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The role of stem cell transplantation in follicular lymphoma

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ABSTRACT

With the introduction of novel treatments paradigms to if or when to use transplantation strategies for patients with follicular lymphoma have changed substantially. Autologous transplantation has been intensively evaluated as consolidation after first induction treatment with positive effects, however the introduction of Rituximab led to comparable improvements and HDT has been moved to relapse treatment. In this indication HDT was frequently use already at first relapse, but now is dominantly used in patients with a highrisk profile, e.g. failure of response, early or multiply relapse and/or signs of transformation. The ideal place for allogeneic transplantation is even harder to define, as the curative potential might be outweighed by the substantial side effect profile and the indication must always be discussed in the light of available alternatives. In consequence, transplantation strategies remain an important therapeutic instrument for patients with FL, however timing within the treatment course has to be defined individually.

1. Introduction

Stem cell transplantation (SCT) strategies have initially been developed in light of limited treatment options for relapsed lymphomas decades ago. Whereas high dose therapy followed by autologous stem cell re-transfusion aimed to allow for intensified dosing of cytotoxic agents, allogeneic transplantation employed the postulated “graft versus lymphoma effect” for immunologic eradication of the malignant clone. During recent years, mainly technological advances and improved supportive care have optimized the results of transplantation approaches, mainly by reducing treatment related mortality of allogeneic SCT. Consequently, transplantation could be offered to a greater proportion of patients at lower risk, however, in FL with the advent of a variety of novel treatment options with beneficial side effect profile it has become challenging to define the right place for intensive treatments within the therapeutic algorithm. Therefore, a thorough balancing of the benefits of transplantation procedures and other available treatment options recognizing their benefits and their toxicities is needed for appropriate advice to the patient.

1.1. Principles of stem cell transplantation

Failure of chemotherapy was always thought to be associated to absolute resistance based on the biology of the distinct disease or relative resistance due to under-dosing of cytotoxic agents. To overcome relative resistance escalation of available drugs imposed promising, however this approach was limited due to side effects of escalated drug dosing, dominantly

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hematotoxicity. With the improved understanding of the role of stem cells and the development of technologies to preserve autologous stem cells, already in the 1970's first reports of *autologous transplantation* were reported [1] which allowed for dose escalation of cytotoxic agents and long term remissions have been observed. At this time a rather mixed population of patients diagnosed based on historic classification systems had been included. More than a decade later, with the proof of the value of SCT in a randomized trial compared to conventional chemotherapy in aggressive lymphoma [2], the interest in autologous transplantation raised and subsequently specific series of trials have been performed for FL, too.

Results in other hematologic malignancies, dominantly leukemias have shown the efficacy of graft-versus-tumor effect induced by *allogeneic transplantation* to control/cure hematologic cancers. Consequently a potential graft-versus-lymphoma (GvL) effect was assumed and early results showed evidence of long term tumor control in FL patients [3–5], although there are conflicting data about the existence and extent of the GvL effect [6,7]. A second argument in favor of an allogeneic rather than autologous stem cell support was the potential of contaminating tumor cells to cause relapse [8] – which is not the case with an allogeneic stem cell source. Treatment related morbidity and mortality has always been a major concern about allogeneic SCT, especially with myeloablative conditioning regimen. The introduction of reduced intensity transplantation has given new and important input in this field, as a much better safety profile is present and promising results have been found [7].

1.2. Approaching the patient with follicular lymphoma

FL is the most common indolent lymphoma in western countries. It arises from the germinal center of the lymph node and is frequently characterized by the t(14;18), which occurs in 85% of cases and inactivating mutations of MLL are found in 80% of samples analyzed. FL represents a heterogeneous group either based on histology or on the clinical disease course. Grading separates FL to different subgroups, where grade 1, 2 and 3A are considered indolent; in contrast 5% of cases have an increased number of centroblasts and are named grade 3B which is considered to be an aggressive lymphoma. Unfortunately, clinical trials on transplantation often include different patient collections, some including only grade 1 and 2, others including grade 3A and again others lumping grade 3A and B together making interpretation more complex.

Clinically, a substantial proportion of patients with FL experience a protracted course and die of reasons other than lymphoma, whereas others experience rapid progression and lymphoma leads to a substantial loss of life years.

Standard treatment options are reviewed elsewhere, however, there is a substantial variety available and these are used in a personalized fashion [9]. Besides observation (watch and wait), these options include chemotherapy (mainly Bendamustine, CHOP, CVP and others), monoclonal antibodies (Rituximab and now Obinutuzumab as single agent, combination partner or maintenance treatment), radio-immunotherapy, radiation, and small inhibitors as Idelalisib. Furthermore, Lenalidomide has shown great promise and might enter first line treatment soon and a variety of novel options is tested in clinical trials including bcl-2-inibitors, checkpoint inhibitors and CAR-T-cells. Importantly, in patients being responsive or achieving long term remissions options might be used repeatedly, thereby increasing the potentially available treatment choices.

With all these options available, one might consider transplantation strategies obsolete and somehow this is reflected in the reluctance of patients and treating physicians in selecting a transplantation procedure. However, the capability to induce long term remissions with autologous transplantation [10] or even the probably curative potential of allogeneic transplantation [11] justifies offering these options to selected patients, which is line with current expert based treatment recommendations. Here we review available data for the different scenarios in which transplantation might be used and discuss where to place these strategies within a treatment algorithm.

2. Data on autologous transplantation

2.1. HDT with autologous transplantation for consolidation of first line treatment

Although developed primarily in relapsed disease use of autologous SCT early during the treatment course was considered a promising strategy to induce deepened and prolonged remissions and to eventually induce cure at least in some patients. Various trials have been initiated; however all but one of those have been performed in the pre-Rituximab era (s. Table 1a). Some of the trials were able to demonstrate a benefit in progression free survival but failed to show a benefit in OS [12,13], or failed to show any difference [14] even if several data-sets are used for a meta-analysis [15]. More importantly, the only trial including Rituximab failed to show an overall survival benefit, even in a high risk group of patients [16]. In addition, some of the trials described excessive toxicity in the transplantation arms, especially secondary cancers [13]. The last and still unpublished trial of the GLSG did prospectively evaluate the value of Rituximab in the context of first line FL treatment and in addition compared the value of consolidative HDT vs. Interferon. In this trial HDT proved to be superior to IFN, but dominantly in patients without Rituximab during induction, a final readout for overall survival is still pending, a clear and early difference is now unlikely to be detected (Unterhalt et al., unpublished).

HDT in first line has been depleted from therapeutic algorithms today. This is not only based on the conflicting results but mainly on the introduction of Rituximab in induction and maintenance treatment with excellent results for a majority of patients, with up to 60% of patients being in continuing remission after 5 years [17]. Even if some patients indeed might experience cure like long term remission after HDT [13], this type of remission can also be found in patients after chemo-

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