite, nausea, emesis, mucositis, diarrhoea. Liver: transitory transaminase increase, rarely cholestasis; *Urogenital*: hemorrhaging cystitis when applying cumulative dosage; *Renal toxicity*: renal insufficiency; *Dermatologic Toxicity*: alopecia, rarely urticaria, hyperpigmentation; *Neurotoxicity*: acute encephalopathy, cerebellum neurotoxicity, confusion, psychosis, ataxia, spasms, somnolence, coma. Prophylaxis natriumbicarbonat, therapy: methylene blue; *Gonadal Complications*: infertility; *Other*: fever, allergy reactions. (Berger D.P. et al, 2002)

3.13 Lomustin (CCNU)

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Pulmonary Toxicity*: rarely lung infiltration, lung fibrosis; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, mucositis, diarrhea; *Renal toxicity*: renal insufficiency when applying cumulative dosage; *Dermatologic Toxicity*: alopecia, dermatitis, hyperpigmentation; *Neurotoxicity*: peripheral and central neurotoxicity; *Gonadal Complications*: infertility, amenorrhea, azoospermia. (Berger D.P. et al, 2002)

3.14 Mechlorethamine/Nitrogen mustard

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression, hemolytic anemia; *Gastrointestinal complications of Chemotherapy*: nausea, vomiting (almost 100%) onest may be within minutes of drug administration, diarrhea, and anorexia. Liver: hepatotoxicity; *Dermatologic Toxicity*: alopecia, hyperpigmentation of veins, contact and allergic dermatitis (50% with topical use); *Gonadal Complications*: azoospermia, chromosomal abnormalities, delayed menstrual cycle, oligomenorrhea, amenorrhea, impaired spermatogenesis; *Neurotoxicity*: peripheral neuropathy; *Second Malignancies after Chemotherapy*: carcinogenicity, mutagenicity, teratogenicity.

3.15 Melfalan

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Pulmonary Toxicity*: rarely lung fibrosis; *Gastrointestinal complications of Chemotherapy*: loss of appetite, nausea, emesis, mucositis, diarrhoea; *Dermatologic Toxicity*: rarely alopecia, exanthem, erythema, urticaria, pruritus, oedema; *Gonadal Complications*: infertility; *Other*: rarely allergy reactions. (Berger D.P. et al, 2002)

3.16 Methotrexat

Application of this drug can cause following toxicities:

Hematotoxicity: myelosuppression; *Gastrointestinal complications of Chemotherapy*: mucositis, nausea, vomiting, emesis, diarrhea, gastrointestinal bleeding; Liver: acute and chronic liver insufficiency; *Renal toxicity*: Renal insufficiency; *Dermatologic Toxicity*: exanthem, dermatitis, pruritus, conjunctivitis, allergy reactions; *Neurotoxicity*: reversible acute encephalopathy after intravenous and intrathecal application, leukoencephalopathy; *Other*: rarely allergies. (Berger D.P. et al, 2002)

3.17 Mitoxantron

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: chronic cardiotoxicity, cardiomyopathy, heart insufficiency; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, mucositis, rarely gastrointestinal bleeding. Liver: transitory transaminase increase, rarely cholestasis
Renal toxicity: rarely renal insufficiency; *Dermatologic Toxicity:* alopecia, allergy reactions, dermatitis, pruritus; *Gonadal Complications*: infertility; *Second Malignancies after Chemotherapy*: secondary acute leukaemia. (Berger D.P. et al, 2002)

3.18 Prednisone

Application of this drug can cause following toxicities:
Immunosuppression, affects apoptosis in internal signal path, thrombosis with consequential infarct of the affected tissue, suppression adrenal gland, retention Na, decrease of K, iatrogenic diabetes mellitus, psychoses especially severe in older patients.

3.19 Prokarbazin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: tachycardia, hypotonia; *Gastrointestinal complications of Chemotherapy*: nausea, emesis, rarely mucositis, dysphagia, diarrhoea, Liver: transitory transaminase increase; *Dermatologic Toxicity*: alopecia, erythema, exanthem, photosensitivity, hyperpigmentation, allergy reactions; *Neurotoxicity*: reversible peripheral neurotoxicity, rarely CNS disorders (Somnolence), agitation, depression, hallucinations; *Gonadal Complications*: infertility; *Second Malignancies after Chemotherapy*: secondary malignancies; *Other*: fever, shivering, myalgia, arthralgia, gynecomasty. (Berger D.P. et al, 2002)

3.20 Vinblastin

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Cardiotoxicity*: cardiovascular complications, hypertonia, hypotonia; *Pulmonary Toxicity*: acute interstitial pneumonitis, bronchospasm; *Gastrointestinal complications of Chemotherapy*: rarely constipation, ileus, nausea, emesis, diarrhoea, mucositis, rarely gastrointestinal bleeding; *Dermatologic Toxicity*: alopecia, erythema, exanthem, photo sensation; *Neurotoxicity*: peripheral neurotoxicity when applying cumulative dosage, paresthesia, rarely motoric disorders; *Other*: muscle spasms, Local toxicity: necrotizing extravasation. (Berger D.P. et al, 2002)

3.21 Vinkristin

Application of this drug can cause following toxicities:

Hematotoxicity: myelosuppression; *Cardiotoxicity*: cardiovascular complications, hypertonia, hypotonia; *Pulmonary Toxicity*: acute interstitial pneumonitis, bronchospasm; *Gastrointestinal complications of Chemotherapy:* constipation, Ileus, nausea, emesis, mucositis, rarely pancreatitis.*Renal toxicity*: polyuria (decrease of pad secretion ADH), dysuria; *Dermatologic Toxicity*: alopecia, erythema; *Neurotoxicity*: peripheral neurotoxicity (cumulative dosage), CNS disorders: hypesthesia, paresthesia, motoric disorders, areflexia, rarely severe complications like paralysis, ataxia, paralytic ileus, optic atrophia, blindness, spasms; *Gonadal Complications*: infertility. Local toxicity: necrotizing extravasation; *Other*: rarely fever, shivering. (Berger D.P. et al, 2002)

3.22 Vinorelbina

Application of this drug can cause following toxicities:
Hematotoxicity: myelosuppression; *Gastrointestinal complications of Chemotherapy*: rarely constipation, nausea, emesis, diarrhoea, Mucositis; *Dermatologic Toxicity*: alopecia; *Neurotoxicity*: peripheral neurotoxicity when applying cumulative dosage, paresthesia, rarely motoric disorders; *Other*: muscle spasms, Local toxicity: necrotizing extravasation. (Berger D.P. et al, 2002)

4. Toxicities that occur when applying most often used protocols

4.1 Chemotherapy toxicities

Early complications: nausea, vomiting, emesis, alopecia, myelosuppression.
Late complications: Sterility (primarily with MOPP-based regimens, BEACOPP, least with ABVD), Neuropathy (primarily with Vincristine), Cardiomyopathy (primarily with doxorubicin ABVD, COPP/ABVD), Pulmonary fibrosis (primarily with Bleomycin COPP/ABVD, BEACOPP) and Secondary leukaemia (primarily with MOPP, Radiotherapy (RT), BEACOPP escalating more than baseline). (Griffin R. et al., 2010)

4.1.1 ABVD vs. BEACOPP

The most used protocol is ABVD and most studies suggest that it is protocol with least toxicity. One of the largest randomized studies, conducted in multiple centres, is "The GHSG- Successor-trials De-escalation of BEACOPP Advanced stages of Hodgkin lymphoma". It summarized data from three studies (**HD9, HD12 and HD15**) and is still conducted on **HD18**. In analysis of the treatment of advanced HL stages it used data from more than 500 centres including 220 oncologists and over 4500 patients treated with BEACOPP and ABVD. The study confirmed that ABVD had less toxicity (40-90%), lower infertility rate (90% male/52% female in BEACOPP E vs. 34% in ABVD), AML/MDS (1.2% in BEACOPP E vs. <0.5% in ABVD). On the other hand BEACOPP E had higher CR rates (>90%), Higher tumour cell kill PFS (90% vs. 79% in ABVD), Cure rate of 11% (higher at 10 years) and 20% less need for salvage therapy. (Diehl V, 2009)

Study **GHSG HD14** compared BEACOPP with ABVD in early unfavourable HL. Two cycles of BEACOPP escalated followed by 2xABVD and IFRT results in a significant improvement in tumor control compared to 4x ABVD + IFT. Toxicities for ABVD x4+IFT were following: acute grade III/IV toxicity 50.7 %, leucopoenia 24%, thrombocytopenia 0.1%, anemia 1%,

Gr.III/IV infection 3.4% and total of 19 secondary malignancies. On the other hand, toxicity in group 2x BEACOPP E + 2xABVD+IFT were: acute grade III/IV toxicity 87.1%, leucopoenia 79%, thrombocytopenia 22%, anaemia 9%, Gr.III/IV infection 7.3% and total of 16 secondary malignancies. It is important to state that OS was same in the two groups. (Engert A. et al, 2010).

Results from the **HD 2000** - Gruppo Italiano study conducted on patients with advanced stage HL indicate that BEACOPP improved FFS/PFS but has no difference in RFS or OS with increased toxicity, especially hematotoxicity. Hematotoxicity in the BEACOPP group (98 patients) was Gr.3/4 WHO, WBC/Plts 57/22, and in the ABVD group (99 patients) it was 3/34. BEACOPP was associated with higher severe infection rates than ABVD. (Federico M. et al, 2009) In the study "ABVD vs. BEACOPP for Hodgkin's lymphoma when High Dose Salvage Is Planned" Simonetta Viviani also concludes that "Treatment with BEACOPP, as compared with ABVD, resulted in better initial tumour control, but the long-term clinical outcome did not differ significantly between the two regimens". (Simoneta V. et al, 2011).

A randomized trial conducted from 2000 to 2007 by the Michelangelo, GITIL and IIL cooperative group in the analysis of the 3 year outcome ABVD vs. BEACOPP in advanced HL analyzed 321 patients diseased with HL stage IIB/IV and/or ≥3IPS, compared efficiency of 6-8 ABVD cycles vs. BEACOPP 4 escalating cycles + BEACOPP 4 baseline cycles in the first line. It confirmed significant difference of FFP (71±4% vs. 87±3%) but non-significant 3-yr OS (91±3% vs. 90±3%). Results of later relapses and secondary malignancies were not represented due to a longer follow up. (Gianni A.M. et al, 2008).

Other **HD12** study of GHSG at IIB and advanced stage III and IV with IPI ≥ 3 in application of 8 cycles BE vs. 4 BE+ 4BB confirmed that treatment-related toxicity of WHO grade III/IV was observed in 97% of patients. Most prominent differences between pooled chemotherapy (8x BEACOPP escalating + 0 Gy), was anaemia (65% 8BE vs. 51% 4BE+4BB) and thrombopenia (65% vs. 51%). There was 9.9% deaths (22 vs. 32 acute or salvage treatment toxicity; 15 vs. 24 HL; 22 vs. 13 secondary neoplasia). Secondary neoplasias were observed in 77 patients (4.9%). (Diehl V. et al, 2009)

Analysis of BEACOPP baseline vs. BEACOPP escalating confirmed acute haematological toxicity: Leucopoenia gr.4 WHO 37% vs. 93%, thrombocytopenia gr.4 WHA 5% vs. 49%, anemia gr. 3 WHO 17% vs. 50%, anemia gr. 4 WHO 4% vs. 19%. (Diehl V. et al, 1998)

4.1.2 Secondary malignancies

Increased risk of solid tumours was noted by numerous authors (Tucker MA et al, 1988; Boivin JF. Et al, 1984). When applying ABVD protocol, risk of NHL is increased where DLBCL can occur both early and later after treatment. (Van LF. et al, 1989)

After 10 years of follow up of the GHSG **HD9** study final results in the treatment of advanced stage and application of 6 COPP/ABVD vs. 6 BEACOPP baseline vs. 6 BEACOPP escalating, confirmed following toxicity: total of 74 secondary malignancies (6.2%) were documented including acute myeloid leukaemia (0.4%, 1.5% and 3.0%), non Hodgkin Lymphoma (2.7%, 1.7% and 1.0%) and solid tumours (2.7%, 3.4% and 1.9%). Corresponding

overall secondary malignancy rates were 5.7%, 6.6% and 6.0% respectively. (Andreas E. et al, 2009). The same study with results published in 2007 confirmed that cardiac toxicity is mostly expressed in COPP/ABVD, pulmotoxicity in COPP/ABVD and baseline BEACOPP. Cardiotoxicity was 1.2%, 0.9% and 0.9%, while pulmotoxicity 0.4%, 0.4% and 0.2%. (Diehl V. et al, 1998)

Preliminary results of the HD9 Causes of Death at 10 years indicate higher death events at COPP/ABVD 24% vs. 19% vs. 12%. (Diehl V. et al, 1998)

When applying MOPP regimen in more than 6 cycles +/- irradiation confirm risk of acute leukaemia. (Kaldor JM, et al, 1990) Early splenectomy increased this risk by two times. (Van LF, et al, 1989; Kaldor JM, et al, 1990) Application of alkylating agents proportional to cumulative dose confirmed 1-10% of cases caused toxicity after 7-10 years. (Boivin JF et al, 1984; Blayney DW, et al, 1987; Arseneau JC, et al, 1972; Coleman CN, et al, 1977)

4.2 Radiotherapy toxicities

Early Complications: Mantle field radiation can cause mouth dryness, pharyngitis, cough, dermatitis**.** Sub-diaphragmatic radiation can cause anorexia and nausea.

Late Complications: Hyperthyroidism, Graves' ophthalmopathy or thyroid neoplasm was seen after neck radiotherapy. Elevation of TSH level with or without lowered T3 or T4 was seen at 30% of patients which had mantle irradiation with often followed with Hypothyroidism.

4.2.1 Toxicity after lungs irradiation

Pericarditis and pneumonitis can occur. Incidence of radial pneumonitis (characterized by shivering, dyspnoea and cough) depends on volume of lung irradiation and total dose, with recovery seen from 12 to 24 months. (Smith LM, et al, 1989; Horning SJ, et al, 1994; Griffin R, et al, 2010)

4.2.2 Toxicity after heart irradiation

Toxic effect is possible on pericardium, myocardium, blood vessels, cardiac valve and conduction system. Cardiac mortality is significantly improved at patients who were administered with > 30 Gy on mediastinum. Mediastinum radiotherapy is joined with increased risk of heart disease. Increased risk and mortality rate due to coronary arterial disease and acute infarct of myocardium was seen both at adult and child patients. (Hancock SL, et al, 1993; Boivin JF, et al, 1992)

Patients whose heart was irradiated have increased risk of coronary arterial disease. Hence continual monitoring and evaluation is needed together with other risk factors. Follow up of these patients, according to NCCN (National Comprehensive Cancer Network, 2010) predicts basic ECHO of the heart 10 years after treatment with control of the lipid profile once per year. On the other side, according to ESMO base ECHO of the heart should be done 4-10 years after treatment, stress ECHO in patients with earlier RT and follow up of lipid profile at patients which had RT in their therapy. (Bovelli et al. 2010)

4.2.3 Secondary malignancies (solid tumour and secondary acute leukaemia as consequence of irradiation)

According to Stanford study, risk of secondary solid tumours 15 years after treatment was about 18%. (Boivin JF, et al, 1984). Patients that were primarily treated with radiotherapy had increased risk of tumour formation on lungs, breast, bone marrow, soft tissues and thyroid gland.

Possibility of lung cancer, 5 years after irradiation treatment and further during next 20 years, was two to eight times higher what was especially true with patients that smoke. (Griffin R, et al, 2010).

Increased risk of breast cancer was noted at female patients that were treated before age of 30 and was increased in children and adolescent population as well. (Donaldson SS, et al, 1982). Radiotherapy toxicity was especially noted at patients aged from 15-30 years what restricts irradiation of females before age of 30. Average interval of irradiation and diagnostics Ca Thyroid and breast cancer is 10 - 15 years. Hence it is needed to do routine mammography 8 years after completion of irradiation treatment in this group of patients. (Griffin R, et al, 2010) These findings influenced new recommendations in irradiation application by reducing mantle radiotherapy volume. By modifying mantle field and aborting axilla and heart from the radiation area treatments converged towards involved field radiotherapy (IFTT).

Reduction of the radiation area involved exclusion of irradiation of thyroid gland, heart and axilla and decrease risk of Brest Cancer and lung cancer. Low-dose (20Gy) IFRT was associated with decrease risk of Brest Cancer by 77% and lung cancer by 57%. (Hodgson DC, et al, 2007)

Contemporary therapy approach is using IFRT and is preferred for the patients that respond to the first line therapy with PR/SD and/or have bulky. High dose therapy followed by ASCT therapy in large measure suppressed irradiation or it was postponed for after ASCT for unfavourable disease, advanced disease, bulky, borderline zone and transformation.

15 % of patients that were administered with mantle field radiation can develop electric shock sensation radiating down the back of the legs when the head is flexed. This happens 6 to 12 weeks after the treatment due to transitory demyelination of spine cord and what resolves spontaneously. (Griffin R, et al, 2010)

4.2.4 Toxicity after thyroid gland irradiation

The data provided by the Christofer F. suggests that the actual risk of hypothyroidism after radiation therapy for HL at 26 years was 47%. Other less common thyroid abnormalities observed include: Graves's disease, thyroiditis, thyrotoxicosis, thyroid nodules and thyroid malignancies. (Christopher F, 2010).

My personal experience involves a study on patients diagnosed with HL from 1992 to 2001 and treated at Haematology Clinic at Clinical Centre University Sarajevo. The study was aimed to determining secondary malignancies as a consequence of late toxicity in HL treatment. Total of 126 patients were assessed aged from 14 to 75 years (median of 44.5 yr).

Our treatments at that time involved RT for I and IIA stage and for IE, IIB, III and IV stage MOPP or ABVD or ChLVPP with PR+MOPP or RT. In that study 10 patients (7.9%) were with secondary malignancy out of which one was with myelodysplasia, three with Non Hodgkin Lymphoma, six with solid carcinoma (Ca planocellulare papilarae – one patient, Ca planocellulare laringys – one patient, Neo palatum molae – one patient and Brest cancer– three patients). In the same group, epidemiologically observed, the most patients ware aged from 14 to 24 years. In the further follow up of 10 years (2002 to 2011) of the patients diagnosed by 2001, we noted 3 more diseased with secondary malignancy (1 with breast cancer, 1 Myeloma Multiplex and one with MDS). (Sofo Hafizovic A. 2002).

Second analyzed period is targeted towards analyzing patients with HL treated from 2002 – 2011 with applying chemotherapy using ABVD and BEACOPP protocol with or without IFRT. This study is currently being conducted and its results will be published in the upcoming period.

Chemotherapy ± RT 1992 – 2001	Chemotherapy ± RT 2002 - 2011
Hematology complications – total 4 (3.2%) sAML: 0 MDS: 1 (0.8%) NHL: 3 (2.4%)	**Hematology complications – total 2 (1.6%)** MDS: 1 (0.8%) Myeloma Multiplex: 1 (0.8%)
Solid neoplasm – total 6 (4.8%) Ca planocellulare papilarae: 1 Ca planocellulare laringys: 1 Neo palatum molae: 1 Brest cancer 3 (2.4 %)	**Solid neoplasm – total 1 (0.8%)** Brest cancer 1 (0.8%)

Table 2. Therapy toxicity in HL treatment (secondary malignancies) in KCUS.

In follow up of 10 years, secondary malignancies occurred in 10 cases (7.9%) and in follow up of 20 years secondary malignancies occurred in 13 cases (10%).

Case report: One 63 years old patient which had HL (NLP) CS IIA bulky diagnosed in August 2001. In the first line therapy the patient was treated using chemotherapy using ABVD protocol with irradiation of mediastinum and CR1 achieved. After 6 years Myeloma Multiplex was diagnosed and further VAD protocol therapy was applied. Next autologous transplantation of peripheral stem cells was conducted without significant complications. However, in 2010 she develops POEMS (Polyneuropathy Organomegaly Endocrinopathy M-protein Skin-abnormalities) followed with thrombocytopenia immunogene which were successfully treated with Prednisolon and Imuran. On her last control in April 2011 she is still in HL and MM complete remission with good life quality.

5. Gonadal complications in Hodgkin lymphoma treatment

Teratogenic influence of chemotherapy is formed in application of individual, or as a synergy effect of more drugs or in combination with radiotherapy. It is especially stressed in the first trimester of pregnancy. Incidence of difficult congenital malformations in chemotherapy application is 3% from the total number of born and 90% is incidence of minor malformations. (Michael CP. 2008b)

Factors during pregnancy (FDP) determine risk factors from teratogenic effect. According to that Prednisone is in B group, Methotrexte is in X group, Rituximab and Dacarbazine are in C group, and finally Cytosin arabinosid, Gemcitabine, Chlorambucil, Ifosfamid, Mepphalan, busulfan, Cisplatin, carboplatin, Procarbazine, Doxorubicin, Bleomxcin, Mitoxantron, vincristin, Vinblastin, Etoposide, Cytarabine are in D group. (Michael CP. 2008b) [1]

Reproduction effect: about 90% males become permanently sterile if they were administered with 6 cycles of MOPP chemotherapy. (Chapman RM, 1979a) Risk is correlated with cumulative dose of alkylating agents and 2-3 cycles result in azoospermia in about 50% patients. (Da CM, et al, 1984) Fertility in females, after applying MOPP chemotherapy, is in relation to age and treatment and as well as cumulative dosage of alkylating agent dose. (Da CM, et al, 1984; Horning SJ, et al, 1979; Chopman RM, et al,1979b). Also females in the age around 25, which are treated with 6 cycles of MOPP have 80% chance of sterility. ABVD is joined with temporary amenorrhea or azoospermia with total recovery which was noted in 50-90% of patients. (Anselmo AP, et al, 1990; Viviani S, et al, 1985)

Study conducted by Karolin Behringer confirmed teratogenic influence in males and females as follows COPP/MOPP/COPP+ABVD: Azoospermia 86-100%, Recovery of spermatogenesis between 12-20% after 2 years, Dysspermia prior to therapy 70-77%. In treatment of advanced stage HL with use of BEACOPP regimen had 89% azoospermia. In all early stage and use of alkylating agent elevation of FSH is 60%, recovery of fertility 52% and with use of RT recovery was 3%. Using Non-alkylating agent elevation of FSH is 8%, recovery is 82%. Fertility in female HL patients' therapy associated amenorrhea 0-4% ABVD, 51% BEACOPP escalating. (Karolin B. 2008)

Same author states that Ovarion toxicity is 2 years after chemotherapy treatment and in usage of 4xABVD regular cycle 95.9% Amenorrhea 4.1%, 2xABVD regular cycle 98.8% Amenorrhea 1.2%. 4xBEACOPP base regular cycle 87.1% Amenorrhea 12.9%. 8xBEACOPP escalating regular cycle 55% Amenorrhea 45%, 4xBEACOPP baseline +4xBEACOPP escalating regular cycle 81% Amenorrhea 19%. (Karolin B. 2008)

Christopher Flowers discovered that irradiation influenced fertility as follows: 1x dose 0.35 Gy or higher can cause transitory azoospermia (recovery time is longer when higher dose was administered). Dose 2 Gy and higher in germinal epithelium can result in permanent azoospermia. Dose of 15 Gy and higher Leydig cell function can be affected with potential need for testosterone replacement therapy. Ovarion dose of 4 Gy may cause a 30% incidence of sterility in young women but 100% sterility in women ≥ 40 years. (Christopher F. 2010).

Sterility formation stresses importance of applying procedures that will create good conditions for healthy offspring in the population of diseased and treated HL patients. Females should use contraception to protect the unwanted pregnancy on one side, and on

[1]FDA category B drugs are those for which studies in pregnant women did not demonstrate a risk to the fetus in any trimester; For C drugs animal reproduction studies have shown an adverse effect on the fetus and even though there are no adequate studies in humans potential benefits justify use in pregnant women; D drugs are those for which studies demonstrated human fetal risk, but the benefit from use in pregnant women patients justify the risk; for X drugs studies demonstrated fetal abnormalities and clearly risk of using this drug in pregnant women outweighs potential benefits. (Michael CP. 2008b)

the other to keep the hormonal level in boundaries that do not cause amenorrhea. Also cryopreservation enables offspring planning even before HL treatment application.

Among adults and adolescents after puberty, semen cryopreservation is proposed before first line treatment with BEACOPP or salvage treatment for relapse, and it is optional in cases of localized Hodgkin lymphoma treated with ABVD and radiotherapy. For women with a stable partner, in vitro fertilization for embryo cryopreservation is a standard procedure but it can be offered to only a small number of patients and requires delayed treatment initiation. Oocyte cryopreservation remains experimental, although its usage is being increased. Ovarian tissue cryopreservation is still experimental. (Harel S. 2011)

6. Conclusion

Optimal treatment of Hodgkin Lymphoma understands therapy application that will achieve complete remission with as few toxic effects as possible. This is especially true for the late toxic effects. Taking care of secondary malignancies and sterility is of uttermost significance and this is the force that drives constant treatment modification and creation of new therapy options of Hodgkin Lymphoma treatment. In current treatment options there is still large percentage of early and late toxicities which reduce life quality of the affected patients. Keeping in mind that high life quality is one of the main goals of any treatment, it should be assessed with appropriate attention and toxicities should be reduced to as low level as possible.

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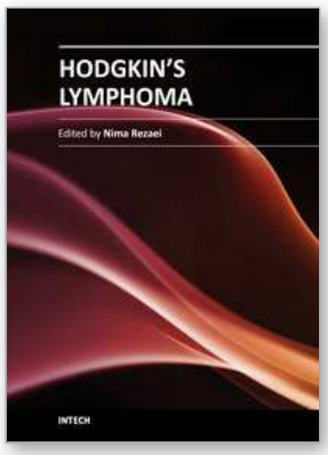

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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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