

Improving Outcomes and Evaluating Novel Treatment Approaches for Patients With Follicular Lymphoma 改善滤泡性淋巴瘤患者的预后和评估新的治疗方法

Medscape EDUCATION

Improving Outcomes and Evaluating Novel Treatment Approaches for Patients With Follicular Lymphoma

James O. Armitage, MD
Professor, University of Nebraska
Joe Shapiro Distinguished Chair of Oncology
University of Nebraska Medical Center
Omaha, Nebraska

Hello. My name is Jim Armitage. I am the Joe Shapiro Professor of Medicine at the University of Nebraska Medical Center. I am here today to talk to you about follicular lymphoma (FL).

我的名字叫Jim Armitage，我是那布拉斯加大学医疗中心的医学教授。我今天来谈一谈滤泡性淋巴瘤。

The overall goals of this activity are to summarize current data on the relevance of staging and pathology, evaluation, and prognostic indices; evaluate current and emerging treatments for patients with this disease in all of the different settings; and identify strategies that might be used to see that the patients get benefit without undue toxicity.

我们这个活动的总体目标是总结分期，病理，评估和预后指标的当前数据；评估在所有不同情况下这种疾病的当前和发展中的治疗方法；确定可以让患者获益而不必接受过分毒性的策略。

Program Goals

- Summarize the current data on staging and the relevance of prognostic indices in the care of patients with follicular lymphoma (FL)
- Evaluate current and emerging treatment options for patients with FL in the first-line setting, maintenance setting, and subsequent lines of therapy
- Personalize therapy on the basis of patient- and disease-related factors as well as on patient goals

FL is a relatively common disease. Lymphomas themselves in the United States occur somewhere on the order of 70,000 to 80,000 times a year. FL is the second most common lymphoma. Diffuse large B-cell lymphoma (DLBCL) is the most common, and Hodgkin lymphoma is the third most common.

滤泡性淋巴瘤是一个相对常见的疾病。淋巴瘤在美国每年大约发生7万到8万例，滤泡性淋巴瘤是第二常见的淋巴瘤。弥漫大B是最常见的淋巴瘤，霍奇金排在第三位。

FL seems to be relatively stable in incidence, but it is quite variable around the world. It is a disease that is quite common in North America and relatively common in Europe, but it is much less frequent in parts of Asia.

滤泡性淋巴瘤的发生率似乎比较稳定，但是在世界范围内变化很大。这种疾病在北美很常见，欧洲较为常见，但是在亚洲的一些地区发生率不太高。

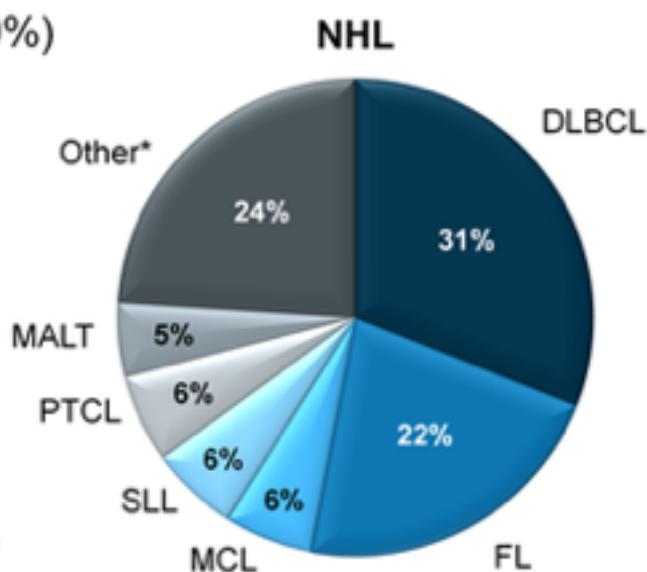
Lymphomas are often difficult to diagnose. Yet, FL is kind of an exception to that rule. While you need to have an adequate bit of tissue to give to the pathologist, this is one time when pathologists can usually reach a reproducible diagnosis based just on the slides they see initially or on those slides plus relatively straightforward immunohistochemical studies. There are characteristic genetic abnormalities such as the t(14;18) translocation, but generally the pathologist won't need that information to make this diagnosis.

淋巴瘤一般很难确诊。可是，滤泡性淋巴瘤却是个例外。当然你需要给病理医师一点像样的活检组织，这时病理医师通常可以仅凭最初看到的几张切片或者加上比较直接的一些免疫组化就得出可验

Lymphoma

Common Subtypes

- Non-Hodgkin (~89%)
- Hodgkin (~11%)



MALT = mucosa-associated lymphoid tumors; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; PTCL = peripheral T-cell lymphoma; SLL = small lymphocyte lymphoma

*Each of the remaining subtypes occurred in $\leq 2\%$ of cases.

Armitage JO, et al. *J Clin Oncol*. 1998;16:2780-2795.

Jemal A, et al. *CA Cancer J Clin*. 2010;60:277-300.

证的诊断。这种疾病有一些特异性的基因变异例如t(14;18)染色体易位，但是总的来说病理医师不需要这种信息来作出诊断。

When we did a study years ago, FL was the particular type of lymphoma that pathologists were most likely to agree on more than any other and the least likely to require more sophisticated studies to be certain of that diagnosis. That certainty, however, very importantly depends on having adequate tissue. It is still not appropriate to diagnose this or any other lymphoma, for example, on the basis of FNA.

许多年前我们做研究的时候，滤泡性淋巴瘤是那种病理医师经常意见一致和最不需要通过复杂的手段来确诊的淋巴瘤。当然，这种确定性，非常重要的取决于是否有足够的活检组织。细针穿刺仍然不应当用于诊断这种以及任何其它类型淋巴瘤。

As with any cancer, once you know the patient has FL, you need to proceed with an evaluation. The imaging studies that are used most widely for staging today are either a CT scan or a PET scan. A bone marrow biopsy is also typically done, and of course, the patient has a careful evaluation and routine laboratory studies. Usually those evaluations would be enough to establish the localization of disease.

和其它恶性肿瘤一样，一旦确定病人是滤泡性淋巴瘤，你需要做一个评估。应用最广泛的影像学分期技术是CT或者PET。骨髓活检也要做，当然还包括仔细的评估和常规的检查。通常这些检查足以确定疾病的分期。

For a long time, it was felt that PET scans were not as useful in FL as they are in some other lymphomas. This conclusion was partly based on the fact that PET scans in FL have

a much lower SUV (standardized uptake value), a much less intense uptake than in DLBCL. Yet, today it is clear that PET scans are as likely to be abnormal in FL as in DLBCL. So it really is a very valuable test and something that I would routinely order in the initial evaluation of a patient with this disease.

长期以来，有观点认为PET对滤泡性淋巴瘤的重要性不如其它的淋巴瘤。这个结论的依据一部分是来源于滤泡性淋巴瘤的SUV较低，比如比弥漫大B低得多。但是现在我们明确的知道对滤泡性淋巴瘤的PET扫描和对弥漫大B的扫描一样可以清晰的显示出异常。因此PET是一个非常有用的工具，我在对病人进行最初评估的时候会常规化的要求做这项检查。

The Ann Arbor system is the standard used for staging. However, the staging methods used to predict prognosis, also called prognostic indices, are not so straightforward. It turns out that when the IPI, the International Prognostic Index, was developed for DLBCL, it made a huge impact. It has lasted now almost 20 years -- it really works. You could not publish a

Follicular Lymphoma

Diagnostic and Staging Evaluation

- Careful history and physical examination
- Performance status
- Routine laboratory studies
- Bone marrow aspirate and biopsy
- CT or PET scan

PET scans have lower SUV in FL lesions, but the abnormal scan results remain clinically useful

Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9:484-560.
Bishu S, et al. *Leuk Lymphoma*. 2007; 48:1548-1555.

paper about an aggressive lymphoma without including the IPI information. But it actually does work quite well for FL.

Ann Arbor系统是分期的标准。但是，用于预测预后的分期方法，即预后指数却不是那么直截了当的。当初为弥漫大B开发出IPI，即国际预后指数时，产生了重大的影响。几乎20年过去，IPI依然有效。但是它对滤泡性淋巴瘤却不是那么准确。

If you remember, the IPI is popular partly because it is so simple to remember. If you can misspell the word "apples" and spell it A-P-L-E-S, you have age, performance status (PS), LDH (lactate dehydrogenase), multiple extranodal sites, and Ann Arbor stage. Add them up and you have all the bad risk factors, yielding a score of 0 to 5.

IPI之所以如此流行是因为简单好记。如果你把苹果这个单词误拼为APLES，那么你就有了年龄（A），一般情况（P），乳酸脱氢酶（L），多发结外病灶（E），和分期（S）。把这些加起来你就有了所有不良预后因素，得出一个从1到5的评分。

The reason the IPI has not been as popular in FL is because patients with FL almost always have a good score. When a patient has a bad score, it is a very serious disease, and the prognosis is as poor as with a DLBCL with a very high IPI score. But patients with FL don't usually have very high IPI scores.

IPI对滤泡性淋巴瘤不流行原因是基本上所有的滤泡性淋巴瘤的病人都会有一个好评分。当病人评分很差时，说明疾病非常严重，预后和拥有很高评分的弥漫大B病人一样差。但是滤泡性淋巴瘤病人很少有高分。

Follicular Lymphoma

IPI Score

- More clinically relevant for DLBCL
- In FL, most patients have a good IPI score
- Therefore, less clinically predictive (unless high IPI score)

Risk Factors

Age > 60 years

PS 2-4

LDH elevated

Extranodal > 1 site

Stage III-IV

• Risk

- Low: 0-1
- Low-intermediate: 2
- High-intermediate: 3
- High: 4-5

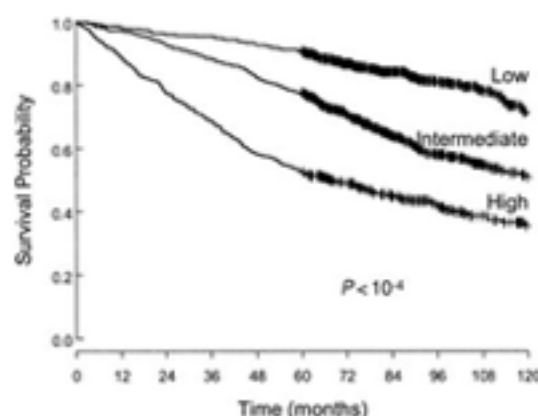
The International NHL Prognostic Factors Project. *N Engl J Med.* 1993;329:987-994.

Because of that, there have been attempts to try to improve the prediction of treatment outcome in FL. The most popular of those has been the FLIPI or Follicular Lymphoma International Prognostic Index, which substitutes number of nodal sites and hemoglobin level for some of the things in the IPI. The problem is that it is more complicated to count the

Follicular Lymphoma

FLIPI Score

Parameter	Relative Risk (Death)
> 60 years of age	2.38
Stage III-IV	2.00
Hemoglobin < 12.0 g/dL	1.55
Elevated LDH	1.50
Nodal sites > 4	1.39



Risk Group	Risk Factors (n)	5-Year OS (%)	10-Year OS (%)
Low	0-1	91	71
Intermediate	2	78	51
High	≥ 3	53	36

Solal-Céligny P, et al. *Blood*. 2004;104:1258-1265.

OS = overall survival

Follicular Lymphoma

Impact of Infiltrating Immune Cells

- Nonmalignant tumor-infiltrating immune cells affect clinical outcome
- Their gene expression signatures are not surrogates for clinical prognostic variables
- T-cell predominance has good prognostic significance

Expression Signature (Prognosis)	Relative Risk for Death	P
Immune response 1 (favorable)	0.15	< .0001
Immune response 2 (unfavorable)	9.35	< .0001

Dave SS, et al. *N Engl J Med*. 2004;351:2159-2169.

nodal sites. The FLIPI is relatively frequently used in publications, but it is less frequently used in routine practice than the IPI.

因此，人们试图改进对滤泡性淋巴瘤的预后的预测准确度。最流行是FLIPI，即滤泡性淋巴瘤国际预后指数，这个指数将IPI中的一些指标换成了侵犯的淋巴结区域数量和血红蛋白水平。问题是计算淋巴结区域的数量比较复杂。所以，FLIPI在学术论文中较常见，而临床上的使用频率依然不如IPI。

Aside from the issues we have already discussed, there is another complicating factor with respect to the initial characterization of FL. When pathologists make the diagnosis of FL, they assign a grade. This has nothing to do with staging. It has to do with the number of large cells or blast cells in the tumor. Given that, it is not surprising that the grade directly reflects the proliferative rate of the tumor.

除了如上讨论的问题之外，对滤泡性淋巴瘤的最初诊断还有一个复杂的因素。当病理医师确诊滤泡性淋巴瘤的时候，他们还会给出一个分级。这与分期无关，只和肿瘤中的大细胞或者母细胞的数量有关。因此，如果说分级直接反应了肿瘤的增殖率一点也不奇怪。

FL is graded as grade 1, grade 2, or grade 3. Grade 1 has the fewest and grade 3 has the greatest number of large cells, the blast cells. We and others have reported that patients with grade 3, or at least a subset of those with grade 3, have a disease that is likely to behave like DLBCL. FL often has diffuse areas. Even FL that is grade 1 can have diffuse areas where it grows without a follicular pattern, but that is most common in FL that is grade 3.

滤泡性淋巴瘤分为1级，2级和3级，1级的母细胞数量最少，3级最多。我们和其他人都报告过3级的滤泡性淋巴瘤，至少可以说一部分3级的滤泡性淋巴瘤的临床表现和弥漫大B一样。滤泡性淋巴瘤通常也有弥漫区域。即便是1级的滤泡性淋巴瘤也会有弥漫区域，生长方式突破了滤泡的限制，但是这种情况还是3级更常见。

There is controversy about this, but our team feels that enough patients with follicular grade 3 lymphoma behave like those who have DLBCL to warrant potentially curative intensive chemotherapy regimens with immunotherapy, like CHOP-R (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone-rituximab). We treat patients with grade 3 FL as if they had DLBCL and we approach the other FL, the so-called low-grade FL, differently.

尽管有争议，我们的团队还是认为由于有很多3级滤泡的临床表现和弥漫大B一样，因此应该采用具有潜在的治愈可能的免疫化疗方案，例如CHOP-R。我们将3级滤泡当成弥漫大B一样治疗，而对低级别滤泡性淋巴瘤区别对待。

There have been attempts to try to identify those cases of FL grade 3 that behave in a more indolent fashion. What is frequently done is to divide grade 3 into grade 3a and 3b, with 3b representing those tumors with lots of noncleaved or blast cells and 3a representing those with more cleaved cells that really belong in the low-grade FL category. My concern is that it is unclear whether pathologists can reproducibly make that distinction. As such, I would approach all grade 3 FL in the same way.

有人试图将3级滤泡中呈惰性发展的病例分离出来。经常的做法是把3级分为3a和3b，3b代表那些肿瘤中有很多无裂或母细胞的，3a代表那些有较多有裂细胞从而实际上属于低级别滤泡性淋巴瘤的。我的担心是病理医师是否能够准确做出这种区分。因此，我倾向于把所有的3级都一视同仁。

FL is complicated in another way. There is a whole lot going on between the tumor and the host. This became apparent with the first microarray studies. Microarrays have been

Follicular Lymphoma

WHO Classification

Grade 1	0-5 centroblasts/hpf
Grade 2	6-15 centroblasts/hpf
Grade 3	> 15 centroblasts/hpf
• 3a	Centrocytes present
• 3b	Solid sheets of centroblasts

- Disease in patients with grade 3 behaves like DLBCL
- More aggressive treatment may lead to cure

hpf = high-power field

Winter J, et al. *Hematology Am Soc Hematol Educ Program*. 2004;203-220.
Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9:484-560.

tremendously helpful in predicting outcome in DLBCL based on the gene expression pattern of the tumor cells. In contrast, the most powerful predictor of outcome in FL was the gene

Follicular Lymphoma

Is Survival Improving?

- Yes; natural history appears to be modifying over time
- Improvements:
 - From 1980s to 1990s
 - 1990s to 2000s, more dramatic
- Is it a statistical trick? Or therapy?

Fisher RI, et al. *J Clin Oncol*. 2005;23:8447-8452.

Liu Q, et al. *J Clin Oncol*. 2006;24:1582.

Pulte D, et al. *Arch Intern Med*. 2008;168:469-476.

Vose JM, et al. *Leuk Lymphoma*. 2005;46:1569-1573.

expression pattern of the infiltrating immune cells, not the tumor cells.

滤泡性淋巴瘤在其它方面也很复杂，肿瘤和宿主之间也有很多互动。这在第一个微阵列的研究中就体现出来。微阵列研究基于肿瘤细胞的基因表达模式在弥漫大B的预后预测中非常有用。相反的是，对于滤泡性淋巴瘤，最强有力的预后指标不是肿瘤细胞的基因表达模式，而是侵入的免疫细胞的基因表达模式。

The subset of patients who had predominantly T-cell infiltration in the tumor bed had a significantly better outlook than those who had predominantly dendritic cells and macrophages present. This has been confirmed with immunohistochemistry; it is clearly important. We don't know quite what to do about it, how our treatments interact with the tumor cells vs the microenvironment, or how much of the positive effect of our treatments is based on altering which aspect, tumor cells or host microenvironment.

肿瘤中有以T细胞为主的渗透的患者有着比以树突状细胞和巨噬细胞为主的患者明显更好的预后。这是经过免疫组化确认的，这显然非常重要。我们还不知道应该做些什么，我们的治疗方案如何影响肿瘤细胞和其微环境，以及我们的治疗方案在多大程度上对肿瘤细胞或宿主微环境起到正面的作用。

Considerable efforts have been made to try to understand the relationship between the tumor and the host. Given its importance, it is one of those things we need to watch. It may turn out that some of our treatments work predominantly because they affect the microenvironment.

在试图理解肿瘤和宿主之间的关系上已经付出很大努力。鉴于其重要性，我们将继续予以关注。也许会发现我们的治疗方案之所以有效是因为对微环境改变。

It was very popular to say that patients with FL live a long time, which those with low-grade FL do, and that our treatments may not modify the natural history. We might relieve symptoms. We might shrink the lumps. But it was very popular for a long time to say that, in fact, we do not alter the ultimate survival.

一种非常流行的说法是，惰性滤泡性淋巴瘤病人可以活很长时间，但是我们的治疗不能改变自然的病程。我们也许可以缓解症状，我们也许可以缩小肿块。但是很长时间以来流行的说法是，我们无法改善最终的生存率。

However, in the last 10 to 15 years, it has become apparent that such a conclusion is not true. Survival is changing. If you look at SEER (Surveillance, Epidemiology, and End Results) data in the United States, there was a survival change between the 1980s and the 1990s. The Southwest Oncology Group (SWOG) has shown, by their generations of studies that survival has steadily increased. Data from MD Anderson has shown the same thing. Data from Stanford show the same thing, and our data at Nebraska have shown a steady improvement in survival from the 1980s to the 1990s and after 2000, with the most striking improvement after 2000.

然而，在过去的10到15年间，这种理论逐渐变的站不住脚。生存率在改变。如果你查阅美国SEER的数据，在1980年到1990年间生存率发生了改变。西南肿瘤小组（SWAG）几代的研究显示生存率提高了。安德森医疗中心的数据也是一样，斯坦福也是，我们那布拉斯加也发现从1980到1990以及从1990到2000之间生存率在稳步上升，最大的改变发生在2000年以后。

There is no question that, for whatever reason, patients with low-grade FL are living longer. The question is why. It could be a lot of things, of course. It could be we are making the diagnosis earlier, but I don't believe that is true.

毫无疑问，不管出于什么原因，低级别滤泡性淋巴瘤病人活的更长了。那么问题就来了，究竟是什么原因？当然可能有很多因素。也许是确诊的更早，但是我不认为是这个原因。

It could be a statistical trick that is often referred to as the "Will Rogers phenomenon," which has frequently bedeviled oncologists over the years. This is a statistical phenomenon that came from a joke Will Rogers told. The joke was that when the Okies moved from Oklahoma to California, they raised the median IQ of both states. (I can tell that joke because I was born in California.) The reason that works is that if you take 2 groups of patients, one with a good outcome and one with a bad outcome, and take some of the good ones that you found really don't do very well -- so they are the worst of the good ones -- and you move those to the bad group, the outcome in the good patients goes up because you removed the poorest performers. Similarly, the outcome in the bad patients goes up because you added what are now the best performers in that group. Yet, in reality, nothing

has changed at all. There have been many times in oncology when that has been a trap, but I do not believe that that is the explanation for the change in survival in FL. That is, I do not believe we changed our diagnosis.

也许是一个统计学上的伎俩，即所谓的Will Rogers现象，这个现象让肿瘤学家们困惑了很多年。这种统计学现象源于Will Rogers讲的一个笑话。笑话说的是当俄克拉荷马的游民从俄克拉荷马移民到加利福尼亚，两个州的平均IQ都提高了（我敢讲这个笑话是因为我出生在加州）。如果你有两组病人，一组预后良好一组预后较差，然后将预后良好组中相对较差的病人放到预后较差组去，于是两个组的预后都提高了。但是实际上，什么也没有改变。在肿瘤学历史上有很多次专家们掉入了这个陷阱。但是我不认为这个可以解释滤泡性淋巴瘤生存率的改变。就是说，我不认为我们改变了我们的诊断。

What might it be? The most likely explanation, I believe, is improved therapy. There are still several choices. It could be new drugs. It could be treating patients earlier. It could be the use of transplant. You can make arguments for any of those, I suppose. Maybe the best argument would be for treating patients earlier, as our treatments are more effective.

那究竟是因为什么呢？最可能的解释，我相信，是治疗的改善。还有几个选项，可能是新药，可能是更早开始治疗，可能是移植。我想你可以为这些都找出依据。可能最佳的理论是更早开始治疗，我们治疗方案更有效。

Follicular Lymphoma

Impact of Immunotherapy

- Advent and use of monoclonal antibody rituximab has altered disease course and prognosis
- Across collective FL data and research, survival has been improving

Nebraska patient pool

- Rituximab-naïve, median survival
 - Average, 8-10 years
- Salvage rituximab recipients
 - 10-13 years
- Rituximab in front-line recipients
 - Not reached yet

Sousou T, et al. *Semin Hematol*. 2010;47:133-142.
Internal Review, University of Nebraska Lymphoma Study Group.

I think the easiest to defend, and most likely the right answer, is the advent of immunotherapy, monoclonal antibodies directed against the tumor. Particularly, the advent of rituximab in the late 1990s has had a huge impact on the treatment of patients with this disease. Thus, I believe it is the most likely explanation for the recent dramatic improvement in survival.

我想最有说服力的，最有可能是正确答案的，是免疫疗法的出现，即用单克隆抗体直接对付肿瘤。特别是90年代后期美罗华的出现对这种疾病的治疗产生了巨大的影响。因此，我相信这是近年来生存率大幅上升的最好解释。

When we look at our data from Nebraska, patients who never received rituximab have a median survival of around 8 to 10 years, the characteristic median survival for FL. Patients who received rituximab as salvage therapy have a 2- to 3-year longer median survival. Patients who received rituximab as part of their initial therapy have not reached their median survival or are even close. You might expect it to be really quite long based on the shape of the curves right now, so I think targeted immunotherapy is the most likely reason for the improving survival.

当我们回顾那布拉斯加的数据，未接受美罗华治疗的患者中位生存期为8-10年，这是滤泡性淋巴瘤的典型生存期。接受美罗华挽救性治疗的患者中位生存期会延长2-3年。而将美罗华作为一线方案组成部分的患者尚未达到甚至还未接近中位生存期。根据目前的生存曲线，可以预期中位生存期相当的长，所以我认为靶向的免疫治疗是生存率改善的最可能的原因。

How do we take that information and translate it into making the best treatment choice for our patients? There are many treatments you might consider for FL, and it is still a perfectly legitimate thing to observe patients. Presumably, the reason that "watch and wait," ie, observation without therapy, is a useful way to manage some patients is because of what we talked about earlier. In some cases, the microenvironment and the tumor relationship is controlled by the microenvironment. These patients have the tumor held in control for a long period of time.

我们应该如何解读这个信息并将其转化为为我们的病人做出最佳的治疗选择呢？对于滤泡性淋巴瘤，有多种治疗方案可以考虑，同时观察仍是一个完全合理的策略。也许，观察等待，即观察而不治疗，

Follicular Lymphoma

Durable Remissions and Possible Cure

- ASCT^[a,b]
 - 44% FFR
- Allo-SCT^[c]
 - Higher FFR, but higher treatment-related mortality
- Other durable remission possible
 - Radiolabeled antibodies
- If incurability is defined as the presence of, not as a potential for, actual relapse → cure is possible

a. Vose JM, et al. *Biol Blood Marrow Transplant*. 2008;14:36-42.

b. Brown JR, et al. *Biol Blood Marrow Transplant*. 2007;13:1057-1065.

c. Khouiri, IF, et al. *Blood*. 2008;111:5530-5536.

基于我们先前讨论的原因对某些病人不失为一个可行的策略。在某些情况下，微环境和肿瘤之间的

关系由微环境来主导。这些病人的肿瘤可以在很长时间内被控制住。

Follicular Lymphoma

Treatment Options

- "Watch and wait" (observation)
- Monoclonal antibodies
- RIT
 - ^{131}I -tositumomab
 - ^{90}Y -ibritumomab
- Radiation
- Single-agent therapy
- Combination chemotherapy
- Hematopoietic stem cell transplantation
- Clinical trials

Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9:484-560.
Ardeschna K, et al. ASH 2010. Abstract 6.

So observation is still a legitimate option, although if you are going to do it, the emphasis should be on the watch, not the wait. Patients should be seen regularly and not ignored.

所以，观察仍是一种合理的选择，尽管如果你要这么做，重点应该是观察，而不是等待。病人应该经常复查，而不是置之不理。

The majority of patients are going to be treated and there are many choices. You could use an antibody alone. You could use an antibody with radiation attached, a radioimmunotherapy (RIT). You could use a whole variety of combination chemotherapy regimens. You could incorporate hematopoietic stem cell transplant into the first treatment. And on and on -- there are many different choices.

大部分病人需要治疗，而治疗有多种选择。你可以只用抗体。你可以用免疫放射治疗。你可以有一大批联合化疗方案供选择。你可以把干细胞移植也放进一线的方案中。各种各样的选择很多。

As a practical matter, the decision is usually between an antibody alone, usually rituximab, and a combination of more traditional chemotherapy drugs with an antibody. That distinction is typically made by taking into account the age of the patient, the health of the patient, and the patient's preferences. There are some people who just simply don't want to lose their hair. They have read about rituximab and that is what they want to have. Or, they are really

very old and you are afraid to treat them more aggressively. There are a whole variety of reasons why people often choose a treatment. I think in the United States, rituximab as a single agent is, to some degree, replacing watch and wait as one of the initial strategies.

实际上，通常是单独选择一种抗体，即美罗华治疗，或抗体加传统的联合化疗。决定的因素包括病人的年龄，健康状况，病人自己的偏好。有些人就是不想失去头发。他们听说过美罗华而这就是他们想要的。或许他们已经非常老了，你不敢给他们用激进的方案。人们出于各种不同的原因去选择一种方案。我认为在美国，美罗华在一定程度上逐渐替换了观察等待而成为首选的策略。

A study, reported at ASH recently from the United Kingdom, pointed out that if you give people with FL the antibody rituximab, they are more likely to respond than if they are observed -- not a big surprise -- and they are less likely to have progression of disease -- again not a big surprise. That study might well further the treatment shift.

最近在ASH年会上来自英国的一项研究指出，你如果用美罗华初治，患者应答率比观察组要高-当然没什么奇怪的-疾病进展会更少-依然不奇怪。这项研究也许会进一步改变治疗的策略。

If the patient is going to get a traditional chemotherapy regimen, it is almost always with an antibody. That is a really complicated decision.

如果病人使用传统化疗方案，几乎一定会加上一种抗体。这是个非常复杂的决定。

Chlorambucil is still, in some parts of the world, one of the treatment choices. In the United States, there really are 4 approaches that are widely used. I have joked that there are 4 phenotypes of oncologists: the Stanford phenotype, who believes that you absolutely must use CVP (cyclophosphamide, vincristine, prednisone); the MD Anderson phenotype who in the past has felt that you had to use fludarabine; the SWOG phenotype, which favors CHOP; and now we have to have a new phenotype for bendamustine. I don't know if we have a name for that.

留可然在世界上某些地区依然是可以选择的药物之一。在美国，有四种广泛应用的方案，我经常开

Follicular Lymphoma Chemotherapy Choices

- Bendamustine, rituximab
- R-CVP
 - Rituximab, cyclophosphamide, vincristine, prednisone
- R-CHOP
 - Rituximab, cyclophosphamide, doxorubicin, prednisone
- Fludarabine-based
 - Because of prolonged myelosuppressive effect, not favored if ASCT considered

Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9:484-560.
Cheson BD, Rummel M. *J Clin Oncol*. 2009;27:1492-1501.
Marcus R, et al. *J Clin Oncol*. 2008;26:4579-4586.
Hiddemann W, et al. *Blood*. 2005;106:3725-3732.

玩笑说肿瘤学家有四种表型：斯坦福表型，坚信你必须用CVP方案；安德森医疗中心表型，曾经坚持使用氟达拉滨；西南表型，最喜欢CHOP；现在又有一种表型用苯达莫斯汀，我还没给起名。

Some people remain strong advocates for their choice of those 4. I think it is unclear so far that survival changes depending on which one you use. I prefer not to use fludarabine because of its prolonged myelosuppressive effect and the difficulty it might cause before transplant in a patient who would need it.

一些人坚持这四种之一的选择。我想目前还不清楚选择哪一种在生存率上有什么区别。我倾向不用氟达拉滨，因为其持久的骨髓抑制可能为未来的骨髓移植造成困难。

The PRIMA (Primary Rituximab and Maintenance) group that did the big study about maintenance rituximab has gone back and reanalyzed their data. They have shown that patients who receive CHOP have a higher proportion of complete remissions (CRs) and better remissions than those who get CVP. Of those 2, I would favor CHOP.

对美罗华维持做了大规模研究的PRIMA小组又重新分析了他们的数据，他们证实接受CHOP方案的病人比接受CVP的病人有更高比例的CR。两者之间我更喜欢CHOP。

Follicular Lymphoma Maintenance Therapy: PRIMA Study

- At 36 months, the PFS (75%) was significantly better in those patients receiving rituximab maintenance vs the control arm (58%) ($P < .0001$)
 - Patients who received R-CHOP induction therapy had a higher proportion of complete remissions (CRs) than those who received R-CVP
- Rituximab maintenance was beneficial for patients regardless of their age group, their FLIPI score, or their choice of induction chemotherapy
 - Difference was not statistically significant for those patients receiving R-CVP

- **Maintenance rituximab prolongs remission**
 - We do not know yet whether it improves survival
- **Today, maintenance rituximab considered standard approach**

N = 1018

Salles GA, et al. *Lancet*. 2011;377:42-51.

There is one study that showed bendamustine might be superior to CHOP, although I am waiting to see that confirmed. We usually use CHOP-R as the initial treatment.

有一项研究显示苯达莫斯汀比CHOP更好，不过我仍然在等待更多研究来证实。我们通常用CHOP-R作为一线方案。

All of us are waiting for radio-antibody trials in combination with chemotherapy to see whether they are in fact better. We do not know the answer to that yet.

我们所有人都在等待放射免疫与化疗联合的试验结果。我们还不知道答案。

After the treatment is successfully completed, maintenance therapy works. After single adjuvant rituximab or after any combination of chemotherapy with rituximab, it appears that maintenance rituximab improves the clinical outcome.

治疗成功结束后，维持治疗是有效果的。经过美罗华单药治疗或联合化疗，用美罗华维持可以改善临床结果。

We know that maintenance rituximab prolongs remission; we do not know that it improves survival. One report of rituximab alone done in Switzerland more than a decade ago gave patients a very modest amount of maintenance rituximab after 4 induction doses of rituximab. Patients only received 4 maintenance doses. Now 10 years later, it appears that survival was improved in those patients who received that brief maintenance course, despite that patients in both groups subsequently received rituximab.

我们知道美罗华维持延长缓解时间，但我们不知道是否可以改善生存。来自瑞士的一个报告说十年前一批病人在接受了四次美罗华诱导治疗后仅仅接受了四次美罗华维持治疗。十年过去了，看起来接受短暂的美罗华维持的病人生存期更长，尽管两组病人后来又都接受了美罗华治疗。

The PRIMA study, using chemotherapy plus antibodies followed by maintenance, showed a very dramatic improvement in remission duration with maintenance rituximab. I won't be surprised at all if the study also shows a survival advantage. I believe that today you should have a reason not to give maintenance rituximab after starting with the standard chemotherapy regimen. Whether or not radiolabeled antibodies will change this, time will tell.

PRIMA研究，采用化疗加抗体以及维持治疗，显示经过美罗华维持缓解时间有非常显著的延长。如果研究显示维持治疗在生存期上也有优势的话我一点也不会奇怪。我相信今天你应该没有理由在开始标准化疗治疗后不给予美罗华维持治疗。是否放射免疫制剂能够改变这个策略，时间会告诉我们。

Follicular Lymphoma

Treatment Options for Relapsed Disease

- Repeat prior regimen
- Repeat monoclonal antibody
- Radiolabeled antibody
- Newer drugs
 - Bortezomib
 - Lenalidomide
 - Bendamustine
- Hematopoietic stem cell transplantation
 - ASCT
 - Allo-SCT
- Watch and wait
- Radiation alone
- Clinical trial

Unfortunately, the majority of patients with FL will have subsequent relapse. Not everyone does, but most do. This is particularly true for the low-grade FL in contrast to the grade 3 lymphoma.

不幸的是，大部分滤泡性淋巴瘤病人会复发。不是每个人都会复发，但是大部分会。对于低级别的来说相对于3级更是如此。

How do we approach a patient with relapsed disease? It is still fair to watch and wait. However, there are many, many treatment options available if the patient wants or needs treatment. You can repeat a standard chemotherapy regimen. The patient could receive the antibody again if some time has passed. He or she could receive a radiolabeled antibody or could participate in a clinical trial of new drugs. There are many new and exciting drugs. Bortezomib is active, lenalidomide is active, and we have already mentioned bendamustine. There are a variety of new antibodies that are interesting. Patients could also have an autologous [stem cell transplant] (ASCT) or allogeneic stem cell transplant (allo-SCT).

对复发病人怎么办？观察等待依然可行。如果病人需要或者要求治疗，有很多治疗手段可以选择。你可以重复标准化疗方案。如果一段时间过去了病人还可以再次用抗体。可以用放射免疫疗法或参加新药的临床试验。有很多新的令人兴奋的药物。硼替佐米有效果，来那度胺有效果，还有我们先前提到的苯达莫斯汀。还有很多有意思的新的抗体。病人还可以接受自体或者异体干细胞移植。

If you look at the data supporting these various treatments, one thing that isn't always appreciated and should be kept in mind is that transplantation appears to be most likely to produce a durable second remission. Our data and the data from the combined St Bartholomew's Hospital in London and the Dana Farber Institute in Boston experience are almost identical and show between 40% and 50% freedom from relapse (FFR) at 10 years after an ASCT done at first treatment failure. Patients who undergo allo-SCT have a much higher FFR -- these transplants are also associated, unfortunately, with a higher treatment-related mortality. However, allo-SCT can certainly be curative. I believe that some patients who undergo ASCT are, in fact, cured as well.

如果你观察支持各种治疗方案的数据，应该注意并记在心里的是移植最有可能带来持续的二次缓解。我们的数据和伦敦以及波士顿的经验都是几乎相同的，都显示在首次治疗失败后经过自体干细胞移植十年的无病生存率达到40%到50%。经过异体干细胞移植的患者有更高的无病生存率，但不幸的是也有很高的移植相关死亡率。但是，异体移植的确是可能治愈疾病的。我相信部分经过自体移植的病人其实也被治愈了。

If the patient is not a candidate for either kind of transplant, then radiolabeled antibodies also occasionally produce these extremely durable remissions. There are a number of patients now, one who I treated years ago, who are well past 10 years in continuous remission. My particular patient had 6 treatments before receiving the radiolabeled antibody. Although that does not give patients a very high chance for long survival, with a median remission duration of less than a year, it is still a chance.

如果病人不能做上述任何一种移植，那么放射免疫疗法有时也能实现非常持久的缓解。我有一些病人接受了这种治疗，其中一位已经过了10年，依然还在缓解中。这位病人先前经历过六次治疗，后来接受了放射免疫抗体。尽管不能给病人带来长期缓解的很高几率，中位缓解期还不到一年，但是机会毕竟是机会。

Further chemotherapy regimens can occasionally yield a wonderful response. It is always wise to remember that 1, if the patient is well, you don't absolutely have to treat and 2, FL is one of the most radiosensitive malignancies. If relieving symptoms and making the patient feel better is the primary goal, relatively simple brief courses of radiotherapy might be the easiest and most effective way to accomplish your goal.

进一步化疗有时也能产生很好效果。一定要记住，首先如果病人情况良好，你不一定必须治疗，其次，滤泡性淋巴瘤是放疗最敏感的肿瘤之一。如果主要目标是缓解症状从而让病人更舒服，那么相对简单和短暂的放疗可能是最容易和最有效的实现目标的手段。

Several times now I have alluded to whether patients with this disease might be cured. That is a complicated issue. It depends partly on what you mean by cure. I would argue that cure means the patient lives for however long he or she will live and dies from some other disease or cause, and the lymphoma did not recur. Incurability is not about the potential for relapse, but about the presence of actual relapse. With that definition, in fact, we certainly cure people with FL. The reason I think that is important to recognize is that while it is common to tell the patient, "You have an incurable disease," that is really a pretty scary thing to hear. I think it makes more sense and is more accurate to say, "Most people with this disease eventually have relapse, but not everybody does. If we treat you, we are going to aim for a complete remission. We are going to hope you are one of those who will never have relapsed disease." I think that is a lot better message for the patient.

有几次我曾经暗示这种疾病是否能治愈。这是个很复杂的问题，部分取决于你认为什么叫治愈。我同意治愈是指病人度过应有的生存期而最终死于其它疾病或原因，淋巴瘤没有再犯。不可治愈不是存在复发的可能，而是存在确实的疾病复发。从这个定义来看，我们的确可以治愈滤泡性淋巴瘤。这一点很重要，原因是尽管告诉病人“你有一种不可治愈的疾病”对我们来说很平常，但是对病人来说听到这个消息还是很恐怖的。我觉得更合理和准确的说法应该是，“患有这种疾病的人大部分都会复发，但不是每个人都会复发。如果我给你治疗，我们的目标是完全缓解。我们希望你是不再复发的病人之一”。我认为这给病人的更好的一个信息。

That is a review of how we manage people with this disease. How do you treat somebody today? When you see a new patient with this disease, I would start out with what I said before: Find out whether the patient is well and whether he or she is comfortable being observed for a period of time. If yes, observation is a perfectly legitimate thing to do.

以上回顾了我們如何应对患有这种疾病的病人。你今天会怎样治疗病人呢？当你见到一个患有这种疾病的新病人，我会像我前面说的那么做：确定病人的状况是否良好，以及是否愿意长时间观察。如果是，观察是非常合理的策略。

If the patient is going to be treated, you need to determine how important it is that treatment be administered quickly and how important it is to have a rapid response. If a rapid response is needed, you will probably want to use a combination of chemotherapy and an antibody. If that is not a pressing matter, an antibody alone, a combination of drugs and an antibody, or a clinical trial of a new agent might be a perfectly appropriate choice.

如果病人要治疗，你需要确定快速治疗和获得快速的应答是否重要。如果需要获得快速的应答，你可能会选择联合化疗加抗体。如果治疗并不着急，那么单独使用抗体，抗体加化疗，或者新药的临床试验都是很好的选择。

Follicular Lymphoma

Personalizing Treatment Decisions

- Patient preference
- Patient health status
 - If young and fit with good PS
 - Consider upfront chemoimmunotherapy
 - If elderly or decreased PS
 - Adjust treatment based on toxicity profile (neutropenias, fevers, infections, etc) based on patient tolerability
- Determine treatment goals
 - If rapid response is needed → chemotherapy + antibody
 - If less rapid response is sufficient → chemotherapy or antibody alone
- Maintenance rituximab: standard
- Recurrence: consider transplantation

If the patient achieves remission, there is no question today that you can on average prolong those remissions significantly with maintenance rituximab. In the absence of a good reason not to, maintenance ought to be offered to the patient. Of course, people need to be followed closely afterward. If they have recurrence of disease, it is very wise to consider ASCT or allo-SCT if the patient is eligible and amenable because that is the treatment most likely to result in long-term remission.

如果病人获得缓解，现在毫无疑问你可以通过美罗华维持显著延长平均缓解时间。如果没有很好的理由不这么做，应该向病人建议美罗华维持。当然，病人应该在其后密切观察，如果出现复发，可行的话考虑自体干细胞移植是比较明智的选择，如果可行而且病人愿意也可以考虑异体干细胞移植，因为最有可能带来长期缓解。

Even in the relapsed disease setting, there are many, many treatment choices. Selecting the treatment that best meets the patient's needs and desires is being a good physician in treating patients with FL.

即使在复发的情况下，依然有很多很多治疗选择。选择最能够满足病人需要和愿望的治疗方案是一个好医生的职责。