Second Primary Cancers in Myeloma: A Status Report

February 2011

During the past few weeks members of the International Myeloma Working Group (IMWG) have been considering and discussing results presented at ASH 2010 (See Table 1). Three large randomized trials showed excellent prolongation of remissions with lenalidomide use, although second primary cancers (SPCs) were noted. A working subgroup of the IMWG met to review the results, and the full IMWG (144 myeloma expert members) has been developing a consensus statement to provide appropriate recommendations for the myeloma community. The data that form the basis for discussions are summarized in Table 1 below.

Table 1	**2010 ASH Presentations***		
		SPCs /Total	**% SPCs**
IFM			
Attal et al ASH 2010	Lenalidomide	17**/299	5.5%**
	Placebo	3/292	1.0%
CALGB			
McCarthy et al ASH 2010	Lenalidomide	15/231	6.5%
	Placebo	6/229	2.6%
MM015			
Palumbo et al ASH 2010	MPR/MPRR***	11/355	3.1%
	Placebo	2/154	1.3%

* Cases of SPCs: numbers and percentages as of February 2011

** These SPCs are: AML/MDS 5 (2 in placebo); Hodgkin's disease 4 (0 in placebo); B-cell ALL 2 (0 in placebo); colon cancer 2; prostate cancer 2; breast cancer 1; and esophageal cancer 1.

*** Includes Melphalan, Prednisone, Revlimid (MPR) with and without continued Revlimid (MPRR-R: Revlimid = lenalidomide)

It can be seen that there is an increase in the number of second cancers reported in two trials (IFM & CALGB: see Table 1) in which lenalidomide was administered as maintenance after high-dose melphalan-based stem cell transplantation. In the third trial (MM015: see Table 1), an increase in the number of second cancers was reported with the use of lenalidomide in combination with melphalan in the frontline setting.

The second primary cancers included solid tumor cancers such as breast, prostate, and colon cancer as well as hematologic cancers such as acute leukemias and lymphoma; there were also some cases of myelodysplastic syndrome (MDS). The numbers and percentages listed are simply the numbers of patients with SPCs in each study reported thus far. More sophisticated

analyses plus studies of risk factors are underway to assess occurrence of SPCs over time, the different types of SPCs, as well as other details of the cases.

The IMWG has reached some interim conclusions and can provide preliminary recommendations.

Known Occurrence of Second Primary Cancers

The occurrence of second primary cancers in myeloma patients has been recognized for several decades. In an analysis by the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) Program from 1973-2000, approximately 5.1% of MM patients developed a second primary cancer within twenty years. The overall number of second primary cancers in the three ASH studies are thus consistent with the frequency expected in an older population (92% > 50yrs old). Of the leukemia cases, 80% were AML. The risk of developing AML and/or MDS following the use of alkylating agents to treat MM has also been recognized for several decades (Cuzick et al. 1987; Bergsagel et al. 1979). This risk typically increases with increasing cumulative dose and/or duration of therapy of the alkylating agent. The risk is predominantly with melphalan, and to a lesser degree, with cyclophosphamide (Cytoxan). The risk of developing second primary cancers following transplantation has also been recognized. In a retrospective study of 800 patients who underwent high-dose therapy (HDT) and autologous stem cell transplant (ASCT) from 1982-2000, the cumulative risk of developing a second primary cancer at 15 years was 11% (95% CI, 5-18%) (Forrest et al. 2003). Thus, depending upon the time frame, second primary cancers in the range of 5-10% (1-2% per year of follow-up) are to be expected, especially as the population ages and patients live longer, taking advantage of more and better therapies. According to SEER, the risk of second cancers is 1.4-2% per year of follow-up. The annual incidence rates of SPCs per 100 person-years for individuals over age 65 can also be calculated, and is 2.1/100 person-years. There are thus some comparators for ongoing assessments.

Importance of the Recent Trial Results

- The important observations in the ASH 2010 randomized trials are the differences between the placebo or control groups and those patients receiving lenalidomide.
- The main difference to note is that the lenalidomide-treated patients had remissions (Progression Free Survival [PFS]) on average twice as long (for example, 42 months vs. 21 months) as patients not receiving lenalidomide. This means that many more patients are relapsing or progressing on the placebo, especially in the 2nd, 3rd, and later years of the trial. This is clearly evident in the IFM trial, the one with the longest follow-up. At the present time, the follow-up is much shorter in the CALGB trial.

- Since ASH 2010 the IFM team has carefully reviewed the study results. In their study, all the lenalidomide-treated patients had received at least 2 years of lenalidomide treatment as of December 2010. Because substantial benefit had already accrued (that is remission lasting approximately twice as long) and since it is unknown if further lenalidomide will increase the risk of second primary cancers, the IFM decided to stop the trial for safety reasons. Thus, 70 patients in remission after 2 years or more of lenalidomide treatment have been taken off treatment. Since this is the first trial in which this situation has occurred, the strategy to stop the lenalidomide in this particular trial has been understood and acknowledged.
- Follow-up in the CALGB trial is one year shorter. CALGB/NCI, after reviewing all the issues, recently announced that the study will continue with additional monitoring in both arms of the trial.
- Other ongoing trials are also continuing with appropriately enhanced monitoring.
- During the time frame that patients in the placebo group are relapsing, patients in the treatment group are remaining in remission; but ultimately (thus far) 3.1-6.5% are developing a second primary cancer. The numbers involved are illustrated in Table 2, which lists both the percent in remission (PFS%) and the SPC data.

Table 2 Comparison of Relapse-Free and Cancer-Free Survival With and Without Lenalidomide (Placebo)

		Still In Remission (PFS%)	SPCs
IFM			
At 4 yrs from diagnosis	Lenalidomide	60%	5.5%
	Placebo	33%	1.0%
MM015			
At 2 yrs from diagnosis	MPR-R	54.11%	2%
	MPR + placebo	24.18%	5%
	MP	18.84%	1%

- These are some of the data that form the basis for “risk-benefit” discussions. Other elements in this discussion include:
  - What are the details of the reported cancers?
  - Are the cancers occurring in a particular type of patient?
  - Are these the same types of patients (related to risk factors such as age, chromosome changes, or melphalan therapy) reported to develop second primary cancers in the past, or are different kinds of patients at risk?
  - Are chromosome abnormalities such as microsatellite instability and p53 mutations important as in other types of therapy-related leukemia (t-AML)?
  - What is the expected outcome for patients developing a second primary cancer had they not received lenalidomide?

- Do the SPCs only occur in the setting of certain other types of treatment?
- Is the length of the lenalidomide treatment a critical factor?
- Is the dose and/or schedule (for example, continuous vs. 21/28 days) of the lenalidomide a critical factor?
- Is the exact timing of lenalidomide treatment (related to conventional or high-dose melphalan, for example) an important factor?

Current Recommendations Regarding Second Primary Cancers in Myeloma

Relapsed/Refractory Myeloma

- No increased incidence of SPCs has been reported with use of lenalidomide in relapsed/refractory myeloma.
- No changes are recommended to currently accepted lenalidomide treatment approaches in this setting.

Newly Diagnosed Myeloma

Based upon currently available data, the IMWG does not recommend changes to currently accepted lenalidomide treatment approaches in the frontline setting either as pre-treatment induction or primary therapy.

Post-Transplant Therapy

- There is no consensus recommendation at this time with regard to ongoing treatment with lenalidomide in this setting.
- Enhanced monitoring of patients for SPCs in all clinical trials is strongly recommended.
- If post-transplant therapy with lenalidomide is used, the IMWG recommends that the potential risk of second cancer be discussed with each patient. This treatment decision requires physician/patient discussions to evaluate the benefits of disease control versus potential risks of continued therapy.
- In the clinical trial setting, it is a priority to ensure consistent and thorough data collection, monitoring, and reporting of second primary cancers.
- It is recommended that information about the potential risk of second cancers be included in the informed consent for all clinical trials.

In collaboration with the NIH/NCI, the IMWG has initiated a concerted effort to further characterize the cases of second cancer that have been reported to define underlying mechanisms and identify risk factors, including molecular features and DNA SNPs. In addition, the

IMWG will closely monitor further developments and provide updates as appropriate. Any feedback or comments from patients, physicians, caregivers, or any other interested parties will be appreciated.

BACKGROUND REFERENCES

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