Secondary hematologic malignancies after chemotherapy

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Dr. Tony Blau Discussant
Case 1

- Referral from Dr. Blau (Sibel) of a 60 yo woman 3 years out of therapy for her Stage II ER pos PR pos HER2 neg breast cancer treated with dd Adriamycin/Cytoxan and Paclitaxel presenting with new cytopenias (↓wbc and anemia).

- Bone marrow biopsy showed hypercellular marrow with blasts in the marrow with 85% blasts in marrow FISH positive t(15;17) translocation

- She received ATRA/Arsenic and returned to Dr. Blau’s care, she is doing well as of now.
Case 2

- 50 yo woman patient of Dr. Ellis diagnosed with ER pos (ALLRED 3/8) PR neg HER2 pos stage IIB (T2N2M0) IDC s/p dd Adriamycin/Cytoxan, weekly Paclitaxel and Herceptin (then 9 mo Herceptin) in 2010 and currently on Tamoxifen who presents with 1 mo cytopenias, headache and fatigue.

- **Bone marrow:** 80-90% cellularity, >20% blasts (88% of the bone marrow), FLT3 neg, NPM1 neg, CEBPA neg with t(9;11) MLL translocation by cytogenetics.
Case 2 continued

- Induction with 7+3 and Cladribine
- 9.5% blasts remaining at count recovery, admitted for cytarabine/cladribine
- Received 3 cycles of cytarabine/cladribine and went to MURD transplant with 0.01% blasts present.
- Chemotherapy complicated by NSTEMI with EF 48% after cycle 2.
- Non-myeloablative conditioning 2430 with clofarabine/TBI day 0 1/8/13
- Relapsed by d 84, received 3 cycles Vidaza
- Passed away due to sepsis and CHF ~ day 200 transplant.
WHO criteria therapy related hematologic neoplasms

1. Alkylating agent-related or radiation-related type AML or MDS
2. Topoisomerase II inhibitor-related type AML

-in general these neoplasms are associated with high-risk cytogenetics and respond poorly to conventional therapy.

-also complicating treatment: these patients have had prior cytotoxic therapy and sometimes persistent primary disease

-treatment related AML ~10% AML diagnoses

Why concern for this problem

- Cancer survivors have been increasing 2%/year in the US since 1971
- 2010 US: 3.5% of the population are cancer survivors
- With longer survival after the primary cancers, more long term side effects of therapies are emerging
- Secondary or higher order cancers 18% cancer incidence in the US
- NCI SEER database: cancer survivors 14% risk over general population to develop a second cancer

Thomas Blood (2012) 119: 2731
Incidence depends on rate of disease and prevalence of secondary malignancy

Leone et al Curr Opinion in Oncology (2011) 23:672
Breast Cancer

• Increased risk of secondary cancers including esophagus and lung (secondary to radiation), soft tissue sarcoma (angiosarcoma), and hematologic (NHL, myeloma, leukemia/MDS) as well as ovarian and uterine (genetics or hormone therapy)

• Also recently some concern with using GSCF in the dose dense regimens, one study 5510 women with breast cancer requiring GSCF double risk leukemia (however other studies have shown no evidence of ↑ risk)

• French Cancer Registry: 15 AML/ 5663 women treated for breast cancer, SIR 8.26 (p<0.05) greater risk than general public

• Austrian retrospective study 158 AML/183,123 women with breast cancer (0.09%, RR 2.6 ↑ over general population)

Breast

Dutch Study: 58,068 women with invasive breast cancer 1989-2003
2,578 secondary non-breast cancers (SIR 1.22 95% CI 1.17-1.27)
~10 year cumulative incidence any secondary non breast cancer 5.4%
- SIR Hematologic malignancy 1.13 (95% CI 0.99-1.28)
- SIR AML 2.81 (95% CI 2.15-3.61), SIR NHL 1.23 (95% CI 1.03-1.47)
- HOWEVER, risk of AML if <50 yo when breast cancer treated RR
  2.20 (95% CI 1.19 to 4.08)

-Risk particularly with chemotherapy HR 3.18 (95% CI 1.39-7.28) as compared to radiation HR 1.28 (0.69-2.39) or hormone therapy HR 1.40 (0.78-2.50)

Schaapveld JCO (2008) 26: 1239
Transplant after secondary leukemia

• Registry secondary MDS or secondary AML: 78 patients 2 year survival same if in CR at time of transplant (~60%), if not given a transplant 2 year survival 18% (+/-11%).

• City of Hope: 15 patients s/p adjuvant chemotherapy for breast cancer (13 also had radiation)
- 13 AML, 1 pre B ALL, 1 MDS
- 8 MLL translocation, 2 normal cytogenetics, 1 APL, 1 inv 16, 1 trisomy 8, 1 t(8;16), and 1 t(9;22)
- 12/15 able to go to HSCT (1 auto, 11 allo) and 9 had no relapse at median 20.4 mo, 1 relapsed but currently NED with 5 azacytidine and valproic acid (inv 16 AML), and 1 died 2.4 mo after transplant

Hodgkins Lymphoma

• 15 years after dx, cumulative mortality due to second malignancies exceeds cumulative mortality HL

- risk varies by therapy: German Hodgkin HD9: 1282 patients, 74 secondary malignancies, 14 AML:
  ➔ 3% risk AML at 10 years with BEACOPP escalated
  ➔ 1.5% risk AML at 10 years BEACOPP baseline
  ➔ 0.4% risk AML at 10 years with COPP/ABVD

- in case studies, bone marrow transplant has shown some benefit over cytoreductive therapy.

Testicular cancer

• survivors 3X increased risk of developing secondary malignancy

• US/European Study: 28,843 patients, 27 developed secondary AML/MDS, German study: 302 patients, 4 developed AML.

• Due to therapy with Topoisomerase II inhibitors and cisplatin. Increased risk if >2g/m² etoposide.

• Mean cumulative risk 1.3 to 4.7% in 5 years

Pediatric Malignancies: SEER

- NCI SEER-9 34,867 patients dx 1973-2005 with primary cancer before 20 yo.
- 111 of the patients had a secondary hematologic malignancy with 5 year survival 31% +/- 4.7% (excess risk 2.26/100,000)
- 54: AML (5 yr survival 18% +/- 5.3%, excess risk 1.46/100,000)
- 27: NHL (5 yr survival 49% +/- 9.9%)
- 16: ALL (5 yr survival 38% +/- 14%)
- 6: HL (5 year survival 83% +/- 15%)

Myeloma

• 1979 Bersagel 364 MM patients increased AML with low dose melphalan
• Secondary AML due to increased chemotherapy prior to transplant not ASCT:

  1. Govindarajan et al: 7/117 patients with multiple cycles chemotherapy prior to ASCT developed secondary MDS/AML compared to 0/71 with only 1 cycle (p=0.02) despite both groups receiving same collection and conditioning regimens

  2. 8740 myeloma patients in population-based Swedish study (1986-2005) had same rates of secondary MDS/AML before and after introduction of high-dose melphalan conditioning.

Myeloma Continued

- SEER database evaluation: 36,491 cases multiple myeloma 1973-2008
  - Hematologic SIR 1.63 (95% CI 1.45-1.84)
  - AML 10 fold ↑ risk in 5 years
  - Increased rate of AML after therapy 1973-1977 (12X↑) as compared to 2000-2008 (4X ↑) related to chemotherapy used.
  - No change in AML rate after introduction of novel therapies (e.g. ~2000) or introduction of ASCT (mid 1980s)

- younger patients increased risk of developing AML
  SIR 11.92(CI 8.95-15.86) if <65
  SIR 2.28 (CI 1.40-3.72) if >75

Myeloma continued

- Lenalidomide: 3 multicenter phase III studies of lenalidomide maintenance after ASCT showed increased secondary MDS/AML
  - IFM 2005-02: Lenalidomide until disease progression within in 3-6 mo of ASCT as compared placebo: 5.5% secondary malignancies in Lenalidomide arm as compared to 1% placebo arm
  - CALGB 100104 Lenalidomide induction then maintenance after ASCT: 6.6% secondary malignancies compared to 2.5% placebo control
  - MM-015 maintenance Lenalidomide after Melphalan-Prednisone in patients not tolerate ASCT 0.7% AML in Lenalidomide arm verses 0% in placebo

* Yet all three studies showed benefit of Lenalidomide in either PFS (IFM 2005-02 and MM-015) or PFS and OS(CALGB 100104)

Thomas Blood (2012) 119: 2731
Radiation

• increased risk secondary malignancies, risk due to with dose response
  -includes dose to active bone marrow, dose rate, and % of exposed marrow

• secondary malignancies can include sarcomas, lung and esophageal cancers, and AML

• AML and ALL typically develop 5-9 years after radiation, risk 2X lower than chemotherapy

Secondary MDS

- SEER database 3,938 MDS cases 2001-2004
- 26% MDS cases previous cancer diagnosis, associated with 13% increased risk of death (HR 1.13 95% CI 1.02-1.25)
- Median survival 16 mo (95% CI 14-20) MDS with previous cancer, 23 mo (95% CI 21-26) MDS no previous cancer.
- Lung CA HR 2.0 (95% CI 1.31-3.22) and Lymphoma HR 1.69 (95% CI 1.30-2.20).
- Median time between cancer dx and MDS 6.5 years, if <5 years between cancer dx and MDS worse prognosis

-increased cytogenetic abnormalities (40-50% de novo MDS, 95% therapy-related MDS)

De Roos et al Cancer Causes Control (2007) 18:1199
Alkylating Agents

- Cytotoxic by cross linking guanine nucleotide bases preventing DNA replication
- Leukemia starts to appear ~3 years after therapy with peak incidence between 5-10 years
- AML typically develops after a myelodysplastic stage
- e.g. cyclophosphamide, bendamusine, melphalan, ifosfamide, chlorambucil

Topoisomerase II inhibitors

- Topoisomerases regulate winding/unwinding of the DNA needed for replication: Topoisomerase II inhibitors are cytotoxic by inhibiting the topoisomerase II/DNA complex.
- Leukemia appears between 2-3 years after chemotherapy.
- Do not have a myelodysplastic pre-leukemia stage.
- E.g. etoposide, mitoxantrone, and anthracyclines (doxorubicin, epirubicin, and daunorubicin).

Cytogenetic Abnormalities

• **Alkylators**
  - Abnormalities of chromosomes 5 and 7.

• **DNA Topoisomerase II inhibitors**
  - MLL (11q23) translocations
  - balanced chromosomal translocations: t(15;17), t (9;22), inv (16), and 21q22.
  - DNA break points cluster around topoisomerase cleavage sites

Therapy related APL

• typically secondary hematologic malignancies poor prognosis

• Secondary APL (like Case 1) appears to have similar prognosis to de novo APL (latest study 2003)

• Beaumont et al: Multicenter 106 secondary APL (60 from breast, 15 NHL, 25 other solid tumors)
  - 30 had chemo alone, 27 radiation alone, and 49 chemo and radiation
  - Tx Anthracycline/Cytarabine (pre ATRA) or ATRA/chemo:
    - survival 59% at 8 years
    - 87% (Chemo alone) or 80% (chemo/ATRA) had CR and only 10 patients relapsed

Discussion Papers

Clinical characteristics and outcomes of therapy-related chronic myelomonocytic leukemia
Koichi Takahashi, Naveen Pemmaraju, Paolo Strati, Graciela Nogueras-Gonzalez, Jing Ning, Carlos Bueso-Ramos, Rajyalakshmi Luthra, Sherry Pierce, Jorge Cortes, Hagop Kantarjian and Guillermo Garcia-Manero

Second malignancies after multiple myeloma: from 1960s to 2010s
Anish Thomas, Sham Mallankody, Neha Korde, Sigurdur Y. Kristinsson, Ingemar Turesson and Ola Landgren
358 CMML Patients

39 (11%) therapy related
50% intermediate/high risk cytogenetics

319 (89%) de novo CMML
26% intermediate/high risk cytogenetics

p=0.011
Previous cancers

Takahashi Blood 2013
Median latency between primary therapy and secondary malignancy
6 years (range 1-32)

Takahashi Blood 2013
Overall survival secondary CMML

Takahashi Blood 2013
Leukemia free survival secondary CMML

Takahashi Blood 2013
Conclusions

• Single institution retrospective study: MD Anderson
• tCMML and dCMML did have similar therapies (p=0.537)
• in multivariate analysis including RBC transfusion, WHO Classification, CMML-specific cytogenetic risk, LDH, WBC, SCT, and therapy tCMML lost significance OS or LFS
• High risk cytogenetics appears in this analysis to have the most affect on outcomes.
Thomas et al. Second Malignancies after Multiple myeloma from 1960-2010

- Multiple factors in myeloma causing increased secondary malignancies:
  1. Treatment: alkylating agents and radiotherapy
  2. Multiple myeloma factors: Bone marrow abnormalities from disease e.g. 5652 patients with MGUS had 8 fold increased risk MDS/AML particularly IgG and IgA myeloma
  3. Host related factors: two studies (n=2418 and n=82) of patients who will develop MDS or cytogenetic abnormalities had lower CD34 yield on collection.
  4. Environmental factors: chronic allergens, exposure to chlorinated solvents, autoimmune disorders (immune dysregulation?) may play role.
  5. Behavioral factors: Alcohol and tobacco use.

Chemotherapy may not be only cause of secondary malignancies

Contributing in multiple myeloma

Figure 1. Proposed model of second malignancies after multiple myeloma. Examples for the categories include the following: (1) alkylating agents, immunomodulatory agents, autologous stem cell transplant, and radiation; (2) molecular subtypes of disease, bicalon disease, and bone marrow microenvironment; (3) polymorphisms in germline genes (eg, drug-metabolizing genes, erythropoietin promoter gene), chronic antigenic stimulation, and genetic susceptibility with other malignancies; (4) occupation, pesticides, and chlorinated solvents; and (5) tobacco, obesity, alcohol, and diet.

Incidence of secondary cancers in melanoma

SEER data 33,229 patients dx Multiple myeloma between 1973 and 2008

Conclusions

• Treatment related hematologic malignancies small but increased risk for patients after primary therapy:

1. Alkylating agent/radiation like: pre-AML MDS stage ~5-10 years after therapy. Abnormalities chr 5 and 7.

2. Topoisomerase II inhibitors: no pre-AML MDS, Leukemia 2-3 years after therapy. Abnormalities balanced translocations (MLL 11q23, t (15;17), inv 16, t(9;22)). Both cases were probably examples of this type of t-AML with different outcomes.
Take away points

• Solid tumor people: Be nice to your hematology friends, you will need their help during your career.

• Always be aware of/ follow the hematologic effects of therapies given particularly in younger patients.

• Further research has to be performed to find agents (PD1 inhibitors, CTLA4 inhibitors, immune therapy, directed agents, personalized therapy....) which can reduce the amount of cytotoxic therapy used to try to avoid this side effect.
Thank you

- Dr. Blau for preparation and acting as discussant
- Fellowship program
- Hematology group