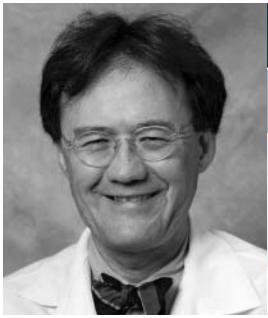

INTERVIEW

Philip L McCarthy, MD

Dr McCarthy is Professor of Oncology and Internal Medicine at the Roswell Park Cancer Institute and State University of New York at Buffalo in Buffalo, New York.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you comment on the current role of transplantation in the management of multiple myeloma (MM)?

DR MCCARTHY: Patients who require a transplant need some form of induction therapy. In the past we've used the "CRAB" criteria to help us decide when to initiate therapy. Once you've decided that the patient needs treatment, you should administer therapy until the best response is reached and collect stem cells. We typically offer patients single ASCT.

A current topic of investigation is the use of up-front versus delayed transplant. Some registry data seem to indicate not much difference between the 2 strategies, but other data suggest a benefit with early transplant, so this is an open question. A number of studies are ongoing, and we're anxiously awaiting those results. One such study is a joint French

and American venture called DETERMINATION (NCT01208662), spearheaded by Dr Paul Richardson. Patients receive RVD (lenalidomide/bortezomib/dexamethasone) induction therapy, have their stem cells collected with cyclophosphamide mobilization and are then randomly assigned to either an autotransplant or continued RVD. Patients who undergo autotransplant then receive RVD consolidation. The trial organizers discussed at length the duration of lenalidomide maintenance therapy. The French decided to administer a year of maintenance, and in the United States it was decided that a year was short so US patients will receive maintenance therapy until disease progression.

Track 5

DR LOVE: What do we know about the oral proteasome inhibitor ixazomib in the treatment of MM, and where do you think it's heading?

DR MCCARTHY: Shaji Kumar recently published data in *Blood* on once-weekly ixazomib, and Paul Richardson published data on the twice-weekly schedule in relapsed/refractory MM (2.1). It appears as though the weekly schedule will be preferred with lenalidomide/dexamethasone. Some rashes and gastrointestinal toxicity occur, but this schedule seems to be efficacious and fairly well tolerated. The likely scenario is a completely oral administration of lenalidomide and weekly ixazomib.

An upcoming trial will evaluate maintenance ixazomib versus placebo after a single autotransplant (NCT02181413), although I don't know if that will be used much in the United States. The trial will be limited to 2 years, which may not be long enough. The duration of maintenance therapy is a current debate. I would have been more interested in a placebo-controlled trial of lenalidomide versus lenalidomide/ixazomib.

2.1

Weekly versus Twice-Weekly Ixazomib for Patients with Relapsed and/or Refractory Multiple Myeloma

Efficacy	Weekly ixazomib[1] (N = 50)	Twice-weekly ixazomib[2] (N = 55)
Complete response	0%	1 (2%)
Partial response	18%	6 (11%)
Stable disease	30%	33 (60%)
Progressive disease	50%	18%
Adverse events (Grade ≥3)	**Weekly ixazomib[1] (N = 60)**	**Twice-weekly ixazomib[2] (N = 60)**
Thrombocytopenia	33%	37%
Neutropenia	18%	17%
Skin/subcutaneous skin disorders	3%	8%
Peripheral neuropathy	2%	0%

[1] Kumar SK et al. *Blood* 2014;124(7):1047-55. [2] Richardson PG et al. *Blood* 2014;124(7):1038-46.

Track 6

DR LOVE: Would you review what we know about the use of carfilzomib/lenalidomide/dexamethasone (CRd) as up-front therapy in MM?

DR MCCARTHY: The NCI reported deep responses with CRd (Korde 2013), and the Jakubowiak data are certainly encouraging as well (Jakubowiak 2012). ECOG also has a trial evaluating CRd versus RVD followed by limited versus indefinite maintenance therapy with lenalidomide for patients newly diagnosed with symptomatic standard-risk MM (NCT01863550).

I believe carfilzomib is reasonable as a single agent for relapsed or refractory disease, but it's probably better when combined with an immunomodulatory agent. Up front our group is not using it much. For someone with severe neuropathy you could petition the insurance company by saying that the patient won't tolerate bortezomib. Or if neuropathy worsens after 1 cycle of bortezomib — for example, in a patient with diabetes — you might want to use carfilzomib up front. But right now we still use bortezomib.

Some cardiac toxicity occurs with carfilzomib also, and we don't know which patients will be affected by it. We've observed a couple of idiosyncratic cases that arose suddenly, without a clear reason, in patients with no cardiac history, who then developed congestive heart failure. Any marker for this effect remains to be discovered. Not all patients need an echocardiogram, but with an older patient you might want to consider that when you initiate therapy.

Tracks 13-14

DR LOVE: What are your thoughts on the impact of brentuximab vedotin on transplant decisions in HL?

DR MCCARTHY: We've been using it off label for patients with HL who experience relapse after primary therapy. If their disease is not well controlled with chemotherapy, we administer brentuximab vedotin as salvage therapy prior to autologous transplant. We also administer this agent after transplant for patients who experience relapse, according to the FDA label. And we will consider brentuximab vedotin as a bridge to allogeneic transplant for younger patients.

DR LOVE: How does ruxolitinib affect transplant decisions in myelofibrosis?

DR MCCARTHY: In the past, if they had a suitable donor patients often received allogeneic transplant early, especially if they were transfusion dependent. Now ruxolitinib has changed everything. Ruxolitinib provides a survival benefit, and it makes people feel much better. So if it can control a patient's disease, we hold the transplant. Ruxolitinib may not be the "home run" that imatinib was for CML, but I believe it's a great first step because now we have something to offer patients, especially if we can decrease their transfusion requirements and make them feel better. All the systemic symptoms seem to disappear with it. Unfortunately many patients experience disease breakthrough, and then we have to consider other options, such as transplant. ■

SELECT PUBLICATIONS

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801-9.

Korde N et al. **Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide extended dosing (CRD-R) induces high rates of MRD negativity in newly diagnosed multiple myeloma (MM) patients.** *Proc ASH* 2013;**Abstract 538**.

Kumar S et al. **Phase I study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma.** *Blood* 2014;124(7):1047-55.