5 Minute JournalClub

Key ASH Presentations
Issue 2, 2011

Incidence of Therapy-Related Myeloid Neoplasia Among Patients with Chronic Lymphocytic Leukemia (CLL) After Fludarabine/Cyclophosphamide (FC) versus Single-Agent Fludarabine (F) as Initial Treatment

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVES

- Educate patients receiving fludarabine-based induction therapy, with or without cyclophosphamide, about the risk of secondary myeloid neoplasia.
- Consider long-term safety events in the selection of initial treatment for CLL.

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Advisory Committee: Allos Therapeutics, Celgene Corporation, Cephalon Inc, GlaxoSmithKline, Millennium Pharmaceuticals Inc; Consulting Agreement: Millennium Pharmaceuticals Inc.

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To go directly to slides and commentary, **click here**.

It's no secret that the anti-CD20 antibody rituximab has profoundly affected clinical research and management approaches in B-cell neoplasms, and in 2010 we heard about two more landmark trials that help to expand our knowledge of this very interesting agent. First, at ASCO the PRIMA study demonstrated that two years of R maintenance after prior induction with R/chemo delayed disease progression, and the ASH update of this historic study further solidified these outcomes with more follow-up. The second recent important data set came from an **Intergroup trial** that was just presented at ASH. The study randomly assigned patients with asymptomatic nonbulky advanced FL to either rituximab — for what turned out to be two years — or watch and wait (or as our prostate cancer colleagues call it, watch and worry). The trial showed that R led to a substantial delay in progression and in the need for further treatment (usually chemo).

Both of these data sets have sparked considerable debate, and as promised, last Friday in our Miami recording studio I asked the eight distinguished faculty members who participated in our clinical investigator Think Tank the bottom line on these and other seminal ASH data sets:

1. PRIMA: R maintenance after R/chemo
All of the investigators except the always free-thinking Dr Cheson offer but do not insist that patients receive two years of R maintenance.

2. Intergroup study: R versus watch and wait
None of the faculty believe that using R earlier substantially changes the natural history of the disease or overall survival, although it is important to note that there were only 21 total deaths reported in the Intergroup study and less than three years of follow-up. The Think Tank group did acknowledge that many patients find a delay in disease progression appealing in return for the modest and unchemo-like risks of this treatment.

For all the good that R has done, FL and CLL are still not curable and a litany of approaches are being evaluated in these diseases to offer patients even more. At ASH many presentations focused on other promising agents, and at our Think Tank I asked the faculty which ones they found most exciting. Here are some of their thoughts and key related data sets.

Lenalidomide
At ASH **Alessandra Ferrajoli** presented some interesting data on lenalidomide in combination with rituximab for patients with relapsed and refractory CLL. The study demonstrated a 64 percent overall response rate, and the Think Tank faculty showed considerable interest in new trials evaluating this combination up front as a means to potentially avoid the **increased incidence of therapy-related myeloid neoplasia** associated with FC and particularly FCR reported at ASH.

Bortezomib
A much-awaited ASH presentation by **Bertrand Coiffier** reported better PFS, response rate and time to next lymphoma treatment when bortezomib was added to rituximab in FL, but this study did not meet the primary endpoint of a 33 percent improvement in PFS. Ongoing cooperative trials are looking at the agent in the up-front setting, and there was uncertainty among the faculty as to whether these studies will demonstrate an acceptable benefit-risk ratio.

Small molecules
At the Think Tank Brad Kahl presented a patient responding to a new agent, CAL 101, and perhaps not surprisingly there were encouraging data **(click here to view abstract)** at ASH on this oral, relatively nontoxic PI3 kinase inhibitor and several other small molecules targeting the CD20 pathway.

Next up on this series, ASH data sets on a new generation of BCR-ABL TKIs in CML.

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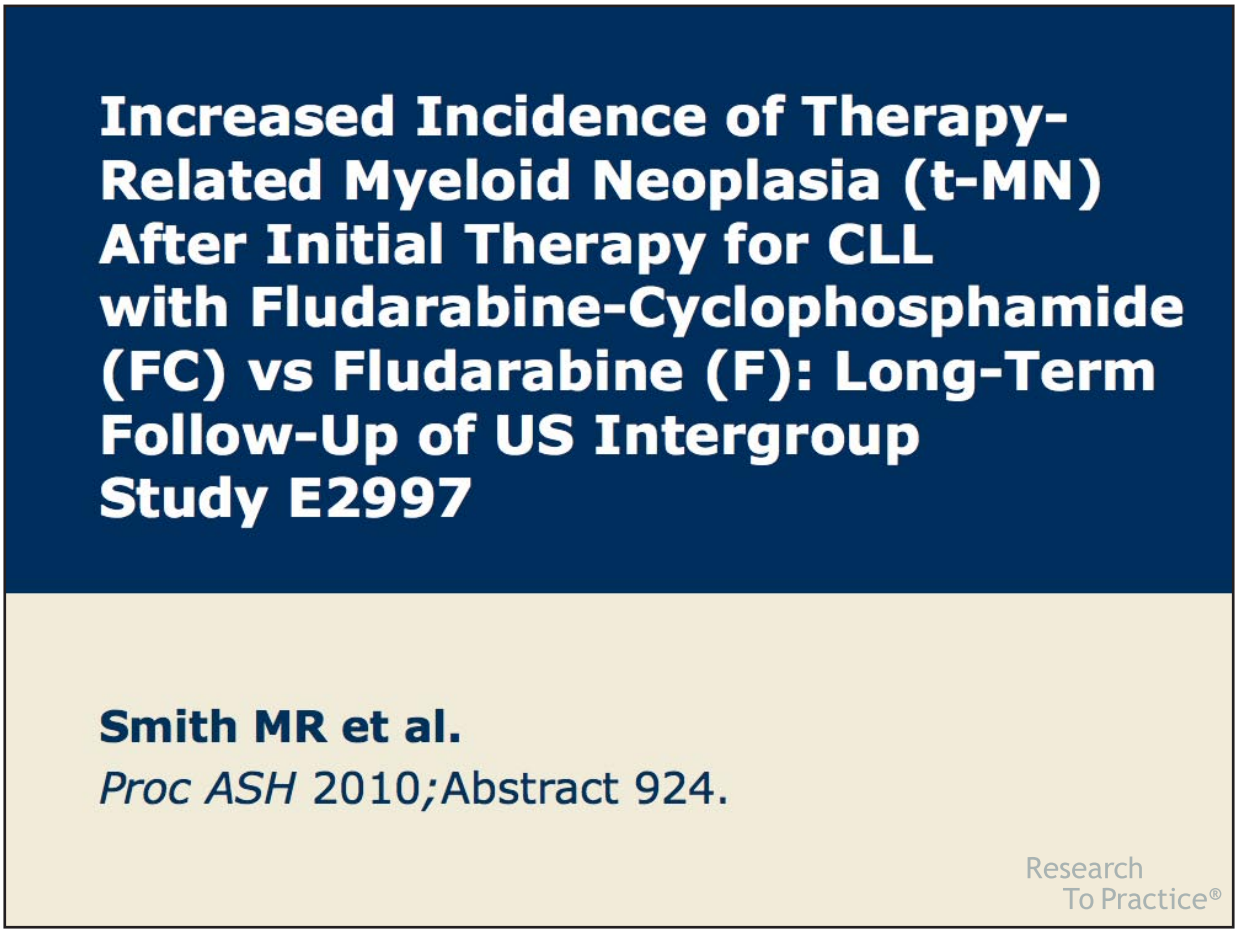
Incidence of Therapy-Related Myeloid Neoplasia Among Patients with Chronic Lymphocytic Leukemia (CLL) After Fludarabine/Cyclophosphamide (FC) versus Single-Agent Fludarabine (F) as Initial Treatment

Presentation discussed in this issue

Smith MR et al. **Increased incidence of therapy related myeloid neoplasia (t-MN) after initial therapy for CLL with fludarabine-cyclophosphamide (FC) vs fludarabine (F): Long-term follow-up of US Intergroup study E2997.** *Proc ASH* 2010;**Abstract 924**.

Slides from an ASH 2010 presentation and comments from an interview with Bruce D Cheson, MD (12/23/10)



Background

- Therapy-related myeloid neoplasia (t-MN) is a serious, long-term consequence of conventional chemotherapy, such as alkylating agents, topoisomerase-II inhibitors, and antimetabolites.
- Combination fludarabine and cyclophosphamide, when compared to fludarabine alone, led to higher complete and overall response rates and longer progression-free survival in Phase III E2997 trial (*J Clin Oncol* 2007;25(7):793).
- Combination therapy also caused more myelosuppression, which could lead to greater long-term effects on myeloid hematopoietic function, including t-MN.
- A follow-up of study E2997, examining the incidence of t-MN, is presented here.

Smith MR et al. *Proc ASH* 2010;Abstract 924.

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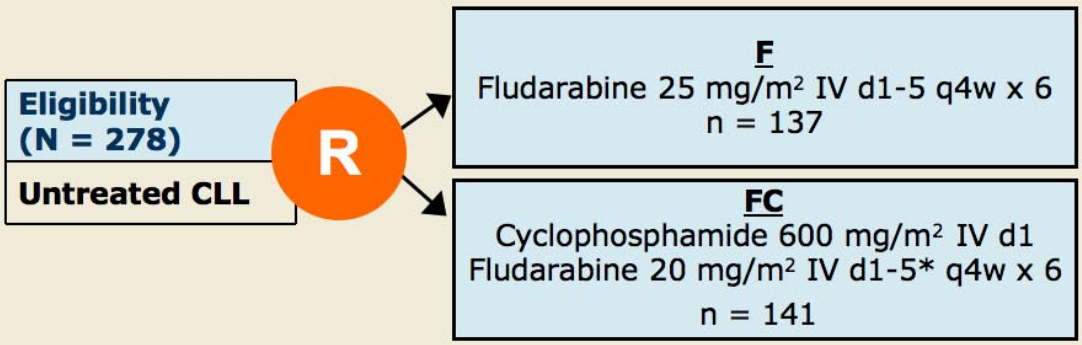
Trial Schema



* Received filgrastim 5 mcg/kg and antiviral prophylaxis

- All patients received allopurinol (cycle 1) and PCP prophylaxis.
- All patients were assessed for t-MN by required reporting of these events.
- Baseline genetic and molecular features of CLL were available for 235 patients (122 on FC and 113 on F).

Smith MR et al. *Proc ASH* 2010;Abstract 924.

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Patient Characteristics

Characteristic	Patients (N = 278)
Median follow-up	6.4 years
Cases of t-MN, n (%)	
Total	13 (4.7%)
After FC (N = 141)	9 (6.4%)
After F (N = 137)	4 (2.9%)
Rate of t-MN at 7 years	
After FC (N = 141)	8.2%
After F (N = 137)	4.6%
Median time from initial therapy to t-MN diagnosis	5 years

Smith MR et al. *Proc ASH* 2010;Abstract 924.

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Characteristics of Patients with t-MN

Characteristics	FC (n = 9)	F (n = 4)
Additional therapy prior to t-MN		
No	7	1
Yes	2	3
IgV_H gene status		
Mutated	7	1
Unmutated	0	3
Data not available	2	0

Smith MR et al. *Proc ASH* 2010;Abstract 924.

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Conclusions

- Higher incidence of t-MN was observed after combination therapy with FC than after single-agent F.
- t-MN after FC occurred most often without additional therapy and in IgV_H-mutated CLL, which is associated with a more favorable outcome.
- The increased incidence of t-MN after FC, usually in the absence of additional treatment, suggests that FC is more leukemogenic than F alone.
- This finding emphasizes a need for longer follow-up of toxicity and survival before concluding that combination FC is preferable to single-agent F as the chemotherapy backbone for initial therapy of both low- and high-risk CLL.

Smith MR et al. *Proc ASH* 2010;Abstract 924.

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Investigator Commentary: Incidence of Therapy-Related Myeloid Neoplasia with FC vs F as Initial Therapy for CLL

Several different therapies are effective for the initial treatment of CLL, including fludarabine/rituximab (FR), fludarabine/cyclophosphamide/rituximab (FCR) and bendamustine-based therapy. However, it is unclear which is the optimal regimen.

FCR versus FR is currently being compared in a large Intergroup trial. One of the concerns of using alkylating agents in patients with CLL is the potential for increased secondary diseases, such as myeloid neoplasia. In this study from the Eastern Cooperative Oncology Group, they found a slight increase in the number of patients who developed therapy-related myeloid neoplasia with FC versus fludarabine alone. The numbers were small, and longer follow-up is needed to determine whether the impression that FC is more leukemogenic is valid, because FCR is widely used as the initial treatment for CLL.

Interview with Bruce D Cheson, MD, December 23, 2010

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