High-dose therapy with autologous stem cell support for lymphoma in Norway 1987–2008

BACKGROUND High-dose therapy with autologous stem cell support (HDT) has been a treatment option for lymphomas in Norway for 25 years. The purpose of the article was to describe the use of the therapy for lymphomas for the country as a whole and by health region, and to reveal the overall survival rate.

METHOD All lymphoma patients ≥ 18 years who received HDT in Norway in the period 1987–2008 are included. Patients, diagnostics and treatment are identified for each hospital. Data for the population base have been retrieved from Statistics Norway.

RESULTS Altogether 726 lymphoma patients received HDT in Norway in the period 1987–2008, with an annual average of 0.72 per 100 000 inhabitants. The annual number of treatments increased until 2004 and has since been stable. The average number of treatments per 100 000 inhabitants per year was 0.94 for Northern Norway Health Region, 0.80 for South-Eastern Norway Health Region, 0.58 for Central Norway Health Region and 0.55 for Western Norway Health Region. Early mortality (death within 100 days) was 6 %. Ten-year overall survival was 55 % (95 % CI 51–59 %), and Hodgkin's lymphoma had the best survival of the lymphoma groups (p = 0.01).

INTERPRETATION The annual number of HDT increased gradually until 2004. The use of the treatment varied according to the patients' place of residence at the time of diagnosis, and was most frequently used for patients belonging to Northern Norway Health Region. More than half of the lymphoma patients are alive ten years after the treatment.

Knut Bjøro Smeland
knusme@ous-hf.no
Cecilie E. Kiserud
National Resource Center for Late Effects after Cancer Treatment
Department of Oncology
Oslo University Hospital

Grete F. Lauritzsen
Anne Kirsti Blystad
Department of Oncology
Oslo University Hospital

Unn Merete Fagerli
Department of Oncology
St. Olavs Hospital
and
Department of Cancer Research and Molecular Medicine
Norwegian University of Science and Technology

Øystein Fluge
Department of Oncology and Medical Physics
Haukeland University Hospital

Alexander Fosså
Department of Oncology
Oslo University Hospital

Jens Hammerstrøm
Department of Haematology
St. Olavs Hospital

Arne Kolstad
Department of Oncology
Oslo University Hospital

Jon Håvard Loge
National Resource Center for Late Effects after Cancer Treatment
Department of Oncology
Oslo University Hospital
and
Department of Behavioural Sciences in Medicine
Faculty of Medicine
University of Oslo

Martin Maisenhølder
Department of Oncology
University Hospital of North Norway

Bjørn Østenstad
Department of Oncology
Oslo University Hospital

Stein Kvaløy
Division of Cancer, Surgery and Transplantation
Oslo University Hospital
and
Institute of Clinical Medicine
Faculty of Medicine
University of Oslo

Harald Holte
Department of Oncology
Oslo University Hospital

High-dose therapy with autologous stem cell support (HDT) is a very intensive, highly specialised and resource-intensive therapy. It has been a treatment option for lymphomas for 25 years. Based on results from prospective studies, it has progressed from being an experimental form of treatment to becoming an established treatment for a number of indications (1). In the first years (1987–95) it was performed only at the Norwegian Radium Hospital in clinical studies. Following recommendation by an expert group appointed by the Norwegian Board of Health Supervision, the treatment was regionalised in 1996 and has since been performed in all four health regions (on a national level has not been produced until now.

We have investigated how many lymphoma patients who have received HDT in Norway as a whole, by lymphoma type and by hospital, based on place of residence and time of diagnosis. We have also investigated survival following this treatment.

Method

This study is part of a national multicentre study in which a broad spectrum of late effects following HDT for lymphoma in Norway is being studied. All lymphoma patients above 18 years of age who have received the treatment up to and including 31 December 2008 are included. The patients are identified through each hospital's records of all HDT therapies, cross-checked against reports from HDT meetings, the clinical quality register for lymphoma at the Norwegian Radium Hospital and radiotherapy registers. In addition, the data collected are double-checked through a retrospective review of patient notes. Where relevant, date of death has been obtained from Statistics Norway.

Data for population base by health region are retrieved from Statistics Norway's annual population census and number of HDT therapies per 100 000 inhabitants is entered. Comparisons between the health regions were made based on the patients' county of residence at the time of diagnosis.

Statistical analyses

Descriptive analyses are used to describe the patient material. For the survival analyses, observation time is calculated as the time from HDT until death or until 31 December 2011.

The lymphoma patients are divided into three groups: Hodgkin's lymphoma, aggressive/very aggressive lymphomas (diffuse large B-cell lymphoma, transformed lymphoma, mature T-cell lymphomas, mantle cell lymphoma, Burkitt's lymphoma and lymphoblastic lymphoma) and indolent lymphomas.

Survival is described using Kaplan-Meier curves, and univariate analysis with log-rank test is used to describe differences between groups. Early mortality is defined as death within 100 days following the high-

MAIN POINTS

The annual number of patients receiving HDT increased from the start-up in 1987 until 2004

The use of HDT was highest for lymphoma patients belonging to Northern Norway Health Region

Many lymphoma patients have been cured of an otherwise deadly disease with the help of HDT

dose therapy, and comparison between lymphoma groups is analysed using Pearson's chi-square test. Statistical significance is defined as $p < 0.05$. The statistical analyses are conducted in SPSS 18.

Ethics

The project was approved in 2011 by the Norwegian Regional Ethics Committee South East (ref. 2011–1353).

Results

How many lymphoma patients received the treatment in the period 1987–2008?

A total of 726 adult lymphoma patients had received HDT in Norway at the end of 2008. Of these, 465 were men (64 %), and median age at treatment was 48 years (range 18–69 years). 230 patients (32 %) received HDT in first remission, while 488 (67 %) received the therapy for relapse or primary chemoresistant/progressive disease (eight unknown – 1 %). Altogether 108 patients (15 %) were treated in the period 1987–95 when the high-dose treatment consisted of total body irradiation and high-dose cyclophosphamide and was only performed at the Norwegian Radium Hospital. In the period 1995–2008 altogether 618 (85 %) received HDT with BEAM (carmustine (BCNU), etoposide, cytarabine (Ara-C) and melphalan) as a high-dose regimen. Median age for HDT in the first period was 39 years, and in the period 1996–2008 it was 50 years.

For the country as a whole, an average of 0.73 patients per 100 000 inhabitants per year were treated in the whole period (1987–2008). The annual treatment activity for the whole country gradually increased from 0.12 per 100 000 in 1987 to a peak in 2004 of 1.49 per 100 000 inhabitants (Fig. 1).

Where were they treated?

In the period 1987–95 an average of 12.0 patients per year received HDT at the Norwegian Radium Hospital. In the period 1996–2008 an average of 28.3 patients per year were treated there, while the University Hospital of North Norway treated 5.7, Haukeland University Hospital 5.8, St. Olavs Hospital 5.0 and Ullevål University Hospital 2.5.

Figure 1 shows the annual treatment activity per 100 000 inhabitants, based on the health region in which the patient was resident at the time of diagnosis. The average number of treatments annually per 100 000 inhabitants was highest for patients belonging to Northern Norway Health Region, with 0.94, while the corresponding figures for the other health regions were 0.80 for South-Eastern Norway Health Region, 0.58 for Central Norway Health Region and 0.55 for Western Norway Health Region.

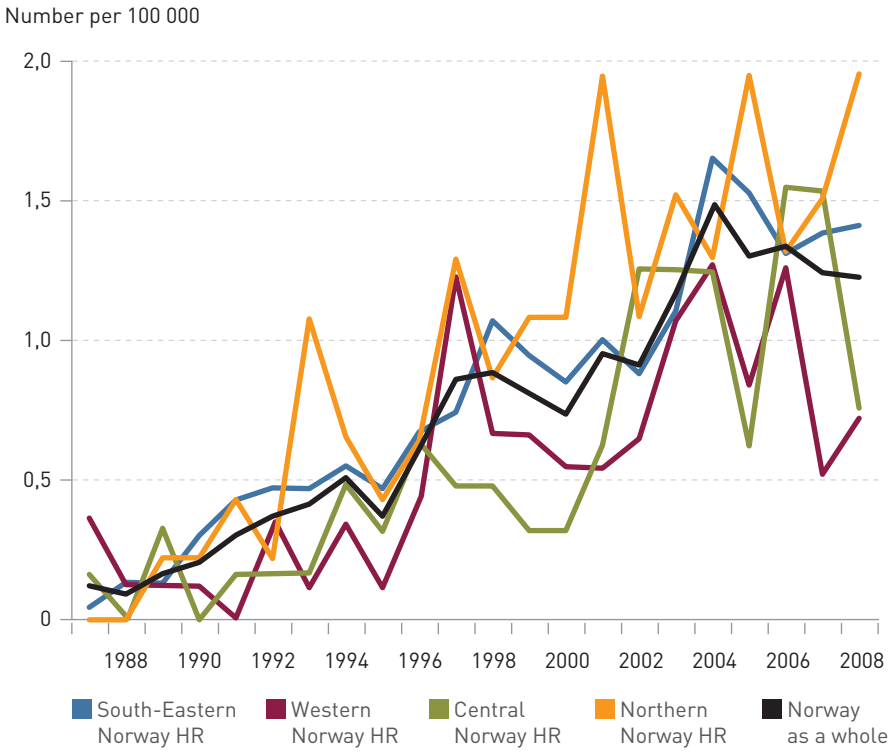

Figure 1 *Number of lymphoma patients treated with high-dose therapy with autologous stem cell support (HDT) per 100 000 inhabitants per year belonging to each of the health regions, calculated based on place of residence at time of diagnosis. Number for Norway as a whole is in black*

Table 1 Number of lymphoma patients treated with high-dose therapy with autologous stem cell support (HDT) in Norway, by hospital. Up to and including 1995, HDT was only performed at the Norwegian Radium Hospital, except for two patients at the University Hospital of North Norway who received the treatment in 1995. Number (%) unless otherwise indicated.

	All, 1987–2008 n = 726	Oslo University Hospital, Norwegian Radium Hospital, 1987–95 n = 108	Oslo University Hospital, Norwegian Radium Hospital, 1996–2008 n = 368	Oslo University Hospital, Ullevål, 1996–2008 n = 32	Haukeland University Hospital, 1996–2008 n = 76	St. Olavs Hospital, 1996–2008 n = 65	University Hospital of North Norway, 1995–2008 n = 77
Age (years): Median (spread)	48 (18–69)	39 (18–60)	50 (18–66)	55 (23–66)	48 (18–65)	51 (19–67)	50 (18–69)
Age groups (years)							
18–20	16 (2)	3 (3)	34 (1)	0 (0)	4 (5)	3 (5)	2 (3)
20–29	101 (14)	23 (21)	49 (13)	4 (13)	11 (15)	8 (12)	6 (8)
30–39	123 (17)	30 (28)	60 (16)	1 (3)	10 (13)	6 (9)	16 (21)
40–49	154 (21)	38 (35)	68 (19)	4 (13)	18 (24)	14 (22)	12 (16)
50–59	202 (28)	13 (12)	106 (30)	15 (47)	21 (28)	21 (32)	26 (34)
60–69	130 (18)	1 (1)	81 (22)	8 (25)	12 (16)	13 (20)	15 (20)
Gender							
Men	465 (64)	76 (70)	237 (64)	23 (72)	40 (53)	41 (63)	48 (62)
Women	261 (36)	32 (30)	131 (36)	9 (28)	36 (47)	24 (37)	29 (38)
Lymphoma group							
Diffuse large B-cell lymphoma	164 (23)	13 (12)	80 (22)	12 (38)	23 (30)	11 (18)	25 (33)
Hodgkin's lymphoma	152 (21)	18 (17)	91 (25)	3 (9)	13 (17)	12 (18)	15 (20)
T-cell lymphomas	91 (13)	7 (7)	49 (13)	5 (16)	8 (11)	8 (12)	14 (18)
Transformed lymphomas	87 (12)	9 (8)	47 (13)	5 (16)	6 (8)	14 (22)	6 (8)
Follicular lymphoma	85 (12)	28 (26)	44 (12)	1 (3)	5 (7)	2 (3)	5 (7)
Mantle cell lymphoma	68 (9)	1 (1)	37 (10)	4 (13)	12 (16)	7 (11)	7 (9)
Lymphoblastic lymphoma	48 (7)	23 (21)	17 (5)	1 (3)	2 (3)	4 (6)	1 (1)
Burkitt's lymphoma	18 (3)	9 (8)	3 (0,8)	0	2 (3)	3 (5)	1 (1)
Other/unspecified	13 (2)	0	0	1 (3)	5 (7)	4 (6)	3 (4)

Which types of lymphoma did they have?

Table 1 shows number of patients, age and gender distribution and the total diagnoses distributed among the various hospitals. Diffuse large B-cell lymphoma (23 %) and Hodgkin's lymphoma (21 %) were the most frequently occurring lymphoma types, followed by T-cell lymphomas (13 %), transformed lymphomas (12 %) and indolent lymphomas (12 %).

Survival

Early mortality, defined as death within 100 days, was 6 % for all lymphoma types collectively, 9 % for aggressive/very aggressive lymphomas, 4 % for indolent lymphomas and 1 % for Hodgkin's lymphoma. Altogether 411 (58 %) of the 726 patients were alive as of 31 December 2011, with five-year and ten-year overall survival of 64 % (95 % CI 60–67 %) and 55 % (95 % CI 51–59 %) respectively. Those who were treated for Hodgkin's lymphoma had the highest survival rate, followed by patients with indolent

lymphomas, thereafter patients with aggressive/very aggressive lymphomas (p = 0.01) (Fig. 2).

Discussion

There was a steady increase in the number of patients who received HDT for lymphoma from 1987 until a maximum was reached in 2004. In the last few years the figure has remained relatively stable, or perhaps shown a slight decrease. This may be attributed in part to the fact that primary treatment for several lymphoma types has substantially improved in the past 10–15 years, which is reflected in the Cancer Registry of Norway's survival figures for lymphoma (5). The main reason for this is most likely the introduction of rituximab (anti-CD20 antibody), which has resulted in fewer and later relapses of all types of B-cell lymphomas (6). The primary treatment of Burkitt's lymphoma over these 25 years has improved greatly, so that these patients now seldom need HDT (7). In addition, most of the indications related to lymphoma have been tested over time. In some clinical situations no benefit has been shown for HDT compared to less toxic cancer treatment (1). In refining the treatment, emphasis is now being placed on improved induction therapy to increase the remission rates before the HDT, in order for more people to undergo this treatment and hopefully reduce later relapse (1).

In the first few years the patient selection was stringent, and only young and otherwise healthy patients were considered for HDT. With increasing experience, improved supportive therapy, and last but not least, progress such as stem-cell harvesting from blood rather than bone marrow, it has been possible to achieve reduced treatment-related morbidity and mortality, as well as lower costs (8). The therapy is thereby also relevant for older patients with more comorbidity, and HDT is currently offered to more elderly patients than in the first few years, as illustrated by the figures for the two periods – those treated in the period 1987–95 were 11 years younger (median) than those treated in the period 1996–2008.

Overall the Radium Hospital of Norway has performed HDT on the greatest number of lymphoma patients. It was the only treating hospital in the period 1987–95 and had 60 % of all HDT patients following the regionalisation in 1996.

For Norway as a whole, the number of HDT therapies for lymphoma has been 0.73 per 100 000, which is comparable to the treatment activity in Western Europe and the rest of Scandinavia (9). When adjusted for the population base, the highest number of lymphoma patients who have received HDT are resident in the Northern Norway Health Region, followed by the South-Eastern Norway Health Region, the Western Norway Health Region and the Central Norway Health Region. Our data do not explain what these differences can be attributed to. One reason may be that it is a matter of discussion whether and when in the course of the disease HDT should be offered for particular lymphoma types, for example transformed lymphomas and follicular lymphomas, in relation to other treatment options. This gives more scope for clinical discretion and local tradition. In addition, participation in international studies may be a contributory factor.

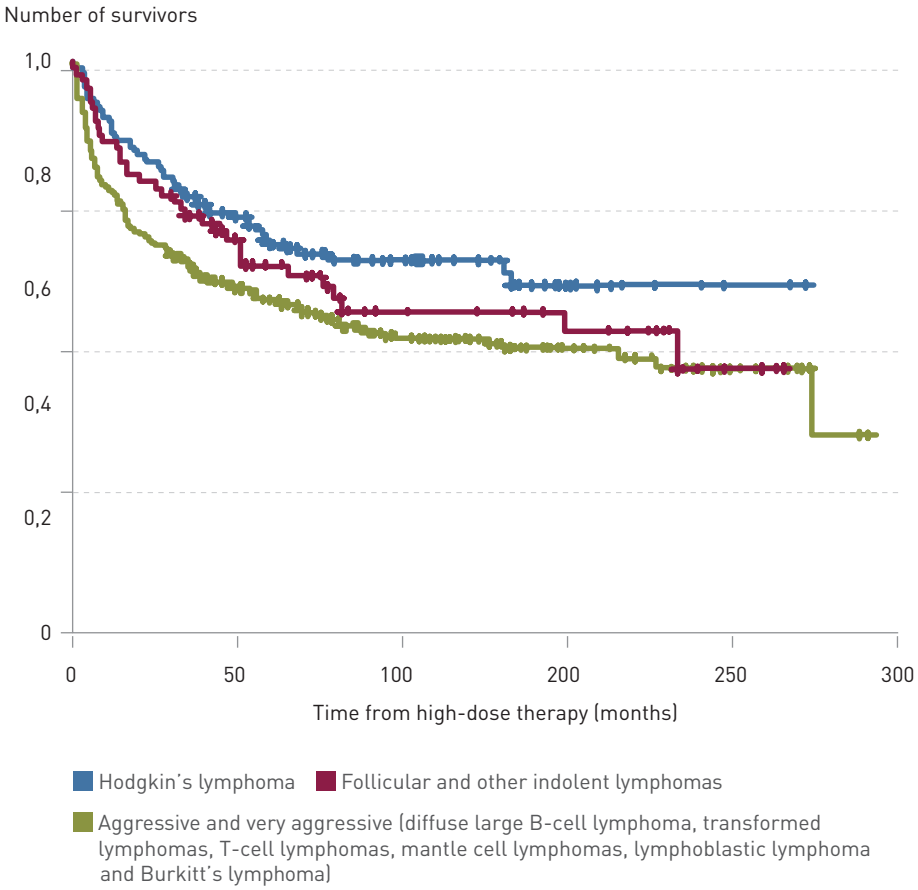

Figure 2 *Overall survival following high-dose therapy with autologous stem cell support (HDT) for Hodgkin's lymphoma, follicular and other indolent lymphomas, and aggressive and very aggressive lymphomas*

Early mortality varied from 1 % for Hodgkin's lymphoma to 9 % for aggressive/very aggressive lymphomas. This corresponds to previously published studies, in which treatment-related mortality of 1–10 % for Hodgkin's lymphoma (8, 10, 11) and 4–10 % for non-Hodgkin's lymphoma (8, 12, 13) was reported. Since we do not have complete details on causes of death for the whole population, in this study we have defined early mortality as death within 100 days following HDT, irrespective of cause of death. This will therefore also include early lymphoma-related mortality in addition to direct, treatment-related mortality.

We found a five-year overall survival rate of 64 % following HDT for all lymphomas combined. In an American single-centre study published in 2012, five-year survival for Hodgkin's lymphoma and non-Hodgkin's lymphoma of 59 % and 62 %, respectively, was found (14). In other studies of specific lymphoma types, three-year survival varies between 55 % and 80 % (11–13, 15, 16). More than half of the lymphoma patients are alive ten years after the HDT. Most of the patients had relapsed lymphoma or a disease that was resistant to conventional treatment, so that the prognosis was poor without HDT. In our opinion, it has been a life-saving treatment for most of these patients.

Altogether 411 lymphoma patients were alive following HDT at the start of 2011, and these represent a group of cancer survivors who have undergone very intensive treatment. A significant proportion of these have also had several rounds of chemotherapy and/or radiotherapy before receiving HDT. According to national guidelines, these patients should be followed up with regular controls (17). We know from earlier studies, both Norwegian and international, that certain groups of lymphoma patients have an

elevated risk of developing late effects after treatment, such as hormonal dysfunctions, cardiovascular diseases, second cancers and chronic fatigue (18–21). The prevalence of and risk factors for late effects have not been specifically investigated in lymphoma patients who have received HDT. This is now being investigated in a national follow-up study in which all the 411 patients who are alive following HDT are also being offered a comprehensive medical control.

Knut Bjøro Smeland (born 1982)
is a doctor in specialist training in oncology and a PhD candidate at the National Resource Center for Late Effects after Cancer Treatment, Oslo University Hospital. The author has contributed to ideas and design, analysis and interpretation, and formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Cecilie E. Kiserud (born 1966)
holds a PhD and is a senior consultant in oncology and a postdoctoral fellow at the National Resource Center for Late Effects after Cancer Treatment, Oslo University Hospital. The author has contributed to ideas and design, analysis and interpretation, and formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Grete F. Lauritzsen (born 1959)
is a medical doctor and senior consultant at the Division for Lymphoma. The author has contributed to analysis and interpretation, and formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares the following conflicts of interest: she has received travel-funding from Roche and Mundi Pharma.

Anne Kirsti Blystad (born 1962)
is a medical doctor and senior consultant at the Division for Lymphoma. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Unn Merete Fagerli (born 1962)
holds a PhD and is a senior consultant for lymphoma tumours at the Department of Oncology. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Øystein Fluge (born 1961)
is a medical doctor and senior consultant at the Department of Oncology. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares the following conflicts of interest: he has received travel-funding/lecture fees from Roche and Amgen and is one of the interested parties in relation to Haukeland Hospital's patent application concerning B-cell depression.

Alexander Fosså (born 1968)
is a medical doctor and senior consultant at the Division for Lymphoma. The author has contributed with analysis and interpretation, and design and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Jens Hammerstrøm (born 1947)
is a professor of medicine and senior consultant. He is the expert adviser on HDT at St Olavs Hospital and former board member of the Norwegian Lymphoma Group. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Arne Kolstad (born 1958)
is a medical doctor, senior consultant at the Division for Lymphoma and head of the Immunotherapy Research Group at Oslo University Hospital, the Norwegian Radium Hospital. He is head of the Norwegian Lymphoma Group. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Jon Håvard Loge (born 1953)
is a professor of medicine and a specialist in psychiatry. He is head of the National Resource Center for Late Effects after Cancer Treatment, Oslo University Hospital. The author has contributed to ideas and design, analysis and interpretation, and formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Martin Maisenhölder (born 1972)
is a senior consultant. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Bjørn Østenstad (born 1955)
is a medical doctor and senior consultant at the Division for Lymphoma. The author has contributed to formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Stein Kvaløy (born 1947)
is a professor of medicine and a specialist in oncology. He is head of research at the Division of Cancer, Surgery and Transplantation, and participated in the introduction of HDT at the Norwegian Radium Hospital. The author has contributed to ideas and design, analysis and interpretation, and formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

Harald Holte (born 1951)
is a medical doctor, senior consultant, expert adviser at the Division for Lymphoma and head of the Lymphoma Research Group at the Department of Oncology. He is the deputy head (and former head) of the Nordic Lymphoma Group. The author has contributed to ideas and design, analysis and interpretation, and formulation and/or critical revision of the manuscript, and has approved the final version.
The author has completed the ICMJE form and declares no conflicts of interest.

References

1. Smeland KB, Kiserud CE, Lauritzen GF et al. Høydosebehandling med autolog stamcellestøtte ved lymfom – fra utprøvende til standard behandling. Tidsskr Nor Legeforen 2013; 133: 1735–9.
2. Høydosebehandling med autolog stamcellestøtte ved maligne lidelser. Helsedirektoratets utredningsserie 1–951995. Oslo: Statens helsetilsyn, 1995.
3. Hammerstrøm J, Aasland IL, Telhaug R et al. Høydosebehandling med stamcellestøtte i Midt-Norge. Tidsskr Nor Lægeforen 2004; 124: 2498–500.
4. Liseth K, Abrahamsen JF, Ekanger R et al. Overlevelse etter høydosebehandling med autolog stamcellestøtte. Tidsskr Nor Lægeforen 2004; 124: 1374–5.
5. Cancer in Norway 2010 – cancer incidence, mortality, survival and prevalence in Norway 2012. Oslo: Kreftregisteret, 2012.
6. Griffin MM, Morley N. Rituximab in the treatment of non-Hodgkin's lymphoma–a critical evaluation of randomized controlled trials. Expert Opin Biol Ther 2013; 13: 803–11.
7. Smeland S, Blystad AK, Kvaløy SO et al. Treatment of Burkitt's/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens. Ann Oncol 2004; 15: 1072–8.
8. Jantunen E, Itälä M, Lehtinen T et al. Early treatment-related mortality in adult autologous stem cell transplant recipients: a nation-wide survey of 1482 transplanted patients. Eur J Haematol 2006; 76: 245–50.
9. Passweg JR, Baldomero H, Gratwohl A et al. The EBMT activity survey: 1990–2010. Bone Marrow Transplant 2012; 47: 906–23.

>>>

10. Linch DC, Winfield D, Goldstone AH et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993; 341: 1051–4.
11. Schmitz N, Pfistner B, Sextro M et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002; 359: 2065–71.
12. Philip T, Guglielmi C, Hagenbeek A et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540–5.
13. Dreyling M, Lenz G, Hoster E et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005; 105: 2677–84.
14. Vanderwalde AM, Sun CL, Laddaran L et al. Conditional survival and cause-specific mortality after autologous hematopoietic cell transplantation for hematological malignancies. Leukemia 2013; 27: 1139–45.
15. Sweetenham JW, Santini G, Qian W et al. High-dose therapy and autologous stem-cell transplantation versus conventional-dose consolidation/maintenance therapy as postremission therapy for adult patients with lymphoblastic lymphoma: results of a randomized trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. J Clin Oncol 2001; 19: 2927–36.
16. Schaaf M, Reiser M, Borchmann P et al. High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane Database Syst Rev 2012; 1: CD007678.
17. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av maligne lymfomer nr. 987-82-8081-113-4/2012. Oslo: Norsk lymfomgruppe, 2012.
18. Abrahamsen AF, Loge JH, Hannisdal E et al. Late medical sequelae after therapy for supradiaphragmatic Hodgkin's disease. Acta Oncol 1999; 38: 511–5.
19. Kiserud CE, Fosså A, Bjøro T et al. Gonadal function in male patients after treatment for malignant lymphomas, with emphasis on chemotherapy. Br J Cancer 2009; 100: 455–63.
20. Ng AK, Mauch PM. Late effects of Hodgkin's disease and its treatment. Cancer J 2009; 15: 164–8.
21. Wethal T, Lund MB, Edvardsen T et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer 2009; 101: 575–81.

Received 13 November 2012, first revision submitted 22 February 2013, approved 25 June 2013. Medical editor Sigurd Høye.