High-dose therapy with autologous stem cell support for lymphoma – from experimental to standard treatment

High-dose therapy with autologous stem cell support (HDT) has been a therapeutic option for lymphomas in Norway since as far back as 1987. By restoring bone marrow function through reinfusion of the patient's own stem cells, it is possible to administer cancer treatment in higher and otherwise lethal doses, and thereby achieve better treatment results. Originally stem cells were harvested from bone marrow and the high-dose therapy included total body irradiation, but since the mid 1990s stem cells have been harvested by apheresis and the high-dose therapy has consisted of chemotherapy alone (BEAM chemotherapy). In 1995 the treatment was regionalised and since then it has been performed in all health regions. The HDT procedure was introduced as an experimental treatment in clinical studies with international collaboration. The indications have changed over time, and this is now established treatment for a number of types of lymphoma.

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High-dose therapy with autologous stem cell support (HDT) for lymphomas has been given in Norway since 1987. The therapy consists of intensive chemotherapy and/or total body irradiation in such high doses that it entails a life-threatening loss of healthy haematopoietic stem cells in the bone marrow. In order to conserve future bone marrow function, stem cells are harvested from the patient before the high-dose therapy is given, and are frozen and reinfused some days later (Fig. 1). From 1987 to 1995 the high-dose therapy itself consisted of total body irradiation followed by chemotherapy in the form of high-dose cyclophosphamide. Since 1996 chemotherapy has generally been used alone (BEAM: carmustine (BCNU), etoposide, cytarabine (Ara-C), melphalan). In the mid 1990s the harvesting of stem cells also changed; at that time stem cells began to be harvested from blood (via a central venous catheter) and not from bone marrow, which required general anaesthesia. Harvesting stem cells from blood also has the advantage that bone marrow function is more rapidly restored, with less resulting treatment-related morbidity, less use of antibiotics and blood products, and thereby lower costs (1).

Lymphomas are a heterogeneous group of cancers that arise in the lymphocytes. They are classified as Hodgkin's and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma is further classified into more than 30 types (2). Around 90 % of non-Hodgkin's lymphomas arise in the B-cells, while T-cell lymphomas represent around 10 %. A traditional classification distinguishes between the clinically aggressive lymphomas (including, for example, diffuse large B-cell lymphoma and most of the mature T-cell lymphomas), the very aggressive forms (Burkitt's lymphoma and lymphoblastic lymphoma) and the indolent lymphomas (of which follicular lymphoma is the most common) (3). Altogether lymphomas represent approximately 4 % of all new cases of cancer in Norway (4).

The incidence of Hodgkin's lymphoma has been stable for the last 50 years, and 130 new cases were reported to the Cancer Registry of Norway in 2010 (4). The incidence of non-Hodgkin's lymphoma has been increasing, with 964 new cases in 2010 (4). Better diagnostics and treatment over several decades has improved survival rates, and the five-year relative survival rate is now around 90 % for Hodgkin's lymphoma and around 70 % for all non-Hodgkin's lymphomas in general (4). However, the five-year survival rate for lymphomas varies according to stage, histological subtype, patient's age and clinical and prognostic factors.

For Hodgkin's lymphoma and for aggressive and very aggressive lymphomas, modern cancer treatment will often result in cure (3). The indolent lymphomas have a more prolonged course. Curing of the disease with conventional treatment is not a realistic objective for these patients, but the treatment reduces disease activity and prolongs life (3, 5). In some patients, indolent lymphomas may change growth pattern and histological appearance over time and become more similar to aggressive forms, known as transformation (6). Certain types of lymphomas still entail a poor prognosis. This is true, for example, of mantle cell lymphoma, peripheral T-cell lymphomas and transformed indolent lymphomas (3).

High-dose therapy with autologous stem cell support is very intensive, also in terms

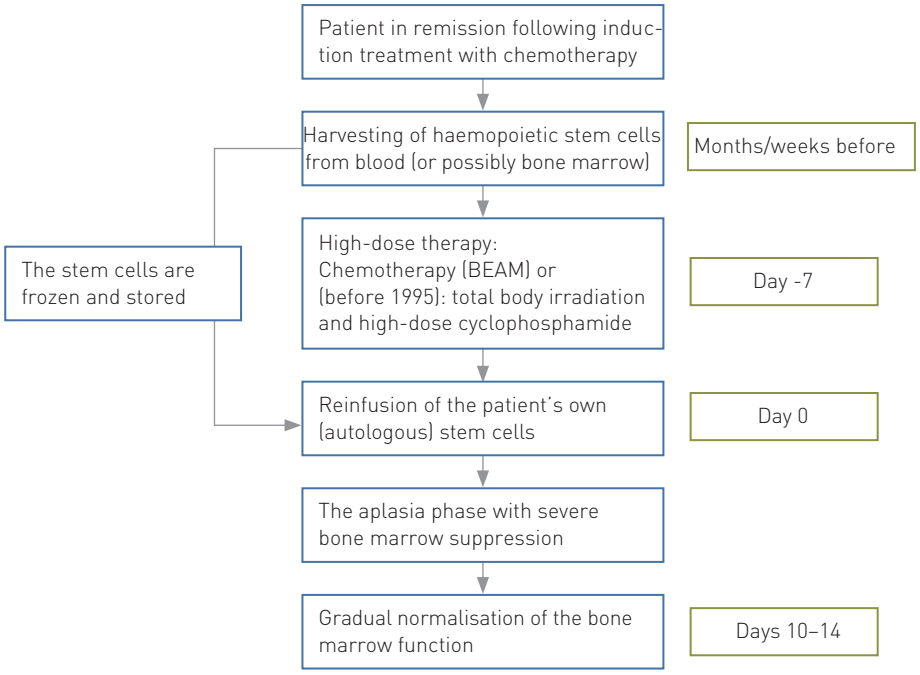

Figure 1 *High-dose therapy with autologous stem cell support (HDT) for lymphomas is conducted as follows. Step 1. Induction therapy: to conduct the therapy it is a precondition that the lymphoma is chemosensitive, and the patient undergoes the first pre-therapy /induction therapy with different chemotherapy regimens depending on diagnosis. Step 2. Stem cell harvesting: if the lymphoma achieves at least a partial response with induction therapy, the patient proceeds to stem cell harvesting. Today these are harvested from venous blood after the bone marrow has been stimulated to release stem cells into peripheral blood using growth factor (G-CSF – granulocyte colony-stimulating factor) in combination with chemotherapy. Step 3. The stem cells are frozen in liquid nitrogen and stored while the patient receives the high-dose therapy. Step 4. The high-dose therapy: in the period 1987–95 the therapy consisted of total body irradiation with a total dose of 13 Gy administered over five days with two fractions of 1.3 Gy daily combined with chemotherapy in the form of high-dose cyclophosphamide. Since 1996 chemotherapy has been used alone with BEAM (carmustine (BCNU), etoposide, cytarabine (Ara-C) and melphalan). Step 5. Reinfusion of stem cells: following completion of the treatment the stem cells are reinfused via a central venous catheter and find their way back to the bone marrow. Step 6. The aplasia phase: while the bone marrow is regenerated with proliferation, differentiation and maturation of the various cell lines, the patient will be pancytopenic without new production of erythrocytes, thrombocytes and granulocytes. During this period the patient is in isolation and is dependent on highly specialised supportive treatment. Step 7. Gradual normalisation of the bone marrow function: After 10–14 days, when the level of neutrophil granulocytes rises, the isolation may be lifted. The bone marrow function will gradually be restored so that the level of circulating blood cells is normalised*

of resources. It has been a treatment option for lymphomas for the past 25 years and provides a clear survival benefit for several types of lymphoma. In this article we wish to provide a historical overview of the use of HDT for lymphomas in Norway.

Material and method

The article is based on literature searches in PubMed, collection of all treatment protocols for HDT studies with Norwegian participation, and personal experience of the treatment environments. Emphasis is placed on studies in which the Norwegian research community has participated.

High-dose therapy with autologous stem cell support for lymphomas

The first documented allogeneic stem cell transplantation (i.e. stem cells from another donor) was performed as early as 1939, when a woman with aplastic anaemia had bone marrow from her brother transferred by intravenous transfusion (7). The treatment was unsuccessful and the patient died five days later. Animal experiments in the 1950s demonstrated that otherwise lethal bone marrow suppression could be overcome by intravenous injection of bone marrow (8). This was ascribed to the re-colonisation of the bone marrow and restoration of bone marrow function by the transfused stem cells.

Bone marrow suppression is the adverse effect that mostly limits the doses of chemotherapy and radiotherapy which can be safely given. It was hypothesised that autologous stem cell support could overcome this and that the doses could be increased, with a correspondingly greater treatment effect. Several clinical studies were therefore conducted at the end of the 1950s and the early 1960s in which patients' own stem cells were used (9). The results of these first clinical studies were disappointing, but in the wake of promising results with allogeneic stem cell transplantation for leukaemia, the concept was again researched in the 1970s. The first successful results of HDT for lymphoma were published in 1978 (10), and during the 1980s several phase 1 and phase 2 studies were conducted with promising results (11).

In Norway the treatment was established at the Norwegian Radium Hospital through three phase 2 studies from 1987. These first studies included selected patients from throughout the country who were under 55 years of age, in good general condition, with little comorbidity and with lymphomas that had very poor prognosis with the treatment given at that time. This mainly consisted of CHOP-based chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone). In a 20-month period in 1988–89 five patients received the high-dose therapy in Heidelberg, Germany, for operational reasons.

In the years that followed, new international multicentre phase 2 and phase 3 studies were launched (Fig. 2) (12–22). In 1993 the Norwegian Directorate of Health therefore established an expert group for high-dose therapy with autologous stem cell support for malignant diseases. The group was asked to advise on the extent and form of treatment that should be offered in Norway (23). The justification was the need for an overview of a rapidly developing field – an area with promising results, but for which the position of treatment in the health services had not been clarified. Stein Kvaløy was appointed as head, and in 1995 the expert group submitted its report. The conclusions were that HDT could be considered an established procedure for aggressive lymphomas in second remission, and that it was a promising, but still experimental, form of treatment for a number of other indications (23).

The report simultaneously defined requirements for documentation in order for HDT to be considered an established treatment for a new diagnostic group: at least two subsequent phase 3 studies of appropriate design which showed benefit from the treatment, with no concurrent studies of the same quality showing other results (applying to common forms of cancer), or at least three subsequent phase 2 studies (relevant to rarer forms of cancer). Furthermore, it was concluded that the use of HDT had increased, both in terms of the number of patients treated and the number of indications, and that the activity should be regionalised. From 1996 the treatment

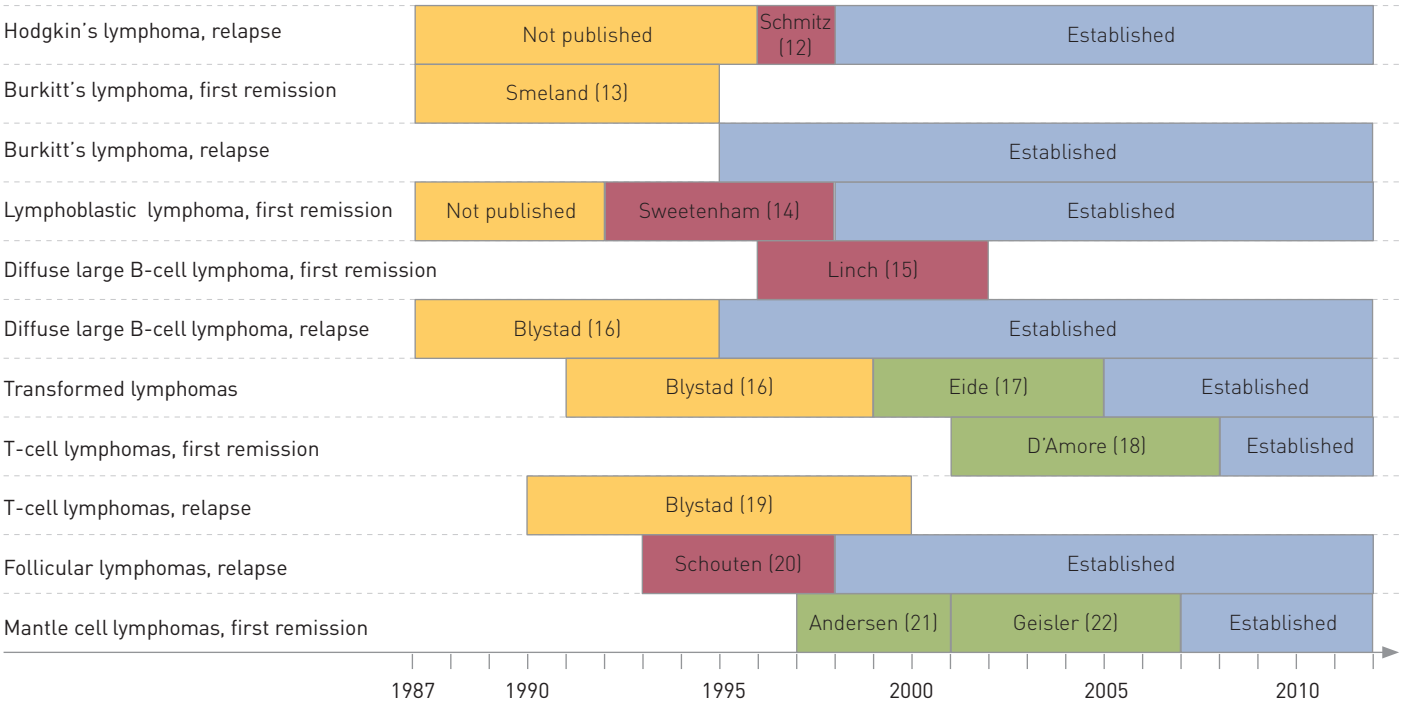

Figure 2 *Clinical studies giving rise to established indications for high-dose therapy with autologous stem cell support for lymphomas in Norway. Yellow boxes indicate single-centre phase 2 studies, green multicentre phase 2 studies, red randomised phase 3 studies and blue established indication/treatment option. Phase 1 studies: trials on a small number of patients where the main purpose is to assess adverse effects and tolerability. Phase 2 studies: testing of new treatment on a small group of patients where the main purpose is to assess effect and adjust level of dosage. Phase 3 studies: testing of new treatment against established treatment (or placebo) in a large patient group to document effect. Preferably randomised, controlled studies*

was therefore provided in all the health regions: at the Norwegian Radium Hospital and Ullevål University Hospital in Oslo (now Oslo University Hospital), at Haukeland University Hospital in Bergen, at St. Olavs Hospital in Trondheim and at the University Hospital of North Norway in Tromsø.

Indications for HDT for lymphomas in the period 1987–2012

Figure 2 (12–22) provides an overview of the studies and indications for HDT for lymphomas in Norway from 1987 up until today. This type of lymphoma treatment was established at the Norwegian Radium Hospital in 1987 with three phase 2 studies for Hodgkin's lymphoma (not published), very aggressive lymphomas (13) and relapse of aggressive lymphomas (16), respectively.

From 1996 the Norwegian Radium Hospital participated in a German phase 3 study in which patients with relapse of advanced and/or high-risk Hodgkin's lymphoma were randomised to either HDT or standard chemotherapy without stem cell support (12). This study showed significantly better disease-free survival for the group that had received HDT (55 % compared with 34 % after three years). Corresponding treatment benefit for relapsed Hodgkin's lymphoma was also demonstrated in a smaller, randomised study (24). These two studies are the main basis for today's established indication for HDT for Hodgkin's lymphoma with relapse within two years, with lack of response to primary treatment, or for other or later relapses (3, 25, 26).

In the phase 2 study that included patients with Burkitt's lymphoma, HDT as consolidation in first remission resulted in substantially improved five-year progression-free survival – from 31 % to 71 % compared to historical controls treated with standard CHOP-based chemotherapy alone (13). The primary treatment of Burkitt's lymphoma has gradually been greatly improved through intensive chemotherapy, so that HDT in first remission no longer provides any survival benefit (13). The treatment is therefore now recommended only for primary chemoresistance or relapse of Burkitt's lymphoma (3, 25, 27).

For lymphoblastic lymphoma, HDT in first remission is still the alternative we recommend in Norway, based on the findings from an international, randomised multicentre study from the period 1992–97, in which Norwegian patients were also included. This study showed improved three-year disease-free survival with HDT compared to maintenance treatment in traditional doses (14).

HDT for diffuse large B-cell lymphoma (DLBCL) in second remission was established as the standard in Norway in 1995 (23), based on several phase 2 studies (16, 28) and one phase 3 study (29). The benefit of the treatment in first remission has also been investigated – without it being found that this results in better response rates or longer survival (15, 30). HDT is therefore not standard procedure for diffuse large B-cell lymphoma in first remission (3, 25, 27).

The above-mentioned phase 2 study of the relapsed aggressive lymphomas also included ten patients with transformed lymphomas in the period 1989–93 (16). From 1999 to 2004, patients with transformed lymphomas were included in a prospective phase 2 study at five Norwegian university hospitals where HDT was given in first remission (17). The results were good compared to historical controls, and when collated with data from several retrospective analyses, the study contributed to the conclusion that HDT is an option for transformed lymphomas (3, 27).

Mature T-cell lymphomas are a heterogeneous group of rare lymphomas with an aggressive clinical picture and poor prognosis (31). In the years 1990–2000, HDT

was given to this group for chemosensitive relapse (19). From 2001 to 2007, patients with several types of mature T-cell lymphomas were included in a prospective phase 2 study led by the Nordic Lymphoma Group, where they received HDT in first remission. This study showed good results – five-year overall survival and progression-free survival of 51 % and 44 % respectively (18). The study confirmed the results of a smaller German phase 2 study (32). This regimen is now regarded as an established treatment alternative for systemic variants of mature aggressive T-cell lymphomas (3, 25, 27).

For mantle cell lymphoma (stage II-IV) the Nordic Lymphoma Group has conducted three prospective phase 2 studies with HDT in first remission (MCL1, 2 and 3). The results of MCL 1 (patients included 1996–2000) were disappointing and not substantially better than for historical controls treated with standard chemotherapy alone. One explanation for this was that few patients achieved good remission from induction therapy with dose-dense CHOP (maxi-CHOP) without rituximab (21). In the MCL 2 study (inclusion in the period 2000–06), both high dose cytarabine and rituximab were used for the induction therapy. This resulted in an increased remission rate – from 76 % in MCL 1 to 96 % in MCL 2 as well as median overall survival of more than ten years compared to the previous three years (21, 22). Based on the results of the MCL 2 study and a German randomised study (33), HDT is today considered to be the established procedure for mantle cell lymphoma in first remission (3, 25, 27).

A randomised European multicentre phase 3 study with Norwegian participation, in which patients with relapsed follicular lymphoma were included, was conducted in the period 1993–97. Fewer patients than desired were recruited, but there was higher progression-free survival and overall survival following HDT than after standard chemotherapy (20). HDT has since been an option for patients with recurrence of follicular lymphoma (3, 25, 27, 34).

As of today, HDT is therefore established procedure or an option for a number of clinical situations in lymphoma patients. Updated guidelines can be found on the website of the Norwegian Directorate of Health (3).

Discussion

HDT is costly and resource-intensive. In 2013 transfusion of autologous stem cells alone has a DRG weight of 6.34, which means that an average course of this type is calculated to cost approximately NOK 250 000. A complete patient course which also includes assessment, stem cell harvesting, follow-up and treatment of complications will cost even more. Although HDT is an intensive procedure and may lead to complications, it provides a significant survival benefit for several types of lymphoma.

This historical overview shows an example of the knowledge-based introduction of a treatment method based on systematic research activity, where Norwegian research communities have participated in international clinical studies. This has ensured a steady development and at the same time it has helped to provide Norwegian lymphoma patients with an optimal treatment option.

In Norway, HDT has now been an option for lymphomas for 25 years. In the first few years the treatment was considered to be experimental and was performed in small national phase 2 studies with a small number of indications and stringent criteria for inclusion. The treatment has over time been tested for more indications in international prospective phase 2 and phase 3 studies and has been established as standard procedure or as an option for a number of indications based on these results. Norwegian guidelines for the use of HDT for malignant lymphomas are accordingly based on findings from clinical studies and are consistent with European and American practice (25, 27).

The documentation requirements set out in the Norwegian Board of Health Supervision's report from 1995 have to a large extent been followed when possible. In certain cases the introduction of HDT has been based on less stringent use of the criteria, for example benefit in progression-free survival rather than overall survival. In several randomised studies, patients in the control cohort have received HDT in next remission, so that the benefit in terms of overall survival is more difficult to document. The patient cohort for some types of lymphoma, for example transformed lymphomas, is also too small to enable prospective randomised trials to be conducted. The treatment indication will occasionally be relative, especially for follicular and transformed lymphomas, and benefit must be clinically weighed against increased risk of serious adverse effects.

The role of high-dose therapy with autologous stem cell support in the treatment of lymphomas has changed and will continue to do so in line with the introduction of new forms of therapy. In the past few decades there has been a marked improvement in survival for several types of lymphoma. This can largely be attributed to new forms of treatment, especially immunotherapy with the anti-CD20 antibody rituximab for B-cell lymphomas. For several types of lymphoma, the knowledge base for HDT is based on studies conducted before the introduction of rituximab. Rituximab is now incorporated in virtually all first-line treatments for B-cell lymphomas, and this has resulted in fewer relapses. However, patients who have an early relapse following treatment with a regimen which includes rituximab show inferior response to second-line treatment, including HDT, than previously (35). New studies and development of improved treatment regimens are therefore needed, especially with a view to improving the induction therapy prior to high-dose therapy with autologous stem cell support.

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