RUSH

Case study:

Novel chemoimmunotherapeutic approaches in the treatment of fibrolamellar carcinoma at Rush

By Paul Kent, MD

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Paul Kent, MD, is a pediatric hematologist-oncologist at Rush University Medical Centerand the medical director of the fibrolamellar carcinoma program at Rush. Dr. Kent is a national leader in the treatment of fibrolamellar carcinoma through his work with Rush's unique, multidisciplinary approach to care of this rare disease.

History

Patient A was a healthy, active 15-year-old high school student. Prior to coming to Rush in 2016, she discovered a 14 cm x 17 cm mass on the left lobe of her liver. Aside from discovering the mass, which protruded from under her ribs, Patient A had no other symptoms. Surgeons at another institution performed a resection and removed one-fourth of her liver, including the cancerous tumor.

In late-2015, Patient A was originally diagnosed with stage I, non-metastatic fibrolamellar carcinoma. She had a complete surgical resection with negative margins and negative adjacent nodes. Her pathology showed a vascular invasion. Oncologists at her original institution recommended adjuvant chemotherapy with cis-platin / doxorubicin, similar to Children's Oncology Group (COG) protocols for hepatoblastoma.

Clinical Remission #1

She and her mother sought a second opinion at another, out-of-state institution, which recommended continuous infusion 5-FU (200mg/m2) for seven days, recombinant interferon alfa-2b rIFNa2b (4 million units/m2) on days one, three, and five, followed by seven days off of treatment. They were both interested in this treatment because they felt the data showed the cis-platin / doxorubicin protocol was not effective at preventing recurrence.

They came to Rush for a third opinion. The hospital where Patient A received her liver resection was unwilling to offer the continuous infusion 5-FU treatment or consult with the out-of-state institution about it. Rush was willing to do this protocol.

Initial Diagnosis

Fibrolamellar carcinoma, stage I, in remission

Facts about Fibrolamellar Carcinoma

According to the National Cancer Institute (NCI), there are so few cases of fibrolamellar carcinoma that there isn't enough data to know conclusively how many people have it, but it is estimated that there are about 50 - 200 new diagnoses in the U.S. every year. The NCI estimates that fibrolamellar carcinoma makes up about 0.8% of all liver cancers, and the median age of a typical patient is 22.

About 25% of patients will be diagnosed early with a stage I or II progression, 60% will be diagnosed late with advanced disease as a stage III or IV progression, and the remaining 15% of patients are diagnosed with such an advanced stage of disease that they end up dying from the disease within three months to a year after diagnosis without the opportunity for resection.

Treatments and Outcomes

1) Continuous infusion 5-FU treatment

Beginning in January 2016, Patient A has eight cycles of continuous infusion 5-FU treatment. She was re-evaluated in May 2016. Both her liver and brain showed no evidence of disease.

However, her lung CT showed several sub-centimeter nodules. Because they were too small to biopsy, we opted to watch, wait and rescan Patient A in a month. In the interim, we gave her a three-week trial of fluconazole and Levaquin. In June 2016, we did not see any significant change in her scans.

Relapse/Progression # 1: In July 2016, we performed a video-assisted thoracoscopic (VATS) lobectomy; a biopsy from one of the nodules showed Patient A relapsed and her diagnosis was updated to stage IV fibrolamellar carcinoma.

Patient A was malnourished and depressed. After meeting with her family, it was decided to try an oral strategy that we hoped would shrink the lung nodules.

2) Sorafenib

In August 2016, Patient A started Sorafenib 400mg po BID. After 10 days on the treatment, she developed a diffuse maculopapular rash. After a five-day course of prednisone with a subsequent taper, her rash improved. In September 2016, she restarted Sorafenib.

In September 2016, the multiple bilateral pulmonary nodules in Patient A's lungs were not significantly changed in size or number. At the time, she showed no evidence of new metastatic disease within the chest or upper abdomen. Stable disease.

Relapse/Progression # 2: In January 2017, we rescanned Patient A and found there has been interval mild increase in size of multiple bilateral pulmonary nodules compatible with disease progression. No new pulmonary nodules were identified.

3) GemOx

Instead of surgical removal of her lung nodules, we discontinued the Sorafenib. In February 2017, Patient A started a 10-cycle regimen of Gemcitabine 1000mg/m2 and oxaliplatin 100mg/m2 (GemOx) every two weeks. She tolerated the treatment reasonably well, aside from some mild neuropathy, sensitivity to cold and post-therapy nausea.

After six cycles, we rescanned Patient A in May 2017. Her smaller (1 mm) lung nodules were stable in number and size, and a few of the larger nodules showed a mild decrease in size. There was also no new or enlarging dominant pulmonary mass identified. Stable disease.

At that point, we added Avastin to her systemic treatment plan, in line with results from a Phase II clinical trial. Patient A then had two additional cycles of GemOx plus Avastin before being scanned again.

Her scan in August 2017 showed the largest nodules had decreased in size and others remained stable. No new or enlarging dominant pulmonary mass was seen. Partial Response.

4) Bilateral thoracotomy + GemOx

Patient A had three additional cycles of GemOX plus Avastin. In October, she had a bilateral thoracotomy, with 124 nodules removed.

From October to December 2017, Patient A continued with the GemOx treatment; Avastin was not included.

Patient A's CT scans in December 2017 showed an interval decrease in the number of pulmonary nodules. Otherwise, the remaining pulmonary nodules were stable in size. No new pulmonary nodules were found. Partial Response.

She then had two ablations: the residual right sided perihilar mass by irreversible electroporation and the residual left sided perihilar mass.

Following the ablations, Patient A had two additional rounds of GemOx, bringing her total count to 21. However, she was no longer tolerating the oxaliplatin, which forced us to change her treatment regimen.

5) Nivolumab and Gemcitabine

Patient A's baseline CT chest showed her existing lung nodules were smaller and fewer, no new nodules presented, and no new disease was present.

In February 2018, she started the first of 22 rounds of Nivolumab and Gemcitabine.

In May 2018, after six cycles of this regimen, a CT PET scan showed stable disease, no new concerning lesions, and several unchanged nodules (< 5mm or scars). Stable disease.

After round 11, Patient A moved to Boston to start college and received her care (cycles 12-15) from an institution there. To improve her quality of life, treatments were spaced out from every two weeks to three.

Relapse/Progression # 3: Scans in November 2018 showed progressive disease in four nodules. Patient A came back to Chicago where we returned to administering treatment every two weeks. We included Avastin in cycles 19 and 21 of her treatment; nevertheless, her CT scans in February 2019 showed progressive disease bilaterally.

We consulted with Patient A and her family on the next steps for treatment, including oral therapy or non-standard / experimental therapy, including any open clinical trials. Patient A decided to ablate the larger nodules in her lungs (in March 2019, three of the six nodules in her left lung were ablated; in April 2019, four of the six in her right lung were ablated).

6) Triple Immune Therapy: 5FU (or Capecitabine) + INF alpha + Nivolumab

In April 2019, Patient A was treated with oral Capecitabine 1000mg / 500mg x 7 days, INF-Alpha on days one, three, five and seven recombinant interferon alfa-2b rIFNa2b (4 million units/m2), and Nivolumab 3mg/kg IV every two weeks.

After the first cycle, Patient A developed a worsening cough and chest pain, which ultimately was diagnosed as an abscess in her right lung from the ablation treatment. She was admitted to the hospital in mid-April 2019 and we resected her right lower lung lobe. From June to November 2019, she had 12 cycles of the 5FU (or Capecitabine) + INF alpha + Nivolumab treatment, administered every two weeks.

Her scan in late-November showed progression of disease.

Relapse/Progression # 4: We consulted with Patient A and her family; Patient A did not want any additional aggressive treatments.

7) "Magic Mike" Therapy: Lenvatinib, Nivolumab and Quercetin

Since December 2019, Patient A has been receiving Nivolumab 3 mg/kg IV, Lenvatinib 8mg po daily, Quercetin 1.5 grams po TID bi-weekly.

Her CT scan in February 2020 showed a partial response: the innumerable bilateral metastatic pulmonary nodules in her lungs were either stable or decreased in size.

Scans in May and August 2020 showed an excellent partial response. The nodules in her lungs have continued to shrink. Very good partial response.

Our current plan is to taper the treatment from every two weeks to three.

Analysis

Today, five years from diagnosis, Patient A is a healthy and strong college student, studying engineering. She is a vibrant young woman, resuming most of her normal day-to-day activities.

With so few fibrolamellar patients, compounded in many cases by late diagnoses, it's difficult to cultivate definitive research or treatment guidelines for patients. Surgery or transplantation alone is not the most effective approach; patients will relapse 85% of the time when using just one of these options. Surgery / transplantation combined with systemic chemoimmunotherapy is an effective combination for treating fibrolamellar carcinoma.

As we learn more about the disease, we will take the protocols that are currently available and continue to iterate new therapies based on sound science, as we did with Patient A. We are hopeful about the success of the Magic Mike therapy, not only for Patient A, but for the other fibrolamellar patients we treat.

We will also continue to send tissue samples to research labs around the country in an effort to gain insight about the mutations that cause fibrolamellar carcinoma, in order to provide targeted, individualized therapies.

For more information, visit rush.edu/conditions/liver-cancer