Therapy and supportive care of a high-grade non-Hodgkin's lymphoma

Objectives:

1. Treatment of high-grade non-Hodgkin's lymphoma (NHL)
2. Supportive care at the R-CHOP therapy

▶ Evaluation

The highly malignant non-Hodgkin's lymphoma patient was successfully treated with 8 cycles of R-CHOP therapy. Owing to the supportive care, the patient tolerated the treatment fairly well. Late cardiac damage caused by the high total cumulative dose of doxorubicin in the protocol must be accepted in this context.

L.K. reached the desired therapeutic goal of complete remission. Other tumor controls 04/2009, 07/2009, 10/2009, 01/2010 and 03/2010 gave no indication of the relapse.

▶ Acknowledgment:

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▶ Literature

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Patient: 75 years old, female, 157 cm, 68 kg, BSA 1.69 m²

Subjective data

At the time of diagnosis L.K. was a 75 year old woman who, in December 2007, was referred by her family doctor to the oncology outpatient department of Nuernberg Hospital. She complained of a persistent dry cough for months, causing her major problems, especially at night. In October 2007, whooping cough was diagnosed by the patient. The subsequent treatment with clarithromycin relieved the cough intensity slightly. Concurrent with the pertussis disease the patient also reported of night sweats.

Objective data

LK, 75 years old, female, 157cm, 68 kg, BSA 1.69 m²

Medical history:

- 2000: thyroidectomy, since than L-thyroxin 100mg qd
- 04/07: chronic, dry cough, progressive over time, repeatedly symptoms at night
- 10/07: pertussis-treatment with clarithromycin relieved the cough, night sweats
- 12/07: Despite the antibiotic therapy no decrease of the Inflammatory markers (CRP)

Drug history:

- Levothyroxine 100mg orally qd
- Allergies: ASA, diclofenac

Laboratory abnormalities:
LDH 470 U/l, AP 145 U/l, GGT 108 U/l, albumin 2.8 g /dl, Hb 10.4 g/dl

Diagnostic imaging:

- Sono: mass in the pancreatic head
  large mass, displacing the middle abdominal aorta
  marked mass of the spleen
- CT: Solitary pulmonary nodule right

Bone marrow puncture:

- no infestation of the bone marrow

CT-guided puncture of retroperitoneal:
The histology of the obtained biopsy specimens revealed a high grade, pleomorphic Ki1 positive B-cell lymphoma, which was set out in this infestation classified as Ann Arbor stage IIISB (stage III = infestation on both sides of the diaphragm, S = infestation of the spleen, B = B symptoms such as fever › 38 °C, night sweats).
The solitary nodule retrospective proved not to be a tumor mass. The B-symptoms are justified from the night sweats.

Prescriptions

Prescriptions

R-CHOP q3w, 6-8 cycles

R rituximab 375 mg /m² i.v. Day 0 or 1
C cyclophosphamide 750 mg / m² i.v. Day 1

Treatment goals

If untreated, the disease will prove fatal within a few months or even weeks.
In contrast, a high grade non-Hodgkin's lymphoma, even in advanced stages, can be cured in

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	H doxorubicin 50 mg /m² i.v. Day 1 O vincristine 1.4 mg /m² i.v. Day 1 P prednisone 100 mg orally Day 1 - 5 * = max. 2 mg McKelvey et al., 1976 The medication was planned to be administered in the outpatient department and scheduled to begin before Christmas.	principle by combining an intensive systemic chemotherapy and antibody therapy. The prognosis is based on the risk factors according to the International Prognostic Index (IPI). This takes into account the age, tumor stage, serum LDH concentration, the general condition and extra nodal infestation. In accordance with the higher age of the patient (› 60 years), increased LDH serum concentration at diagnosis (470 U /l), and the tumor classification according to Ann Arbor as a stage IIIS, the risk of the patient are assessed as high to intermediate. The chances of a patient to achieve a complete remission are at about 75%. In studies, the 5-year survival for the therapy R-CHOP-21 is indicated at about 58%.
Analysis and Plan	**Analysis** The treatment of high grade NHL with curative claim requires a consistent application of chemotherapy to maintain the desired survival prognosis. Dose reductions due to adverse effects are avoided by a detailed planned supportive care. Supportive care treatment is required to avoid dose reduction upon occurrence of: • Infusion-reactions • Nausea, emesis • Myelosuppression • Peripheral neurotoxicity • Cystitis • Skin reactions • Cardiotoxicity	
Infusion reactions – rituximab	Approximately 10% of patients treated with rituximab have infusion-related side effects that are probably caused by cytokine release. These are usually observed during the first infusion. The incidence decreases markedly with subsequent infusions. By interrupting the infusion and the administration of an antipyretic and antihistamine commonly occurring symptoms should be under control Prescription: Premedication: 1000 mg acetaminophen orally Dimetinden 4 mg i.v. Slow increase of the rate of infusion Close monitoring	

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Rituximab dose levels: 630 mg Rituximab in 500 ml NaCl 0,9%				
45	ml/ h for 30 min	10:20 h -		
90	ml/ h for 30 min	10:50 h -		
135	ml/ h for 30 min	11:20 h -		
180	ml/ h for 30 min	11:50 h -		
215	ml/ h for 30 min	12:20 h -	12:50 h	Sweaty
180	ml/ h for 30 min	12:50 h -	13:30 h	Hot flashes
	Infusion stopped			Use of toilette
120	ml/ h for 30 min	13:35 h -		
215	ml/ h for 30 min	14:00 h -	14:20 h	Hot flashes
	Infusion stopped			Solu Decortin H 50 i.v.
215	ml/ h for 30 min	14:50 h -	Stop	

Despite premedication and slowly increasing the rate of infusion LK developed hot flashes during the first rituximab infusion. Only after i.v. administration of 50 mg prednisolone as a short infusion along with a 30-minute infusion interruption, the rituximab infusion could be finished. In the second cycle the infusion rate again was increased very slowly. This time no further infusion-related side effects were observed.

Nausea / emesis

According to the ASCO guidelines (update 2006) a R-CHOP regimen is classified as moderately emetogenic (emesis risk without antiemetics 30 - 90%). According to guidelines an antiemetic prophylaxis should be carried out with a 5-HT3 antagonist on d1, dexamethasone on d1 (d2, d3) and aprepitant on d1, d2 and d3 due to anthracycline/cyclophosphamide combination.
By the protocol-related administration of 100 mg prednisone (intended as anti-tumor therapy) on d1-5, the emetogenic risk of therapy is already being reduced. The administration of dexamethasone and aprepitant may therefore be omitted.

Prescriptions:
8 mg ondansetron orally d1, repeat as needed in the evening d1 and d2
The patient was informed that already at the slightest hint of nausea she should take a further tablet ondansetron. Nausea and emesis could be avoided. The patient never used the extra ondansetron tablets.
L.K. complained of severe constipation in the 5th cycle. It helped her to know, that this is a side effect of antiemetic and not an additional disease. She was encouraged to increase her fluid intake and to take a lactulose preparation if necessary.

Myelosuppression / infection risk

A common side effect of doxorubicin and/or cyclophosphamide therapy is myelosuppression. This may be dose limiting for both substances. It manifests itself in a decrease of leukocytes, erythrocytes and/or platelets. As a result there may be life-threatening secondary infections and bleeding.
The leukocyte nadir is expected 10-14 days after doxorubicin/cyclophosphamide administration. If the leukocyte count is under 1/nl life-threate-

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ning complications are likely to be expected, especially if persisting for a longer period.
By timely administration of G-CSF, the duration of neutropenia is shortened, and potential infections can be prevented.

Prescriptions:
Frequent laboratory monitoring of blood
Filgrastim administration 0.5 mg / kg s.c. qd from cycle 2, d7 (20) until leukocyte count exceeds 2.0 / nl
Filgrastim administration optional in the first cycle

		17.12. 2007	27.12. 2007	02.01. 2008	04.01. 2008	07.01. 2008	10.01. 2008
Leukocytes	/nl	8,6	4,1	1	1,2	4,3	6,9
Erythrocytes	/pl	4,32	4,72	4,23	4,42	4,94	4,36
Hemoglobin	g/dl	11,2	12	11,1	11,6	11,7	11,8
Hematocrit	%	35,2	38,1	34,5	36	35,6	36
Thrombocytes	/nl	470	499	217	274	255	299

Already in the first cycle of R-CHOP therapy on day 13, L.K.'s leukocyte count fell to the critical value of 1.0/nl. From day 14, 30 million filgrastim were prescribed daily for 5 days sc. The leukocyte count recovered by the filgrastim therapy quickly, within 5 days.
On day 2 of filgrastim therapy L.K. claimed about severe bone pain. Bone pain is a side effect of filgrastim. The pain could be controlled by the administration of paracetamol 1000 mg p.o. qd for the duration of the filgrastim therapy.

Peripheral neurotoxicity

Neurological side effects may occur during the treatment with vincristine, which are dose and age related. These side effects are dose limiting for further treatment with vincristine, as severe neuropathy can develop by continuing the vincristine therapy. The most common type of vincristin related neurotoxicity is peripheral neuropathy. It manifests itself in the form of sensory loss, peripheral paresthesia, tingling, numbness of fingers and toes, and neuralgic pain in the jaw.
The risk of neuropathy increases with the total dose administered. The cumulative threshold dose of vincristine is 20 mg. The reactions are highly individual.

Prescriptions:
Monitor signs of peripheral paresthesia
Monitor manual dexterity

The opening and closing of buttons, as well as handling of handicrafts can serve as an indicator for peripheral neuropathies.

L.K. reported of a slight tingling and numbness in the fingers, as well as occasional toothache after the 5th cycle. The doctors decided to discontinue vincristine from 6th cycle. The symptoms of paresthesia increased at first, subsequently decreased gradually and were practically absent at the 8th cycle.

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Cystitis prophylaxis	Urotoxic acrolein is produced during the metabolism of activated cyclophosphamide. It damages the urinary tract and bladder urothelial cells, which is dose-dependent. The most common complications are hemorrhagic cystitis or hematuria, which may require interruption of the therapy. By mesna and hydration a severe hemorrhagic cystitis can be prevented. Prescriptions: Additional 1000 ml NaCl 0.9% infusion Enhanced liquid intake Regular urinalysis Mesna administration according to urinalysis, or voiding problems In addition to the infusion during chemotherapy L.K.'s liquid intake was intensified. There were no indications of complications during the 8 cycles of R-CHOP. Mesna was not given.
Skin reactions	Conjunctivitis and increased lacrimation due to doxorubicin: Starting with the 3rd cycle L.K. reported of burning eyes and strong lacrimation, along with a reduced visual acuity. Prescription: Hylo-Care® eye drops (hyaluronic acid, panthenol); 1 drop 3 times daily as needed in the conjunctival sac of each eye. Alopecia caused by cyclophosphamide and doxorubicin L.K. suffered of hair loss. She wore a wig with self-confidence. Nail changes L.K. reported splintering, relieving toenails after the 7th cycle of therapy.
Cardiotoxicity	Cardiotoxic side effects caused by anthracycline may occur acute, delayed or as a late type. The side effect of the delayed type is clinically relevant and occurs in dependence on the cumulative dose. It manifests itself in a few months to years after termination of therapy. The cumulative threshold dose of doxorubicin for adults is 550 mg/m² or 400 mg/m² for patients with prior chest irradiation or concomitant therapy with alkylating agent. Regular cardiac checkups are the basis for early diagnosis of cardiomyopathy. Prescription: Regular ECG tests: Monitoring of LVEF and ventricular motility L.K. received 8 cycles R-CHOP in a cumulative total dose of 400 mg/m² doxorubicin. Throughout the R-CHOP therapy, as well as one month after the end of therapy, no ECG changes and no significant changes in heart rate were observed. Left ventricular ejection fraction (LVEF) was also in the normal range a month after treatment. In August 2008, about 3 months after stopping the treatment, L.K. developed left chest pain radiating to the shoulder. She complained of 4 weeks lasting exertional dyspnea. She was hospitalized to the cardiology ward of

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	Nuernberg Hospital. The diagnosis revealed congestive left heart failure with pulmonary venous congestion. Prescription: Ramipril 2.5 mg orally qd Bisoprolol 2.5 mg orally qd Torasemide 10 mg orally bid L.K. had to limit her water intake to max. 1.5l/ day and control her weight every day. Today, the patient still takes the prescribed antihypertensives. Her usual walking distance corresponds to the distance between two tram stops. She can climb stairs up to the 2. /3. floor. L.K. has an exercise bike for daily exercise at home.
Tumor follow-up	**Intermediate staging after the 4th cycle** • CT: Good partial response: spleen focus point is no longer displayed **examination 07/08:** • CT: Smaller nodules present • PET: the largest residual nodules were PET negative, only small lymph nodes were visible in the mesentery **Results: Complete remission** An additional positron emission tomography (PET) was performed, since the smallest nodules detectable by CT might be either false positive (50%) or low-grade tumor groups. The PET showed that the most CT-presentable nodules did not constitute residual tumor mass. The newly recognizable small lymph nodes in the mesentery were explained by inflammation (points with high glucose uptake). Hence, the patient achieved a complete remission.