Retrospective Analysis of the Efficacy of Gemcitabine for Previously Treated AIDS-Associated Kaposi’s Sarcoma in Western Kenya

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\textbf{Abstract}


\textbf{Methods:} Retrospective chart review of all patients with KS treated with single agent gemcitabine following failure of first-line Adriamycin, bleomycin, and vincristine (ABV). Baseline demographics were collected, and clinicians’ assessments of response were utilized to fill out objective criteria for both response as well as symptom benefit assessment.

\textbf{Results:} Twenty-three patients with KS who had previously failed first-line therapy with ABV were evaluated. Following treatment, 22 of the 23 patients responded positively to treatment with stable disease or better. Of the 18 patients who had completed therapy, with a median follow-up of 5 months, 12 patients had no documented progression.

\textbf{Conclusions:} Treatment options in the resource-constrained setting are limited, both by financial constraints as well as the need to avoid myelotoxicity, which is associated with high morbidity in this treatment setting. This work shows that gemcitabine has promising activity in KS, with both objective responses and clinical benefit observed in this care setting. Gemcitabine as a single agent merits further investigation for AIDS-associated KS.

\textbf{Background}

Kaposi’s sarcoma (KS), originally described in 1872 as an indolent pigmented mucocutaneous malignancy evolving over 10–15 years, was subsequently described as a malignancy endemic to Africa, with several variant...
oftrials, a gold-standard for therapy remains unclear. Antiretroviral therapy can become paramount combined with relative lack of cART means that systemic chemotherapy with palliative intent has become a mainstay of KS treatment in Sub-Saharan Africa [8–10]. A wide variety of systemic chemotherapeutic agents have been efficacious in KS, both as single agents and as combination chemotherapy, including vincristine [11, 12], bleomycin [13–15], anthracyclines [15–17], interferon [18], paclitaxel [19, 20], and etoposide [21]. In resource-replete settings, liposome-encapsulated doxorubicin is the standard of care, with response rates up to 80% and durable remissions of disease lasting for years are common [22, 23]. However, in resource-limited settings where cost of therapy can become paramount combined with relative lack of trials, a gold-standard for therapy remains unclear [24]. The combination regimen of Adriamycin, bleomycin, and vincristine (ABV) is common, with an approximately 25% response rate and a cost making it feasible to pursue [15, 17, 25].

Western Kenya is the site of an innovative comprehensive HIV/AIDS care program, the Academic Model for Providing Access to Healthcare (AMPATH) – United States Agency for International Development (USAID) Partnership. In conjunction with the Moi Teaching and Referral Hospital and Moi University, the AMPATH-USAID Partnership has developed cancer services over the last 8 years to address the burden of malignancy found in the HIV/AIDS population [26, 27]. Oncology services, limited to chemotherapy and palliative care, are offered at AMPATH’s central location in Eldoret and at 5 satellite clinics throughout western Kenya. Satellite clinics see patients on a 4-week rotation, allowing all patients enrolled in cancer services to be seen monthly at minimum. This has important implications for feasible chemotherapy schedules in this practice environment. Patients presenting with AIDS-related KS, with no improvement in spite of initiation of cART, are offered ABV as first-line treatment. However, with a 75% failure rate, other options for therapy need to be explored. Based on a case series in classical KS, and a kind donation from Eli Lilly and Co. to the USAID-AMPATH Partnership, gemcitabine was explored as second-line therapy in patients who failed ABV [28].

Gemcitabine (2',2'-difluoro-2'-deoxycytidine) is an S-phase nucleoside anti-metabolite that has demonstrated activity in a variety of solid tumors, including sarcomas. The most common dose and schedule of this agent is 1,000 mg/m², given on days 1, 8, and 15 of a 21-day cycle for pancreatic cancer, but schedules for other indications vary (i.e. monthly for refractory non-Hodgkin’s lymphoma). The toxicity profile of gemcitabine is acceptable in resource-limited settings, with a dose-limiting toxicity of thrombocytopenia – avoiding the excessive risks of neutropenia in resource-limited settings (associated with higher morbidity in the developing world) [5]. Under this program, 32 patients were treated with gemcitabine from August 2006 to October 2007. Patients were treated with both single-agent gemcitabine and gemcitabine in combination with other agents (most frequently bleomycin, vincristine, or cyclophosphamide). Based on clinician anecdote, it was felt that there were significant responses to gemcitabine amongst patients who had failed prior lines of chemotherapy. To explore this anecdotal evidence, a retrospective chart review was conducted for 23 consecutive patients who received gemcitabine monotherapy for mucocutaneous AIDS-related KS and had previously failed ABV as first-line therapy.

**Methods**

Of all the patients treated with gemcitabine from August 2006 to October 2007, only patients who received single-agent gemcitabine following documented failure on ABV were selected for further analysis. Twenty-three patients with documented progression of KS lesions while on ABV and cART were included. The following data were collected by paper chart review: patient demographics, opportunistic infections, date of HIV diagnosis, start date of cART, cART regimen, duration of cART prior to gemcitabine, CD4 counts, date of KS diagnosis, lesion description, Karnofsky Performance Status score, pain and analgesic usage (derived from a separate pharmacy database), assessment of chemotherapy dose and cycle, as well as deviations from routine therapy, and incidence and description of adverse events. Using records from initial oncology clinic evaluations and other perti-
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Results

Patient Characteristics

Twenty-three charts were reviewed, the results of which are summarized in Table 1. There were 19 males (82.6%) and 4 females (17.4%), with a median age of 37 years (range: 20–75 years). Patients were on cART for a median of 12 months (range: 4–41 months) before starting gemcitabine. According to the AIDS Clinical Trials Group staging, all patients were poor-risk, based on tumor extent, CD4 cell count <200 cells/mm³, concurrent systemic illness or Karnofsky Performance Status score <70%.

Chemotherapy Regimens

As noted, gemcitabine was delivered in a variety of combinations. This analysis focused on single-agent administration. However, even in this limited utilization of the drug, there were practitioner-level differences in the dosing and scheduling of administration. Two regimens were used, a fixed-dose regimen, and a BSA-adjusted dose. Eighty-three percent (19/23) of patients received a fixed dose of 1,000 mg, 13% (3/23) received 1,000 mg/m², and 4% (1/23) received both dosing regimens.

It was intended that all patients receive gemcitabine on a 14-day cycle. Most patients achieved this, with a median time between doses of 17 days (range: 13–31). The reasons given in the medical record for all missed or delayed cycles are presented in Table 2. The number of patients who missed at least 1 dose was 13 (57%). There was no commonly accepted maximum number of cycles to be delivered in this setting. A median of 7 cycles (range: 3–15 cycles) was delivered to these patients.

Tumor Response Data

The response of KS to single-agent gemcitabine is presented in Table 3. At the time of completion of this retrospective chart review, with a median follow-up of 5.1 months (range: 2–10 months), 2 of the 23 patients were still receiving gemcitabine therapy, 3 patients were lost to follow-up, and 18 patients were no longer receiving gemcitabine. Of the 18 patients who completed treatment, 12 had no documentation of progression, with a median follow-up of 5 months (range: 2.5–7 months), 5 had progressive disease, with a mean progression-free survival of 1.7 months (range: 0–3 months), and 1 died within 2 months of completion of gemcitabine, with no progression of KS, but death secondary to hepatocellular carcinoma.
Clinical Benefit Response

Fifteen of the 23 patients (65%) showed evidence in their records of a clinical benefit response to single-agent gemcitabine. Details of this assessment are presented in table 4.

Toxicity Data

No patients died as a result of receiving gemcitabine. Table 5 summarizes the observed toxicities.

Discussion

Cancer is a global health problem – in the next 10–15 years the incidence of new cancers will rise to 15 million cases annually, of which 75% will be in developing countries [34]. In 2002 in Sub-Saharan Africa alone, there were more than 500,000 cancer deaths [35]. Access to cancer care is limited in Africa – health care providers are infrequently trained in oncology, chemotherapy is extremely limited, and less than half of the countries in Africa have radiation therapy units [36]. Accelerating the
growth of cancer in developing countries has been the HIV/AIDS pandemic – the epicenter of which is Sub-Saharan Africa, accounting for 67% of the world’s HIV-positive population – 2 million in Kenya alone [37, 38]. Improving availability of adequate cART has been limited, with present estimates stating that between 31 and 48% of those who need cART are receiving it [37]. With this degree of disease burden, care for HIV-associated malignancy, both AIDS-defining (cervical cancer, KS, and non-Hodgkin’s lymphoma) and AIDS-associated, is rapidly evolving into a second wave of HIV-associated morbidity and mortality, one not entirely alleviated by initiation of cART [5, 39]. It is critical to develop treatment options for cancer appropriate to the diseases seen as well as the context of care in resource-limited settings.

Combination chemotherapy with ABV has been shown to be both cost-effective and efficacious in resource-limited settings [25]. However, with only a 25% response rate in KS, there is a clear need to find alternative regimens. This retrospective analysis attempted to define the efficacy of gemcitabine for this disease, in spite of administration of the chemotherapy in a non-research environment. Gemcitabine was made available to Kenyan clinicians in this setting through a donation from Eli Lilly and Co., as part of their ongoing philanthropic contributions to the AMPATH-USAID partnership. Local clinicians utilized this drug for KS (based on case reports in the literature) as the next line in palliative treatment of HIV-positive patients with KS, guided by necessity because of an absence of other treatment options for these patients. Data were collected as part of routine clinical treatment, not in the scope of a clinical trial. Utilizing data from routine clinical practice for the analysis presents several difficulties in the interpretation of results; however, given the clinicians’ anecdotal sense of success, making an effort to compile these data and present the results of this analysis to the oncology community at large felt justified.

Specific concerns with these data include a lack of pre-established guidelines for judging response (i.e. RECIST [40]), lack of uniformity in dose and schedule, and inadequate follow-up for toxicity. Many of these issues are reflective of the practice environment of western Kenya, where oncology services have only recently been introduced and many resources are not routinely available (i.e. imaging, ‘routine’ blood work). Additionally, there were a number of missed or delay doses, most frequently due to lack of transportation (13 missed doses) and illness (4 missed doses), again reflective of the resource-limited care environment. However, in spite of these limitations, this analysis offers evidence of reasonable efficacy of gemcitabine for KS – certainly sufficient evidence to merit follow-up with a well-controlled clinical trial, which we are at present preparing to undertake. Further, from the limited evidence available within this analysis, it appears that efficacy is possible without excess toxicity – a critical concern in a practice environment in which excess toxicity does not translate simply to morbidity as it does in resource-replete care settings, but to mortality. It should

Table 4. Clinical benefit response (n = 23)

<table>
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<tr>
<th>Clinical benefit response</th>
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<tr>
<td>≥50% reduction in pain intensity</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>≥50% reduction in analgesic consumption</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>20 point improvement in Karnofsky Performance Status for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4 consecutive weeks</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Sustained weight gain of ≥7% maintained for ≥4 consecutive weeks</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Clinical benefit response achieved</td>
<td>15</td>
<td>65</td>
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</tbody>
</table>

Table 5. Incidence of toxicities (n = 23)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Anemia</th>
<th>Dyspnea</th>
<th>Fatigue</th>
<th>Infection</th>
<th>Leukopenia</th>
<th>Neutropenia</th>
<th>Pain</th>
<th>Pulmonary infiltrates</th>
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<tr>
<td>3</td>
<td>1</td>
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<td>3</td>
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* Hemoglobin: 6.7 g/dl.
* Absolute neutrophil counts: 1,075 and 1,120 cells/mm³.
be noted that there were difficulties in performing an adequate assessment of toxicity that may lead to bias in this interpretation – for instance, the incidence of myelosuppression may be under accounted for as complete blood counts were only obtained prior to 48% of doses, again due to lack of available resources or technology. However, in spite of these methodological concerns, the available evidence presented in this analysis certainly justifies pursuing a prospective study examining gemcitabine for first-line therapy of AIDS-related KS.

Despite modest dosages, gemcitabine appears to have substantial activity in previously treated AIDS-associated KS. Confirmation of activity in mucocutaneous and visceral KS is necessary. While barriers to treatment exist in Kenya, it appears both feasible to successfully administer gemcitabine in this resource-constrained practice environment, as well as effective in therapy for AIDS-associated KS. A phase II clinical trial is currently being designed by oncology physicians from the Indiana University School of Medicine and Moi University Teaching and Referral Hospital.

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**References**

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30 Eli Lilly and Co: Gemzar® (gemcitabine HCl) prescribing information.


