

## Changing role of stem cell transplantation in follicular lymphoma

### 论干细胞移植在滤泡性淋巴瘤治疗中的作用

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Patients with advanced follicular lymphoma (FL) have numerous treatment options, including observation, radio-therapy, single-agent or combination chemotherapy, mAbs, and radioimmunoconjugates. These therapies can extend progression-free survival but none can provide a cure. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curable therapy for FL, with the field shifting more toward the use of reduced-intensity conditioning regimens because of the lower associated nonrelapse mortality compared with myeloablative regimens. However, GVHD and infection are still problematic in the allo-HSCT population. Autologous HSCT (auto-HSCT) confers high response rates and prolongs progression-free survival in relapsed patients who are chemosensitive, and an increasing amount of data suggest that auto-HSCT may be curative if offered to relapsed patients who are not heavily pretreated. Auto-HSCT has no role as consolidation therapy for patients in first remission based on the results from 3 large randomized trials. Novel conditioning regimens with radioimmunoconjugates have been used in both auto-HSCT and allo-HSCT regimens and results have shown efficacy even in chemorefractory patients. Therefore, with the exception of patients in first remission, the optimal timing for HSCT remains controversial. However, the outcomes seen after auto-HSCT and allo-HSCT continue to improve, and HSCT represents a treatment modality that should be considered in all FL patients, especially while their disease remains chemoresponsive.

晚期的滤泡性淋巴瘤 (FL) 患者有多种治疗选择, 包括观察, 放疗, 单药或者联合化疗, 单抗, 和放射免疫制剂。这些治疗可以延长无进展生存期, 但是没有一个可以治愈疾病。对于FL, 唯一可以治愈的疗法是异体干细胞移植, 目前更趋向于降低强度预处理的方案, 因为与清髓性方案相比具有较低的非复发死亡率。但是, 移植物抗宿主病 (GVHD) 和感染对异体移植仍然是很大问题。对于复发但是依然化疗敏感的患者, 自体干细胞移植有很高的有效率, 可以延长无进展生存期, 并且有越来越多的数据表明, 如果对非“重度治疗”的复发患者进行自体干细胞移植, 是有可能达到治愈目的的。根据三个大规模的随机临床试验的结果, 对于首次缓解的患者, 是不必要用自体干细胞移植来进行巩固的。新的包含放射免疫制剂的预处理方案被用在自体 and 异体干细胞移植中, 效果良好, 即使对耐药的患者也是如此。因此, 除了首次缓解的患者之外, 干细胞移植的最佳时机依然存在争议。但是, 自体 and 异体干细胞移植的结局在不断改善, 干细胞移植应当成为被所有FL患者考虑的治疗模式, 尤其是当其疾病还对化疗响应的时候。

### Introduction介绍

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma, with an incidence of approximately 15 000 new cases/year in the United States. The incidence increases with age, with the median age at diagnosis being 60 years. FL cells express surface Ig and the cell-surface markers CD19, CD20, and CD10. Also characteristic is cytoplasmic expression of the bcl-2 protein and the presence of the t(14;18) translocation involving the IgH/bcl-2 genes. The median survival rate from

diagnosis has historically ranged from 8-10 years, and the availability of the chimeric anti-CD20 mAb rituximab (RTX) has improved outcome and survival.

滤泡性淋巴瘤 (FL) 是第二常见的非霍奇金淋巴瘤, 在美国每年大约有15000新发病例。发病率随年龄升高, 在确诊时的中位年龄为60岁。FL细胞表达表面免疫球蛋白, 以及细胞表面标记物CD19, CD20, 和CD10。其特点是细胞质表达Bcl-2蛋白和IgH/bcl-2基因t(14;18)易位。从确诊开始的中位生存期在历史上看是8-10年, 嵌合CD20单克隆抗体的出现改善了预后和生存期。

However, FL remains incurable with standard therapy and the clinical course among FL patients is markedly variable. Some patients develop progressive or transformed disease early, with 15% dying within 2 years from diagnosis, whereas others remain alive for decades without requiring treatment.

但是标准治疗依然不能够治愈FL, FL患者的临床表现相差很大。有些患者很早就出现疾病进展或转化, 有15%在确诊两年内就死亡, 而其他一些患者甚至生存几十年而无需治疗。

The definitive management of advanced FL remains controversial due to the large number of available treatment options. Clinicians who treat patients with FL must tackle a plethora of problems and choices, such as: (1) there is no standard frontline therapy, (2) there is no standard second-line or subsequent therapy, (3) there are a broad number of efficacious therapeutic options with a wide range of toxicities, and finally, (4) there is no consensus as to the optimal sequence in which to offer these various therapies. Within the scope of this chapter, the options for relapsed and refractory patients will be further discussed because hematopoietic stem cell transplantation (HSCT) has no role in first remission patients.

由于存在较多治疗选择, 晚期FL的标准治疗模式还存在争议。临床医生面临一系列的问题和选择, 例如1) 没有标准的一线方案, 2) 没有标准的二线方案或者随后的治疗方法, 3) 有很多种有效的治疗手段, 毒性高低各异, 最后4) 在提供这些疗法的最佳次序上没有共识。在本文中, 将进一步讨论复发和耐药患者的治疗选择, 因为对于首次缓解的患者干细胞移植根本不必考虑。

For relapsed patients with limited stage disease (1 or 2 nodal areas) without constitutional symptoms, involved field radiation therapy may suffice, because FL tends to be highly responsive to external beam radiation therapy. For FL patients with bulky disease and/or constitutional symptoms, the combination of RTX with chemotherapy with regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), FCR (fludarabine, cyclophosphamide, rituximab), R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone), or R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) are commonly used treatment options with low to moderate toxicity profiles and can be administered in the outpatient setting.

对于局限期的复发患者 (1-2个淋巴结区域) 而且没有全身症状的, 可能受累野放疗就足够了, 因为FL患者一般来说对外部射线照射非常敏感。对于有大包块的或者有全身症状的患者, 通常采用美罗华联合化疗, 方案包括R-CHOP, FCR, R-FCM, 或R-CVP, 这些方案毒性属于中低度而且可以在门诊进行。

Bendamustine is an interesting chemotherapeutic agent that has properties of both an alkylator and a purine analog. Bendamustine as a single agent or in combination with RTX represents another efficacious, well-tolerated option. Phase 2 studies have reported responses with lenalidomide and also with the proteasome inhibitor bortezomib.

苯达莫斯汀是一种很有意思的化疗药物，它同时具有烷化剂和嘌呤类的特性。苯达莫斯汀作为单药或与美罗华联合成为另外一个有效的，耐受良好的选择。二期试验也报告了来那度胺以及蛋白酶体抑制剂硼替佐米的疗效。

Yttrium90 ibritumomab tiuxetan and iodine131 tositumomab represent the 2 anti-CD20 radioimmunoconjugates that are FDA-approved for relapsed and refractory FL patients. The response rates for both agents are comparable, ranging from 60%-80% with responses also seen in RTX-refractory patients. A new generation of mAbs also show promise, including GA-101, a humanized bioengineered type II anti-CD20 Ab; galiximab, an anti-CD80 Ab; and epratuzumab, a humanized anti-CD22 Ab.

Yttrium90 ibritumomab tiuxetan (商品名: Zevalin) 和 iodine131 tositumomab (商品名: Bexxar, 已退市-译者注) 代表了两种抗CD20的放射免疫制剂, FDA批准其用于复发耐药FL患者。两种药的有效率差不多, 都是在60%-80%之间, 对美罗华耐药的患者也有效。

HSCT has typically been offered to younger patients later in the course of their disease due to the long natural history of this disease and the higher risk associated with this procedure. However, improved supportive care, more precise donor selection, and allogeneic reduced-intensity conditioning (RIC) regimens have lowered nonrelapse mortality (NRM) and broadened eligibility.

干细胞移植通常会在年轻患者的疾病后期才提供, 原因是这个疾病较长的自然病史以及移植相关的高风险。但是, 改进的支持服务, 更加精确的供者选择, 以及减低强度的预处理 (RIC) 方案降低了非复发相关的死亡率而拓宽了适用性。

## Auto-HSCT自体干细胞移植

### Consolidation therapy 巩固治疗

High-dose chemotherapy with autologous HSCT (auto-HSCT) has been explored as part of consolidation therapy in first remission and in the setting of relapsed disease. Three large, randomized trials from Europe have compared the efficacy of auto-HSCT compared with conventional therapy with IFN-beta maintenance as consolidation. In 2 of the 3 trials, progression-free survival (PFS) was significantly higher in the HSCT arms, but there was no difference in overall survival (OS) between the HSCT and conventional therapy arms across all 3 trials.

自体干细胞支持下的高剂量化疗即自体干细胞移植被探讨作为首次缓解后巩固治疗的一部分, 以及用于复发的患者。来自欧洲的三个大规模的随机临床试验将干细胞移植的效果与常规化疗加干扰素维持进行了比较。在其中两个试验中, 无进展生存率 (PFS) 在移植组明显较高, 但是在全部三个实验中移植组合常规化疗组没有差别。

Most concerning was the significantly increased incidence of therapy-related malignancies seen in the HSCT arms that negated the advantage conferred by the improved PFS. (It should be mentioned that accrual to these trials occurred before the availability of RTX.) Subsequently, the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and Inter-gruppo Italiano Linfomi (IIL) conducted the first randomized trial in the RTX era comparing auto-HSCT with standard therapy in high-risk FL patients. A total of 136 patients received R-CHOP as frontline therapy and were then randomized to receive additional RTX or high-dose sequential therapy. After a median follow-up of 51 months, the 4-year event-free survival (EFS) was 28% versus 61% ( $P = .001$ ) in favor of the HSCT arm, but no difference seen in OS. A higher incidence of molecular remission was achieved in the HSCT arm compared with the conventional chemotherapy arm (80% vs 44%, respectively), with molecular remission being the strongest predictor of outcome. Patients in the conventional chemo-therapy arm who relapsed were crossed over to the HSCT arm, which resulted in a 68% 3-year EFS after a median follow-up of 30 months.

最让人关注的是在移植组出现的显著升高的治疗相关恶性肿瘤发病几率抵消了无进展生存期延长的优势（请注意这些临床试验的入组发生在美罗华出现之前）。随后，意大利的GITMO和IIL小组进行了美罗华时代首次随机试验，在高危FL患者身上比较自体干细胞移植和常规化疗的效果。在51个月的中位随访期后，4年无事件生存率时28%对61%

( $P = .001$ )，移植组较高，但是总生存率没有区别。与常规化疗组相比，移植组中出现了较多的分子级缓解（80%对44%），而分子级缓解是判断预后的最重要指标。常规化疗组复发的患者后来转到了移植组，在30个月的中位随访期后三年无事件生存率为68%。

Based on the results of the above 4 trials, auto-HSCT as consolidation therapy in CR1 patients is not recommended routinely. However, because the majority of these data originated from the pre-RTX era, longer follow-up is necessary in patients who received RTX during initial therapy and in the peritransplantation period to truly determine the efficacy in this specific FL patient population.

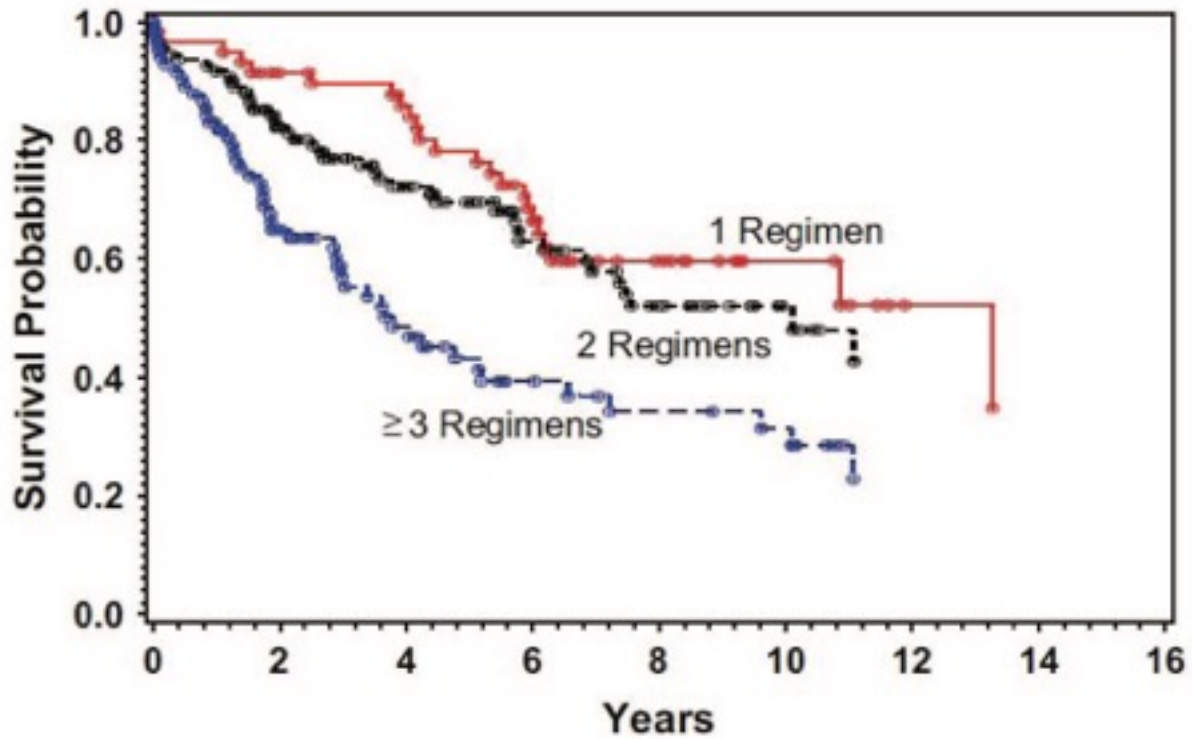
根据上述四个临床试验的结果，对于CR1的患者通常不建议移植。但是，由于大部分数据都来自美罗华出现之前，所以有必要对在初治时和移植前注射过美罗华的患者群体进行更长时间的随访以便明确的判定疗效。

### Relapsed disease 疾病复发

In contrast to patients in first remission, auto-HSCT has a more definitive role in patients with relapsed disease. Both prospective and retrospective studies report high response rates, with 5-year PFS ranging from 40%-50% and one study showing a 10-year PFS of 48%.<sup>21-27</sup> With regard to prognostic factors, patients who are not heavily pretreated (ie, those having received less than 3 prior regimens), patients with chemosensitive disease, and those having a lower risk Follicular Lymphoma International Prognostic Index (FLIPI) score at the time of auto-HSCT had improved OS<sup>21,28</sup> (Figure 1A-B). The impact of histological grade on outcome has been examined, but retrospective studies have yielded conflicting results. One study in Seattle showed no effect of having a higher grade of FL (grade 3 vs grades 1-2 FL) at the time of auto-HSCT, whereas a study in Nebraska found that patients with grade 3 FL had inferior outcomes.

与首次缓解相比，自体干细胞移植对复发的患者有更明确的意义。前瞻性研究和回顾性研究都显示很高的有效率，5年无进展生存率在40%-50%之间，有一项研究显示10年无进展生存率为48%。关于影响预后的因素，非“重度治疗”的患者（即接受的化疗方案小于三个），化疗敏感的患者，和在进行自体干细胞移植时有较低的滤泡性淋巴瘤国际预后指数（FLIPI）的患者总生存率较高。（图1A-B）。组织学级别对结果的影响也进行了研究，但是回顾性的研究得出了互相矛盾的结果。西雅图的一项研究显示在移植时较高级别的FL（3级相对1-2级）对预后没有影响，而内布拉斯加德研究发现3级FL的患者预后较差。

A



B

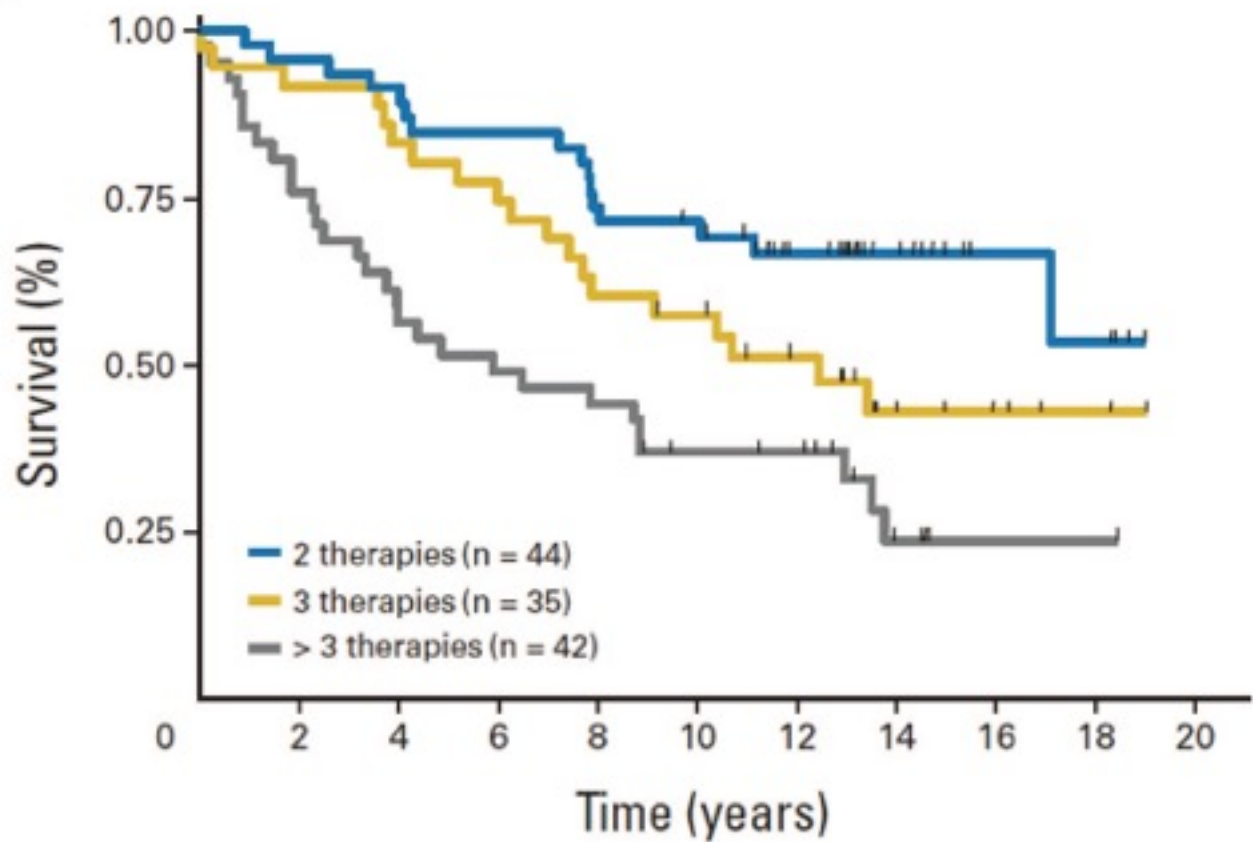


Figure 1. OS after auto-HSCT according to the number of prior treatment regimens. 21-22 (A) Probability of survival by number of prior treatments. (B) Survival by number of prior treatments.

图1. 自体移植后总生存率与先前接受的化疗次数的关系。(A) 先前治疗次数与生存概率。  
(B) 先前治疗次数与生存

Before the use of RTX, a retrospective series from the European Blood and Marrow Transplant Group (EBMT) reported the outcomes of 693 FL patients who underwent auto-HSCT. The 10-year PFS and OS were 31% and 52%, respectively. The relapse incidence was 54%, with relapse occurring at a median of 1.5 years (range, 1 month to 13.5 years) after auto-HSCT. The NRM was 9%. By multivariate analysis, older age, chemoresistant disease and use of a total body irradiation (TBI) – based conditioning regimen correlated with inferior survival. A total of 64 patients (9%) developed a second malignancy at a median of 7 years after HSCT.

在使用美罗华之前，欧洲血液和骨髓移植组（EBMT）的一项回顾性系列研究报告了693名FL患者接受自体移植的情况。10年的无进展生存率和总生存率分别为31%和52%。自体移植后复发的发生率是54%，复发的中位时间是1.5年（1个月到13.5年）。非复发相关死亡率是9%。经过多变量分析，年纪大，化疗耐药，和使用全身照射（TBI）预处理方案与较差的生存率有关。一共有64位患者（9%）在移植后发生了二次肿瘤，中位时间是7年。

Another large retrospective series of 241 FL patents who underwent auto-HSCT in Germany and a median follow-up of 8 years found a 10-year OS and PFS of 75% and 49%, respectively, with a relapse incidence of 47%. The median time to relapse was 20 months (range, 2-128). Five patients developed a therapy-related malignancy. The EBMT also conducted the CUP (chemotherapy vs unpurged arm vs purged arm) trial, which is the only randomized study that addressed prospectively the role of autologous HSCT compared with standard therapy in relapsed FL patients.

另外一项大规模的回顾性系列研究中共有241名FL患者在德国接受了自体干细胞移植，中位随访期八年发现10年总生存率和无进展生存率分别为75%和49%，复发率为47%。中位复发时间是20个月（2-128个月）。5位患者发生了治疗相关的恶性肿瘤。EBMT还进行了CUP（化疗对未净化组对净化组）的试验，这是唯一的一个前瞻性的关注自体干细胞移植比照标准化疗对复发的FL患者效果的随机临床试验。

A total of 140 FL patients with chemosensitive disease after salvage chemo- therapy were randomized to receive further conventional therapy, auto-HSCT with a purged graft, or auto-HSCT with an unpurged graft. There was a significant reduction in hazard rates for both PFS and OS between the chemotherapy-only patients and the combined groups of autologous HSCT patients. The 4-year OS was 46% for the chemotherapy arm, 71% for the unpurged arm, and 77% for the purged arm. The sample sizes in the 2 HSCT arms were too small to measure the effect of ex vivo purging. Unfortunately, this trial closed early due to slow accrual and was also conducted in the pre-RTX era, which limits the relevance of the findings.

共有140名FL化疗敏感的患者在经过挽救性方案治疗后随机分为常规化疗组，移植净化自体移植组或非净化移植组。在仅接受常规化疗的患者组和移植组之间，无进展生存期和总生存期的风险率有显著的降低。4年总生存率在化疗组，非净化移植组和净化移植组分别为46%，71%和77%。两个移植组的样本数量太少，以致无法衡量体外净化的效果。不幸的是，由于入组缓慢这个试验提前结束了，而且这个试验是在美罗华出现之前进行的，因而限制了其结果的重要性。

The Groupe d' Etude des Lymphomes de l' Adulte/Groupe Ouest Est d' Etude des Leucémies et Autres Maladies du Sang (GELA/ GOELAMS) examined retrospectively the impact of auto-HSCT compared with conventional salvage in 175 FL patients at first relapse. Forty percent of patients had prior RTX exposure and 40 patients (25%) underwent auto-HSCT. With a median follow-up of 31 months, the 3-year OS was significantly higher in patients who proceeded to HSCT compared with patients who did not undergo HSCT (92% vs 63%, respectively;  $P = .0003$ ). Frontline RTX exposure did not affect outcome. Because this was a retrospective study, the favorable impact of HSCT may have been affected by selection bias, because only patients responding to salvage therapy proceeded to HSCT.

法国的GELA/ GOELAMS小组回顾性的研究了自体移植和传统的挽救性化疗对175名首次复发的FL患者的影响。40%的患者先前接受过美罗华治疗，40位患者（25%）进行了自体干细胞移植。中位随访31个月，3年总生存率移植组明显高出化疗组（92%对63%； $P = .0003$ ）。一线美罗华治疗并没有影响到结果。因为是一项回顾性研究，选择上的偏向性也许造成了移植组的优势，因为只有对挽救性化疗响应的患者才进行了自体移植。

Based on the current literature, it is easier to determine who is not an ideal patient for auto-HSCT rather than ascertain who is the optimal candidate. Relapsed FL patients who should not be offered auto- HSCT include those who are chemoresistant, had 3 or greater prior regimens, have a poor performance status, and those greater than 70 years of age. Otherwise, patients who are beyond CR1 but chemosensitive, do not have BM involvement, and have a good performance status are excellent candidates for auto-HSCT. However, for patients with limited stage at relapse, thoughtful consideration should include offering only radiotherapy and/or conventional treatment. Naturally, the next question is: when should allo-HSCT be offered instead of auto-HSCT? This perpetually challenging question will be addressed later in this chapter.

根据目前的文献，比较容易确定谁不是接受自体干细胞移植的理想人选，而确定谁是接受自体干细胞移植的最佳对象则比较困难。不宜接受干细胞移植的患者包括化疗耐药的，接受过超过三个或以上方案治疗的，一般状态差的，以及70岁以上的。CR1后复发但化疗敏感，没有骨髓侵犯，一般状态好的则是理想的移植对象。但是，对于在复发时病灶局限的患者，应当认真是否只提供放疗或者常规化疗。自然，下一个问题就是：什么时候进行异体而不是自体干细胞移植呢？这个一直都很具有挑战性的问题将在下面章节阐述。

### Graft purging 移植物净化

With the goal of eliminating autograft contamination and increasing the probability of obtaining a molecular remission after HSCT, both in vitro and, more recently, in vivo methods of graft purging have been explored. Early studies that involved autologous BM purged in vitro with mAbs and complement showed that patients who received PCR<sup>-</sup>grafts had significantly longer PFS compared with patients who received PCR<sup>+</sup>grafts. In an Italian study of 92 FL patients, PCR<sup>-</sup>peripheral blood autografts could also be obtained if patients received intensive salvage followed by a moderately high dose of mobilization chemotherapy just before leukapheresis. As observed in the studies of purged BM grafts, PFS was significantly longer in the patients who received a PCR<sup>-</sup>graft. In addition, achievement of molecular remission after HSCT was predictive of improved PFS compared with patients who never achieved a molecular remission.



着眼于消除自体移植污染和提高移植后获得分子级缓解的概率，对体外和体内移植净化都进行了探索。早期关于自体骨髓在体外经单抗药物净化的研究显示，接受PCR阴性移植物的患者的无进展生存期远长于接受PCR阳性移植物的患者。在意大利针对92名FL患者的研究中，如何患者接受较强的挽救性化疗并在白细胞去除术之前在做一个相对高剂量的动员化疗，是有可能获得外周血自体移植PCR阴性的。在净化骨髓移植物的研究中可以观察到接受PCR阴性移植物的患者的无进展生存期明显较长。此外，自体移植后获得分子级缓解预示着相对于从未获得分子级缓解的患者更长的无进展生存期。

When RTX became available, in vivo purging largely replaced in vitro graft purging procedures. Preliminary studies consistently demonstrated that PCR<sup>-</sup>peripheral blood autografts could be obtained when RTX was incorporated into chemomobilization regimens. An early trial included 36 FL patients with relapsed/ refractory disease who received intensive RTX-based salvage chemotherapy and mobilization chemotherapy. A PCR<sup>-</sup>graft was collected in 97% of patients and after long-term follow-up, the median OS and PFS were not reached. The 12-year OS and PFS were 70% and 76%, respectively, with a plateau observed at 6 years. In a prospective trial from Italy, 61 relapsed FL patients received RTX-based salvage therapy and mobilization chemotherapy. After auto-HSCT with the in vivo purged graft, 2 more doses of RTX were given as consolidation therapy. In patients informative for the bcl-2 rearrangement, molecular response was defined as the absence of this rearrangement in the BM. The peripheral blood autografts were considered free of lymphoma if PCR<sup>-</sup>for the bcl-2 rearrangement. PCR<sup>-</sup>harvests were collected in all of the 33 PCR-informative patients. The 5-year PFS was 59%. Patients who achieved negativity for the bcl-2 rearrangement after HSCT experienced a longer PFS compared with patients who became bcl-2 positive, further underscoring the importance of achieving and maintaining a molecular remission.

美罗华出现后，体内净化大体上取代了体外净化。初步研究一致证明如果将美罗华加入到动员化疗方案中，是可以获得PCR阴性的外周血的。一项早期试验包含了36位复发耐药患者，这些患者接受了含美罗华的高强度挽救性化疗和动员化疗。从97%的患者体内收集到了PCR阴性的移植物，经长期随访，中位总生存期和无进展生存期还未达到。12年的总生存率和无进展生存率分别为70%和76%，在第6年观察到了平台期。在一项来自意大利的前瞻性试验中，61位复发FL患者接受了含美罗华的挽救性化疗和动员化疗。在用体内净化的移植物进行自体移植后，患者还接受了两次美罗华治疗进行巩固。对于有bcl-2重排的患者，分子级缓解定义为在骨髓中没有这种基因重排。如果PCR对于bcl-2重排阴性，则可以认为外周血自体移植没有淋巴瘤浸润。从全部33位PCR阴性的患者收集到了PCR阴性的干细胞。5年的无进展生存率是59%。在自体移植后bcl-2重排阴性的患者比变成bcl-2阳性的患者有更长的无进展生存期，进一步提示获得和维持分子级缓解的重要性。

With the advent of RTX, in vivo graft purging has become the purging method of choice. This method of purging is technically easier and less labor intensive compared with in vitro methods, which are no longer used commonly. In light of the data showing that RTX can render PCR<sup>-</sup> autografts and that achievement of molecular remission after auto-HSCT is a strong predictor of prolonged clinical remission, in vivo graft purging with RTX is recommended.

随着美罗华的出现，体内移植净化变成净化的不二之选。这种方法与体外净化相比技术上简单而且不费时费力，后者已经不常用。鉴于数据显示美罗华可以帮助获得PCR阴性的自体移植，而自体干细胞移植后获得分子级缓解是保持长期临床缓解的最强有力的预后因素，建议用美罗华进行体内移植净化。

#### RTX maintenance after auto-HSCT 自体干细胞移植后的美罗华维持

In randomized trials, maintenance RTX (MR) therapy after conventional salvage therapy improved PFS and OS in FL patients with relapsed disease. There is also evidence that relapsed FL patients may benefit from MR after auto-HSCT. A large randomized study from the EBMT showed significantly higher PFS in patients who received MR after auto-HSCT at a dose of  $375 \text{ mg/m}^2$  every 3 months for 2 years compared with patients who did not receive MR. Before this randomized trial, phase 2 trials administering MR after auto-HSCT demonstrated the feasibility and safety of MR after auto-HSCT and showed that MR could eradicate minimal residual disease persisting after auto-HSCT. Adverse events associated with MR in this setting include prolonged hypogammaglobulinemia, infection, and leukopenia. Therefore, there are data showing that MR prolongs PFS after auto-HSCT for patients with relapsed FL; however, it is not yet clear if OS is improved.

在随机试验中，进行传统的挽救性化疗之后用美罗华维持能够延长复发的FL患者的无进展生存期和总生存期。也有证据表明复发的FL患者在进行自体干细胞后可从美罗华维持中获益。来自EBMT的一项大规模随机临床试验显示，自体移植后接受每三个月一次，每次剂量为 $375 \text{ mg/平米}$ 的美罗华维持两年与未接受维持治疗的患者相比有明显更长的无进展。在此随机临床试验之前，二期试验在自体移植后给予美罗华维持证实了这种做法的可行性和安全性，并且显示美罗华可以消除在自体移植后仍然存在的微小残留病变。在此条件下与美罗华维持相关的副作用包括持续的低丙球蛋白血症，感染，和白血球减少症。所以，现在有数据显示美罗华维持可以延长复发FL患者在进行自体移植后的无进展生存期，但是，还不清楚总生存期是否也有改善。

#### Conditioning regimens 预处理方案

The most frequently used conditioning regimens for FL patients undergoing auto-HSCT include BEAM (carmustine, etoposide, cytarabine, melphalan), BEAC (carmustine, etoposide, cytarabine, cyclophosphamide), and CBV cyclophosphamide, carmustine, etoposide). TBI-based regimens such as TBI plus cyclophosphamide and/or etoposide are also offered, but less so because several retrospective studies have linked the use of TBI with a significantly higher risk of developing therapy-related myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) after auto-HSCT. The cumulative incidence of developing therapy-related MDS/AML after auto-HSCT ranges from 4%-20%, as reported in the literature, and occurs at a median of 2.5-7 years after auto-HSCT.

FL患者进行自体干细胞移植的常用预处理方案包括BEAM，BEAC，和CBV。TBI为基础的方案例如TBI加环磷酰胺或依托泊苷有时也用，但是较少，因为几个回顾性的试验将自体移植后发生治疗相关的MDS和AML的高风险与TBI预处理方案联系起来。文献报道自体移植后治疗相关的MDS/AML的累积发生率在4%-20%之间，中位发病时间是2.5到7年。

The anti-CD20 radioimmunoconjugates, yttrium<sup>90</sup> ibritumomab tiuxetan and iodine<sup>131</sup> tositumomab have been used as single agents or combined with high-dose chemotherapy as conditioning regimens before auto-HSCT. Data reported so far demonstrate that such regimens are well tolerated and adverse effects are comparable to chemotherapy-only regimens. However, these agents are currently not routinely offered with auto-HSCT in light of their high cost and the complex logistical steps needed to administer such agents. In addition, regimens containing radioimmunoconjugates do not appear to increase efficacy compared with chemotherapy-alone regimens. Based on the current data, chemotherapy-only conditioning regimens are favored. Other conditioning regimens should only be offered within the context of a clinical trial.

抗CD20的放射免疫制剂Zevlin 和Bexxer被作为单药使用或与高剂量化疗联合用于移植前的预处理。数据显示此类方案耐受良好且副作用与单纯化疗相当。但是，目前这种制剂在移植中不常使用，因为费用很高以及操作复杂。此外，包含放射免疫制剂的方案似乎并不比单纯化疗的方案效果更好。根据目前的数据，还是更倾向于采用单纯化疗方案。其它预处理方案仅限于在临床试验中使用。

### Allo-HSCT 异体干细胞移植

Allo-HSCT is the only known curative modality for patients with FL. The existence of a GVL effect mediated by donor T cells is supported by the observation of lower relapse rates compared with autologous HSCT for non-Hodgkin lymphoma (NHL) patients. The strength of the GVL effect varies widely among lymphoma histologies, with indolent histologies such as FL being the most sensitive to the GVL effect and the high-grade lymphomas being the least sensitive. In addition, for patients with indolent lymphoma who relapse after allo-HSCT, disease regression has been reported after withdrawal of immunosuppression medications and after donor leukocyte infusions.

异体干细胞移植是FL患者唯一已知的治愈手段。观察到的非霍奇金患者异体移植相对自体移植较低的复发率支持由供者T细胞诱导而存在移植抗肿瘤效应（GVL）。不同淋巴瘤组织学的GVL效应强度差异较大，惰性淋巴瘤例如FL对GVL效应最为敏感而高级别淋巴瘤最不敏感。此外，对于惰性淋巴瘤经异体干细胞移植后再次复发的患者，有报告说在撤掉免疫抑制药物后和供者淋巴细胞回注后疾病缓解。

In the earlier studies of allo-HSCT for FL patients, myeloablative regimens were primarily offered and yielded lower relapse rates compared with recipients of auto-HSCT. Plateaus in relapse incidence were noted after 2-5 years after allo-HSCT, whereas a continuous pattern of relapse occurred in the auto-HSCT patients. However, the high NRM associated with the ablative regimens mitigated the benefit of a lower relapse risk. Two large registry studies from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT compared the outcomes of relapsed FL patients who underwent either auto-HSCT or myeloablative allo-HSCT. In both studies, the relapse risk was significantly lower in the allo-HSCT group compared with the auto-HSCT recipients, but the treatment-related mortality (TRM) ranged from 30%-38%.

在早先的FL患者行异体干细胞移植的研究中，主要采用清髓性方案，复发率比自体移植较低。在完成异体干细胞移植的2-5年后可观察到复发率的平台期，而在自体移植的患者中复

发率曲线是连续的。但是，清髓性方案的高非复发相关死亡率抵消了较低复发风险的好处。国际血液和骨髓移植研究中心（CIBMTR）和EBMT的两项大规模档案研究比较了复发患者分别进行自体干细胞移植和异体干细胞移植的结果。两项研究都证实，异体移植的复发率显著低于自体移植，但是移植相关死亡率（TRM）在30%-38%之间。

Therefore, OS was comparable between the auto-HSCT and allo-HSCT recipients, because the significantly higher TRM in the allo-HSCT group offset any advantage conferred by the lower relapse risk. In both studies, the long-term OS for both the auto-HSCT and allo-HSCT groups ranged from 50%-62%. Three single-institution retrospective analyses with myeloablative regimens have reported durable remissions in FL patients, with 5-year EFS ranging from 45%-75% and outcomes dependent on chemosensitivity at the time of allo-HSCT. The study from Toronto reported a TRM of 15%, which is notably lower than the other series. This notable low TRM could be because all patients in the Toronto series were chemosensitive, whereas the other 2 studies included resistant and refractory patients. In addition, 4 patients (10%) in the Toronto group underwent syngeneic HSCT, which eliminates the risk of TRM related to GVHD.

因此，接受异体移植的患者的总生存率与接受自体移植的患者基本相当，异体移植组较高的移植相关死亡率抵消了较低复发率所带来的任何优势。在两项研究中，自体移植组和异体移植组的总生存率都在50%-62%之间。三个单中心回顾性研究提示清髓性方案可以给FL患者带来可持续的缓解，5年无进展生存率在45%-75%之间，结果取决于在进行异体移植的时候是否化疗敏感。来自多伦多的研究说移植相关死亡率为15%，明显低于其它系列。明显较低的TRM可能是因为多伦多研究的所有患者均为化疗敏感，而其它两个研究包括了耐药难治患者。此外，多伦多组的患者有4人（10%）进行的是同胞全相合移植，因而消除了GVHD相关的TRM的风险。

#### RIC allo-HSCT 降低强度预处理的异体干细胞移植

Allo-HSCT that incorporates RIC regimens rely more on the donor-mediated GVL effect rather than the cytoreduction of high-dose chemotherapy. The goal of RIC regimens is to confer adequate immunosuppression of the recipient to facilitate engraftment with a minimal to moderate amount of cytoreduction. RIC allo-HSCT has been used increasingly in FL patients and results have shown durable remissions and less NRM compared with myeloablative regimens. With the advent of RIC regimens, patient eligibility has expanded significantly and includes patients greater than 70 years of age, patients who had failed a prior auto-HSCT, and patients with comorbid conditions who otherwise would not be eligible to safely receive an ablative regimen.

RIC异体干细胞移植对供者诱导的GVL效应依赖度更高，而不是主要靠高剂量化疗进行消瘤。RIC的目的是让受者达到一定程度的免疫抑制以便植入，同时有小到中度的消瘤作用。RIC移植在FL患者中运用的越来越多，结果显示可持续性的缓解以及与清髓性移植相比较低的非复发死亡率。随着RIC方案的出现，患者的适用范围也显著扩展，可以包括70岁以上的患者，先前自体移植失败的患者，以及有并存病症而不能安全的接受清髓性移植的患者。

Table 1 provides outcomes on 5 selected prospective trials of FL patients undergoing RIC allo-HSCT. Four of the 5 trials included patients who had failed a prior auto-HSCT. All 5 trials included patients above 60 years of age and used a fludarabine-based preparative regimen. With median follow-up ranging from 3-10 years, the

disease-free survival/EFS ranged from 43%-75% and OS ranged from 52%-81%. Chemosensitivity at the time of HSCT was a consistent predictor of outcome.

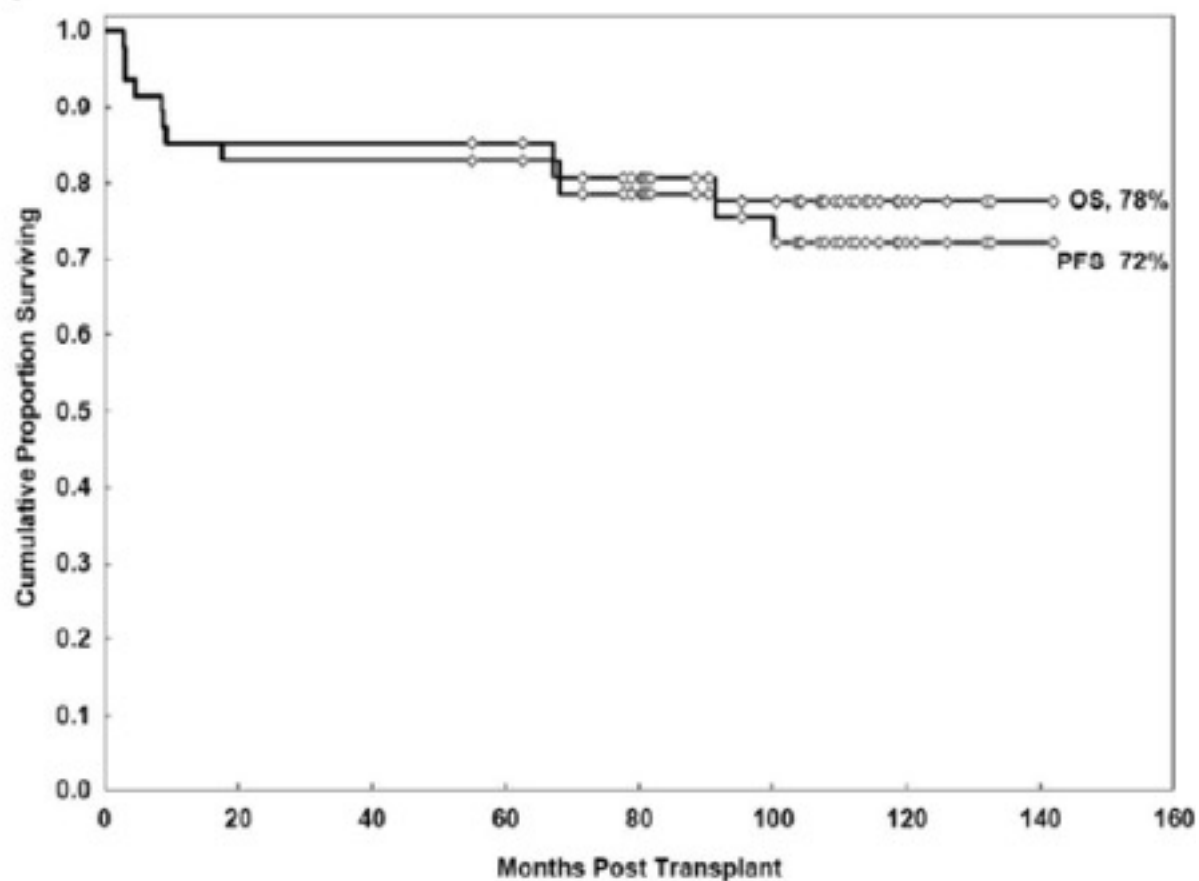
Table 1. Prospective trials of RIC allo-HSCT for relapsed FL

Study	n	Median age, y (range)	Prior auto-HSCT	Prep regimen	Donor type	DFS/EFS	OS	TRM	Median follow-up
MD Anderson <sup>54</sup>	47	53 (33-68)	19%	Flu/Cy/RTX	MRD URD	72%	78%	21%	107 mo
	26	55 (26-66)	0%	Flu/Cy/Y <sup>90</sup>	MRD URD	87% 80%	94% 80%	8%	33 mo
CALGB <sup>71</sup>	44 (16 with FL)	53 (39-68)	0%	Flu/Cy	MRD	75%	81%	9%	4.6 y
United Kingdom <sup>72</sup>	82	45 (26-65)	26%	Flu/Mel/Alem	MRD URD	76%	76%	15%	43 mo
GELTAMO <sup>73</sup>	37	50 (34-62)	46%	Flu/Mel	MRD	57%	54%	37%	52 mo
FHCRC <sup>74</sup>	62 (54 with FL)	54 (33-66)	32%	TBI ± Flu	MRD URD	43%	52%	42%	36 mo

CALGB indicates Cancer and Leukemia Group B; GELTAMO, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea; FHCRC, Fred Hutchinson Cancer Research Center; flu, fludarabine; Cy, cyclophosphamide; alem, alemtuzumab; mel, melphalan; MRD, matched related donor; URD, unrelated donor; DFS, disease-free survival; Y<sup>90</sup>, Y<sup>90</sup>-labeled rituximab.

表1显示了5个FL患者接受RIC异体移植的选择性的前瞻性临床试验的结果。5个试验当中有4个包含先前进行自体移植失败的患者。全部5个试验包含60岁以上的患者，并采用了氟达拉滨为主的预处理方案。中位随访3-10年，无病生存/无事件生存率在43%-75%之间，总生存率在52%-81%之间。在异体移植时是否化疗敏感是可靠的预后判断指标。

A



B

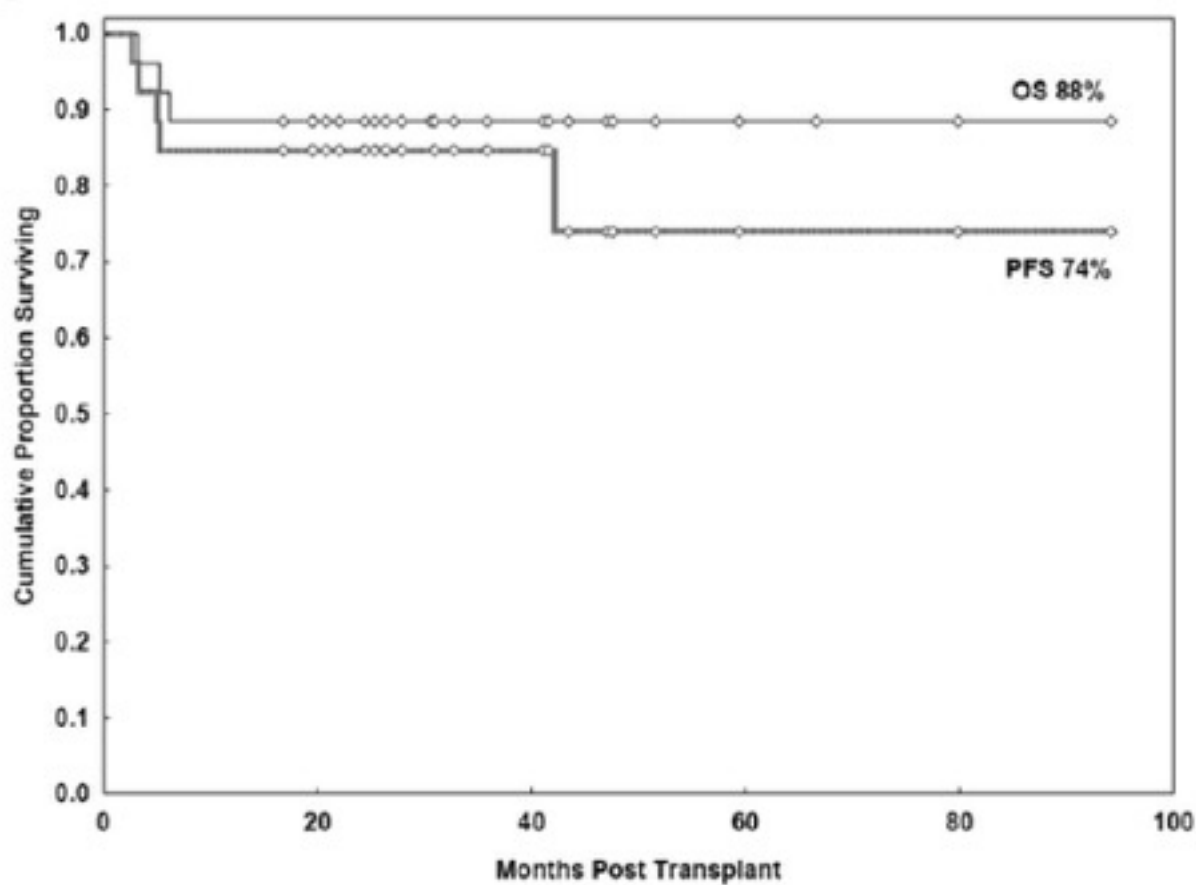


Figure 2. OS and PFS. (A) OS and PFS after the FCR regimen.<sup>54</sup> (B) OS and PFS after the YFC regimen.<sup>54</sup>

图2. OS和PFS。(A) FCR方案后的OS和PFS。(B) YFC方案后的OS和PFS

The trial from the M.D. Anderson group represents the prospective trial with the longest follow-up of 107 months. Forty-seven patients with relapsed FL received the FCR (fludarabine, cyclophosphamide, and RTX) regimen that incorporated a high dose of RTX in which 3 of the 4 planned doses were given at a dose of 1000 mg/m<sup>2</sup>. High-dose RTX results in prolonged serum concentrations, which facilitates cytoreduction and may augment the GVL effect through Ab- dependent cellular toxicity. RTX also may confer a protective effect against acute GVHD via profound B-cell depletion. The 11-year EFS and OS in that study were 72% and 78%, respectively, with only 3 relapses observed (Figure 2A). Based on these impressive results, the BMT CTN (Blood and Marrow Transplant Clinical Trials Network) is conducting a phase 2 multicenter trial using the same FCR regimen in relapsed FL patients with chemosensitive disease who have either a matched related or a matched unrelated donor identified. It is anticipated that accrual will be completed at the end of 2012.

安德森医疗中心组的试验是具有最长随访期（107个月）的前瞻性临床试验。47位FL复发患者接受了FCR方案以及高剂量美罗华，四次美罗华注射中有三次剂量为1000mg/m<sup>2</sup>。高剂量美罗华保证了持久的血清浓度，有利于消瘤并可能通过抗体相关的细胞毒性加强了GVL效应。美罗华可能还通过B细胞的深度清除对急性GVHD起到了保护作用。此项研究的11年无事件生存率和总生存率分别为72%和78%，只观察到了三例复发（表2A）。根据这些可观的结果，血液和骨髓移植临床经验网正在进行一项2期多中心临床试验，对复发后仍然化疗敏感的FL患者用同样的FCR方案，做相关或不相关的全相合移植。预计在2012年底完成入组。

The largest prospective series comes from the United Kingdom and used a preparative regimen with in vivo T-cell depletion. A total of 82 patients received fludarabine, melphalan, and alemtuzumab with cyclosporine alone as posttransplantation immunosuppression. The incidence of grades 2-3 acute GVHD was 13% and the 4-year cumulative incidence of extensive chronic GVHD was only 18%. The relapse risk was 26%, which was higher compared with the relapse seen in non-T-cell-depleted trials. However, this relapse risk was later reduced when donor lymphocyte infusion was given to patients who had mixed chimerism for conversion to full donor chimerism and to patients who had relapsed after HSCT.

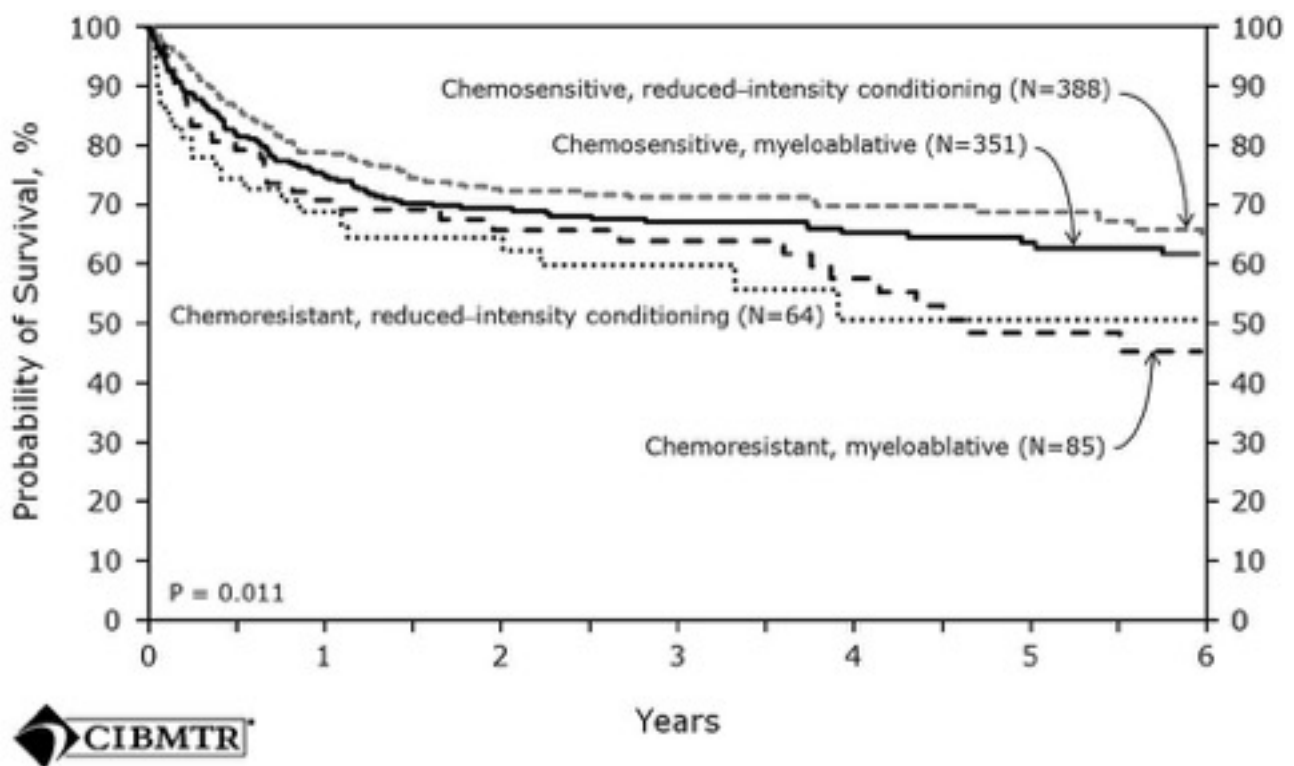
最大的前瞻性系列来自英国，采用了体内T细胞消除的预处理方案。一共82位患者接受了氟达拉滨，马法兰，阿伦单抗的方案，移植后免疫抑制剂用环孢素单药。2-3级的急性GVHD的发生率为13%，4年累计广泛慢性GVHD的发生率仅为18%。复发率为26%，高于非T细胞清除试验。但是，当给复发患者以及处于混合嵌合状态的患者进行供者淋巴细胞回注以促成向全嵌合转化的时候，复发风险就降低了。

These interventions resulted in a 4-year PFS of 76% for the entire cohort. With the specific goal of assessing the effect of in vivo T-cell depletion in FL patients undergoing RIC allo-HSCT, the EBMT examined retrospectively the outcomes of 164 patients who had matched sibling donors. For the analyses, patients were divided into 3 groups: the

first (n =46) received ATG as part of the preparative regimen, the second group received alemtuzumab (n =42), and the third group (n = 76) received neither agent. Although the patients in the T-cell depletion (TCD) group experienced significantly lower incidences of acute and chronic GVHD compared with the non- TCD recipients. There was no observed difference in NRM between the TCD and non-TCD groups; however, the use of a TCD was a risk factor for a significantly higher relapse rate (28% vs 14%,  $P = .05$ ). The strongest predictor of all outcomes (PFS, OS, relapse, and NRM) was disease status at transplantation. Recent data from the CIBMTR further demonstrated that chemosensitivity, rather than intensity of the conditioning regimen, was a strong determinant of outcome (Figure 3).

Figure 3. Probability of survival after HLA-matched sibling donor allo-HSCT for FL 1998-2007 by disease status and conditioning regimen.

图3. 从1998年到2007年FL患者接受全相合同胞供者移植的生存概率



这些干预手段使得整个群组的4年无进展生存率达到了76%。为了专门评估T细胞清除对进行RIC移植的FL患者的影响，EBMT回顾性的审视了164位亲属全相合患者的结果。为了进行分析，患者被分为三组：第一组（46人）将ATG加入预处理方案，第二组（42人）采用阿伦单抗，第三组（76人）什么都不用。尽管T细胞清除组与非清除组相比急性和慢性GVHD的发生率都明显降低，但是在非复发死亡率上没有观察到区别。T细胞清除成了较高复发率的风险因素(28% vs 14%,  $P = .05$ )。所有效果指标 (PFS, OS和NRM) 的最强的预测因素是移植时的疾病状态。来自CIBMTR的最新数据进一步确认，是化疗敏感度，而不是预处理方案的强度，是决定移植效果的强有力的因素（图3）。

Two large registry studies compared directly the outcomes of FL patients who underwent either myeloablative or a RIC allo-HSCT. In both studies, the RIC recipients were significantly older and a higher number had failed a prior auto-HSCT



compared with the ablative recipients (Table 2). The CIBMTR analyses was limited to recipients with matched related donors and found no difference in PFS and OS based on conditioning regimen. However, the risk of progression was significantly higher in the RIC group. The EBMT study had patients with solely unrelated donor grafts. In contrast to the CIBMTR study, recipients of the RIC regimens had a lower NRM and experienced a significantly improved PFS and OS by multivariate analysis, and relapse was comparable between the 2 groups. Therefore, it was suggested that the GVL effect may be more robust from an unrelated donor graft. In both the CIBMTR and EBMT studies, chemoresistance and a lower performance status were found to affect TRM, OS, and PFS adversely.

两项大规模的档案研究直接比较了接受清髓性移植和RIC移植的FL患者的情况。在两项研究中，做RIC移植的患者年纪明显更大并且有更多数量的患者接受过自体移植（表2）。CIBMTR的研究仅限于全相合相关供者的移植，没有发现预处理方案对PFS和OS有影响。但是，疾病进展的风险在RIC组明显更高。EBMT的研究有非相关供者的移植。与CIBMTR的研究相比，RIC移植组经多变量分析有较低的移植相关死亡率和显著提高的无进展生存期和总生存期，两组复发率基本相当。因此，提示非相关供者的GVL效应更强。两项试验都发现化疗耐药和较差的一般状态会负面的影响TRM，OS和PFS。

Based on the results of these studies, when allo-HSCT is indicated, when should the clinician recommend an ablative regimen versus an RIC regimen? Because evidence in both retrospective and prospective trials has revealed that chemosensitivity rather than conditioning intensity is the most reliable predictor of outcome, the absolute indications for an ablative regimen are nearly obsolete. Therefore, a myeloablative regimen should not be recommended for an FL patient outside of a clinical trial.

根据上述研究的结果，当有异体移植的指征时，什么情况下临床医生应该建议清髓性移植，什么情况下应该建议RIC移植？鉴于回顾性和前瞻性试验都显示化疗敏感度而非预处理方案的强度是结果的最强预测因素，进行清髓性移植的绝对指征几乎已经不存在。因此，对FL患者不应该建议清髓性移植，除非是在临床试验范围内。

### Novel conditioning regimens 新型预处理方案

The success of RIC allo-HSCT represents remarkable progress in the treatment and cure of patients advanced FL. Patients with chemosensitive disease at the time of HSCT benefit the most from these regimens; for patients with chemorefractory disease, the options are much more limited. Therefore, strategies to increase the anti-lymphoma activity without increasing toxicity have been examined, most prominently the use of radioimmunotherapy. Radioimmunotherapy confers cytoreduction via targeted delivery of radiation with isotopes conjugated to mAbs. This method has shown efficacy in the treatment of B-cell lymphomas, including in patients who are refractory to RTX and combination chemotherapy.

RIC异体干细胞移植的成功代表了在晚期滤泡性淋巴瘤的治疗和治愈方面的重大进步。在移植时依然对化疗敏感的患者从中获益最大。而对于耐药患者，选择就非常有限了。因此，对增强抗肿瘤活性同时不增加毒性的策略进行了研究，最显著的就是放射免疫疗法的使用。放射免疫疗法通过将放射性同位素嵌合到单抗中以实现靶向辐射。这种方法显示在B细胞淋巴瘤的治疗中有效，包括针对那些对美罗华和联合化疗耐药的患者。

Table 2. Retrospective comparisons of myeloablative versus RIC allo-HSCT

Study	N (dose intensity)	Median age, y	Donor	Prior auto-HSCT	PFS	OS	Progression	NRM	Median follow-up, mo
EBMT <sup>59</sup>	44 (ABL)	42	URD	23%	43%*	47%*	17%†	37%	38
	87 (RIC)	51		59%	49%	53%		33%	34
CIBMTR <sup>60</sup>	120 (ABL)	44	MRD	6%	67%*	71%*	8%*	25%	82
	88 (RIC)	51		10%	55%	62%	17%	28%	54

ABL indicates ablative regimen; URD, unrelated donor; MRD, matched related donor.

\*P value not significant.

†Cumulative incidence for all patients; no difference according to conditioning regimen.

The M.D. Anderson group recently published the results of a prospective trial of RIC allo-HSCT using the novel YFC (90Y-ibritumomab tiuxetan, fludarabine, cyclophosphamide) regimen (Figure 2B). Twenty-six patients with advanced FL, including 10 patients who were chemorefractory, participated. With a median follow-up of 33 months, the 3-year PFS for the chemorefractory and chemosensitive patients were 80% and 87%, respectively. The 1-year TRM was 8%.

安德森医疗中心最近公布了一项前瞻性的非清髓性异体移植的临床试验结果，采用了新的YFC方案（90Y-ibritumomab tiuxetan，氟达拉滨，环磷酰胺）。26位晚期FL患者，包括10名化疗耐药的参加了试验。中位随访期33个月，化疗耐药和化疗敏感的患者3年无进展生存率分别为80%和87%。1年移植相关死亡率为8%。

In another prospective study, a German group used an RIC regimen comprised of 90Y-ibritumomab tiuxetan, fludarabine, and low-dose TBI in 40 patients with advanced NHL, including 17 patients with FL. All patients were high risk as defined by refractory disease or relapse after prior auto-HSCT. The 2-year OS and EFS for the FL patients were 67% and 57%, respectively. However, the 2-year NRM was 45% for all patients, with infection being the leading cause of death. The high NRM was attributed to the age of the patients (median, 56 years), advanced-stage disease, and the predominant use of unrelated donors. There was a trend for a decreased rate of NRM if a related versus an unrelated donor was used (16% vs 58%, respectively,  $P = .07$ ). A small, retrospective study from the Dana Farber Cancer Institute used a conditioning regimen of 90Y-ibritumomab tiuxetan, fludarabine, and low-dose busulfan. This study involved 12 FL patients, including 5 patients with refractory disease and 2 patients with transformed disease. The 2-year OS, PFS, and NRM were 83%, 74%, and 18%, respectively. Based on the results of these 3 studies, the incorporation of radioimmunotherapy in RIC allo-HSCT regimens is feasible because of the acceptable rates of NRM and shows promising efficacy in patients with chemorefractory disease.

在另外一项前瞻性研究中，一个德国小组对40位晚期非霍奇金患者，其中包括17名FL患者，使用了RIC方案，包括90Y-ibritumomab tiuxetan，氟达拉滨，和低剂量TBI。全部都是高危患者，定义为耐药或者是自体移植后复发。FL患者的2年OS和EFS分别为67%和57%。但是全部患者的非复发死亡率高达45%，首要原因是感染。高死亡率主要归结为年龄（中位56岁），疾病处于晚期，大多采用非相关供者。如果采用相关供者死亡率则明显降低（16%对58%， $P = .07$ ）。来自Dana Farber癌症研究院的一项小规模的回溯性研究采用了90Y-ibritumomab tiuxetan，氟达拉滨和低剂量的白消安。这个研究有12位FL患者，包括5位耐药患者和2位转化患者。2年的OS，PFS和NRM分别为83%，74%和18%。

根据这三个研究的结果，将放射免疫制剂加入到RIC移植预处理方案中时可行的，死亡率可以接受，并且在耐药患者身上显示有效。

#### Tandem auto-HSCT followed by allo-HSCT 贯序自体 and 异体移植

The use of tandem auto-HSCT followed by RIC allo-HSCT reported recently by a Canadian group represents the first study offering tandem auto-HSCT/allo-HSCT specifically for FL patients. Twenty-seven patients were enrolled, including patients with chemorefractory and transformed disease. Despite this high-risk population, the 3-year PFS and OS were both 96%, with only 1 death attributed to NRM. A retrospective Italian series reported the results of 34 high-risk NHL patients, including 14 patients with FL, who underwent tandem auto-HSCT followed by RIC allo-HSCT. With a median follow-up of 4 years, the 5-year OS and PFS were 77% and 68%, respectively, with a 2-year TRM of 6%. These results suggest that the intense cytoreduction conferred by the high-dose chemotherapy with auto-HSCT followed by eradication of minimal residual disease via RIC allo-HSCT may overcome the negative prognostic outcome associated with chemoresistance. The low TRM seen in both studies is especially encouraging.

最近一个加拿大小组报告的关于采用贯序自体移植和异体移植的研究是首次专门针对FL患者采用这种治疗方式的研究。共有27位患者入组，包括化疗耐药和转化的患者。尽管都是高危患者，3年的PFS和OS都是96%，只有1例死于移植。一项意大利的回顾性系列报告了34位高危FL患者包括14位FL患者的情况，这些患者贯序的进行了自体移植和RIC异体移植。中位随访期位4年，5年的OS和PFS分别为77%和68%，2年的移植相关死亡率为6%。这些结果提示自体移植中的高剂量化疗的强烈消瘤效应加上RIC异体移植对微小疾病残余的清除可能克服了化疗耐药的负面预后因素。两个研究中的较低的移植相关死亡率尤其令人振奋。

#### Therapy-related malignancies after HSCT 异体移植相关的恶性肿瘤

Although therapy-related malignancies are rare events after HSCT, all patients should be advised of the risks and counseled regarding screening for such complications in the long term. The incidence of these malignancies, including therapy-related myeloid neoplasms (t-MNs) and solid tumors in NHL patients after auto-HSCT ranges from 5%-20%. Risk factors associated with developing t-MNs, such as t-MDS and t-AML, include receipt of prior alkylator agents, fludarabine, older age at the time of HSCT, TBI-based preparative regimens (especially in doses greater than 1320 cGy), and receipt of an in vitro purged autograft. Use of a TBI-based regimen before auto-HSCT was associated with a disturbing 4-fold risk of developing t-MNs in a retrospective EBMT study of FL patients. The risk of t-MNs is reported more often after auto-HSCT compared with allo-HSCT and is attributed to the exposure of autologous stem cells to prior chemotherapy and the ensuing DNA damage. The risk of developing solid tumors after HSCT has also been reported, although it is described more often after allo-HSCT than auto-HSCT. The group from Dana Farber Cancer Institute reported a 10-year incidence of solid tumors of 10% after auto-HSCT in patients with NHL who received a TBI-based preparative regimen.

尽管干细胞移植后发生移植相关恶性肿瘤是小概率事件，所有患者都应该被告知相关的风险并被告诫要准备长期的筛查。这些恶性肿瘤的发病率，包括治疗相关的髓系肿瘤和实体肿瘤，在接受了干细胞移植的非霍奇金患者中在5%-20%之间。发生髓系肿瘤例如MDS和AML的风险因素，包括烷化剂，氟达拉滨，移植时年纪大，TBI为主的预处理方案（特别是剂量大于1320cGy），以及接受体外净化的移植物。在自体移植之前接受以TBI为主的方案根据EBMT对FL患者的研究会带来4倍的发生髓系肿瘤的风险。据报道自体移植发生髓系肿瘤的情况比异体移植更多，这被归结于自体移植的干细胞先前接受过化疗而引起了DNA损害。干细胞移植后发生实体肿瘤也有报道，较多发生于异体移植而不是自体移植。Dana Farber 癌症学院的小组报告非霍奇金患者接受TBI为主的预处理方案做自体移植后10年的实体肿瘤发病率为10%。

Recipients of allo-HSCT are at risk for secondary solid tumors and posttransplantation lymphoproliferative disorders. After allo-HSCT, the cumulative risk of developing a solid tumor ranges from 2%-6%, with the risk increasing over time and reaching up to a 3-fold risk in patients followed over 15 years after allo-HSCT. The strongest risk factors for the development of solid tumors are the use of TBI and chronic GVHD. TBI exposure is associated with nonsquamous cell cancers, especially breast, thyroid, bone, brain cancers and malignant melanoma, and also increases the risk of basal cell skin cancer. The development of squamous cell cancers of the skin and mucosal surfaces increases with the presence of chronic GVHD.

接受异体移植的患者有继发实体肿瘤和移植后淋巴增殖性疾病的风险。异体移植后，发生实体肿瘤的累积风险在2%-6%之间，风险随时间推移而增加，到15年后增加三倍。发生实体肿瘤的最大风险因素是使用TBI和慢性GVHD。TBI与非鳞状细胞癌相关，尤其是乳腺，甲状腺，骨骼，脑部肿瘤和恶性黑色素瘤，还增加皮肤基底细胞癌的风险。慢性GVHD会增加发生皮肤和黏膜表面基底细胞癌的风险。

After HSCT, patients should be strongly encouraged to adhere to cancer screening guidelines for the general population for skin, cervical, breast, and colon cancers. For female patients who received TBI or chest irradiation, annual mammograms should be commenced at the age of 25 years or 8 years after irradiation, whichever occurs later. Patients with chronic GVHD should be especially vigilant in limiting sun exposure, maintaining good oral hygiene, and having regular dental examinations that include screening for oral cancers.

在干细胞移植后，强烈建议患者遵从一般人群关于皮肤，宫颈，乳腺和结肠肿瘤筛查的指导方针。接受过TBI或者胸部放疗的女性患者，25岁后或放疗8年后应该每年进行钼靶检查。有慢性GVHD的患者应当尤其注意限制太阳照射，保持好的口腔卫生，定期检查牙科，包括筛查口腔癌症。

## Summary/recommendations 总结/建议

### First remission 首次缓解

With the exception of patients in first remission, the optimal timing and the optimal conditioning regimen in patients with FL undergoing HSCT remains controversial. The mature results of 3 large, randomized studies show no benefit of auto-HSCT as consolidation therapy for patients in first complete remission.

除了首次缓解的患者之外，FL患者进行干细胞移植的最佳时机和最佳方案还存在争议。三个成熟的大规模随机试验的结果证实对于首次缓解的患者不能从自体干细胞移植作为巩固疗法中获益。

### Relapsed disease 复发疾病

Patients with relapsed FL should be directed to HSCT before they are considered “heavily pretreated.” Two studies have demonstrated that outcomes are more favorable if patients have received less than 3 prior regimens. For patients who are allo-HSCT candidates, chemosensitivity is the most robust prognostic factor for survival after HSCT regardless of conditioning intensity. Based on current data, the relapse rate is unequivocally lower with allo-HSCT compared with auto-HSCT. Fortunately, the NRM associated with allo-HSCT has declined with the use of RIC regimens, and clear plateaus in survival and relapse are now observed frequently after RIC allo-HSCT.

复发的FL患者应该在成为“重度治疗的患者”之前引导做干细胞移植。两项研究表明如果患者接受过少于三个方案的化疗那么移植的效果会较好。对于候选异体移植的患者，化疗敏感时移植后生存的最大的预后因素，与预处理的强度无关。根据目前的数据，异体移植的复发率无可争议的比自体移植低。幸运的是，随着RIC方案的采用，异体移植的相关死亡率有所下降，在RIC移植后经常可以观察到明显的生存平台期。

If a patient has chemosensitive disease and has a suitably identified donor, should he or she be directed toward an auto-HSCT or an allo-HSCT? In our center, with a patient who is past first remission and demonstrates chemosensitive disease, we favor proceeding to RIC allo-HSCT if a suitable donor (matched related or matched unrelated donor) can be found in a timely manner. However, one could rationalize offering a patient auto-HSCT initially, because auto-HSCT clearly extends PFS and a growing body of evidence suggest that auto-HSCT may be curative. RIC allo-HSCT would be reserved for the situation in which a patient relapsed after auto-HSCT, because prospective trials have shown that RIC allo-HSCT can salvage patients who failed a prior auto-HSCT. The obvious advantages of this approach are the low NRM inherent with auto-HSCT and the more expedient recovery. The main disadvantage is that subsequent relapsed disease may not respond to further salvage therapy, which greatly diminishes the potential efficacy of RIC allo-HSCT. However, if a patient has compromised cardiac or pulmonary function, then high-dose chemotherapy may not be feasible and RIC allo-HSCT should be offered. Treatment choices must be individualized based on concurrent comorbidities, age, performance status, donor availability, psychosocial issues, and, very importantly, caregiver availability.

如果患者的疾病依然化疗敏感，并且有合适的供者，那么应该建议做自体移植还是异体移植呢？在我们中心，如果一位患者已经不是首次缓解，疾病依然对化疗敏感，并且能按时找到合适的供者（亲缘全相合或者无关全相合），我们会指导其做RIC异体移植。当然，首先向患者推荐自体移植也是合理的，因为自体移植显然可以延长PFS而且有越来越多的证据表明自体移植也可能治愈。RIC移植可以预留到患者在自体移植后复发的情况，因为前瞻性的试验显示RIC移植可以挽救自体移植失败的患者。这种做法的明显优势时自体移植较低的相关死亡率和更快的复原。主要劣势时之后复发的疾病可能对进一步的挽救性化疗不响应，从而大大降低的RIC异体移植的效力。当然，如果患者心脏或者肺功能有损伤，大剂量化疗可能

不现实，这时应该建议RIC异体移植。治疗的选择应该根据患者的并发疾病，年龄，一般状况，供者的情况，心理和社会问题，以及非常重要的护理情况进行个性化的选择。

#### Refractory disease 耐药疾病

It is controversial whether patients with chemorefractory disease are HSCT candidates, and such patients should only be offered HSCT within a clinical trial. Auto-HSCT is not recommended for chemorefractory patients, but allo-HSCT may have a role in the setting of tandem HSCT (auto-HSCT followed by allo-HSCT) or with the incorporation of radioimmunoconjugates or other novel agents.

对化疗耐药的患者是否可做干细胞移植还有争议，此类患者应该仅在临床试验的范畴内进行干细胞移植。耐药患者不建议做自体干细胞移植，但是可以考虑采用贯序的自体移植和异体移植（先自体后异体）或在方案中加入放射免疫制剂或其它新药。