Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL), accounting for one third of newly diagnosed cases [1]. This is an aggressive lymphoma that is curable with chemotherapy regimens that usually include an anthracycline [2–4]. However, 20–30% of patients will ultimately relapse and require additional treatment [5]. Although intensive chemotherapy followed by autologous stem cell transplant can be curative in patients with relapsed or refractory disease, there are a large number of patients who are not cured with currently available therapies [6–10]. For these heavily pretreated patients, new and effective options are needed.

Anthracyclines have an important role in the treatment of aggressive B-cell lymphomas and have been shown to improve overall survival in patients with DLBCL in the upfront setting [4]. Unfortunately, their use is limited by cardiac toxicity that increases with cumulative dose. In patients with lymphoma who have been treated with doxorubicin doses of 300–400 mg/m², episodes of clinical congestive heart failure (CHF) have been reported in 5% of patients [11–14]. As the dose increases, the risk of cardiac toxicity also increases, with an estimated incidence of cardiac events of 26% with a cumulative dose of 550 mg/m² [14]. It is clear that older patients and those with independent cardiac risk factors are at increased risk of development of CHF. There is no effective method to determine which patients, if any, can safely be exposed to additional anthracycline drug. Unfortunately, left ventricular ejection fraction (LVEF) alone is not predictive of subsequent cardiac toxicity since over half of patients who subsequently develop CHF have a drop in their LVEF of <30% during monitoring while receiving drug [14], but research is ongoing into the ability of serial troponin levels or measurement of diastolic function to predict cardiac outcomes [15–17]. For now, anthracyclines, which are known to have...
high efficacy in the treatment of DLBCL, are avoided in the relapsed/refractory setting. Pixantrone is an anthrancenedione-class drug that was designed to maintain the clinical benefit of anthrancenediones while minimizing cardiac toxicity. It has demonstrated clinical activity in relapsed/refractory DLBCL and its role in the upfront setting is under active investigation.

**Pixantrone**

Anthrancenediones are structurally related to the anthracene nucleus, which has been used as a basis for the development of numerous anticancer drugs. These drugs work by inhibiting topoisomerase II, leading to DNA double-strand breaks [18]. Mitoxantrone is the first drug of the anthracenedione-class to be approved by the US FDA for use in hormone-refractory prostate cancer, acute nonlymphocytic leukemia and multiple sclerosis [19]. Pixantrone dimaleate (6,9-bis[(2-amino)ethyl]amino)benzoi-glucosamine-5,10-dione dimaleate, BBB 2778, Cell Therapeutics, Inc.) is a second-generation anthrancenedione. The cardiac toxicity of anthracyclines and mitoxantrone is at least partially mediated through damage caused by oxygen free radicals [20]. In comparison to doxorubicin and mitoxantrone, pixantrone has side chains that are primary amino groups that do not bind iron, which may lead to decreased production of oxygen free radicals, thereby resulting in less cardiac toxicity [21,22].

**Pharmacokinetics**

Preclinical data in cell lines show that pixantrone is able to quickly form stable DNA adducts [23]. At low concentrations of drug (7.5 µm) complete stabilization of dsDNA occurred in cell lines within 7 h of exposure with a half-life of 2 h [24]. The highest concentration of drug was found in the skeletal muscle, liver and kidney with very low concentrations reaching the brain, suggesting that drug does not extendively cross the blood–brain barrier. Some accumulation of pixantrone has been seen after repeated dosing in rats but not in dog studies. Animal studies have shown that drug is primarily excreted in the feces [25]. In mice with disseminated YC-8 murine lymphoma, pixantrone was able to prolong the long-term survival compared with doxorubicin, mitoxantrone, cyclophosphamide and vincristine [26].

Phase I studies in humans showed linear pharmacokinetics (PK) with a terminal half-life of over 14 h (range: 14 to 20 h) [27]. The drug has a large volume of distribution and <10% unchanged drug is excreted in the urine [28–30]. PK testing has been performed after a first and second dose of pixantrone in one patient and no accumulation was seen, but the data are extremely limited [31].

**Phase I clinical trials: determining the recommended dose of pixantrone**

Neutropenia is the dose-limiting toxicity (DLT) found in Phase I trials of single agent pixantrone. The first published Phase I study of pixantrone was performed in patients with relapsed/refractory solid tumors with a median of two prior treatments (range: 1–6) [32]. Dose escalation was initially determined as per a standard Fibonacci schema and later, due to low plasma concentration of drug and few adverse events (AEs), escalation was decided using an accelerated schema based on toxicity and PK during the first cycle of drug. Thirty patients were enrolled and received a median of two (range: 1–6) cycles of pixantrone. The maximum tolerated dose (MTD) was determined to be 112 mg/m² on days 1, 8 and 15 of a 28-day cycle. Six subjects were treated at the recommended dose for a total of 18 cycles. Grade III/IV neutropenia occurred during 50% of cycles with a nadir at day 14. As a result, the day 15 dose was held during 39% of the cycles due to hematologic toxicity. Pixantrone was otherwise well tolerated at this dose without any thrombocytopenia or nonhematologic side effects other than alopecia, grade I/II nausea and vomiting, and blue discoloration of the urine and skin. There were no symptomatic cardiac AEs reported.

A subsequent Phase I trial in 26 patients with relapsed/refractory NHL with a median of two (range: 1–7) prior treatment regimens demonstrated that the hematologic toxicities were more profound in this patient population [33]. The MTD of only 56 mg/m² on days 1, 8 and 15 of a 28-day cycle was much lower than the MTD of 112 mg/m² that was found in patients with solid tumors [34]. At the dose of 56 mg/m² no significant hematologic toxicities occurred. However, six patients received the next higher dose level of 84 mg/m², and three developed grade IV neutropenia while the other three patients had grade III neutropenia lasting more than a week. In addition, one patient had grade IV diarrhea that was positive for clostridium difficile and another patient had grade IV thrombocytopenia.

Despite the frequent DLTs at the 84 mg/m², the authors recommended using this dose in future clinical trials of pixantrone in patients with relapsed/refractory aggressive B-cell NHL. They made this decision because hematologic toxicities are not only accepted, but are expected in this patient population of relapsed/refractory DLBCL. In addition, the response rate seen at this dose was higher than at the 56 mg/m². Overall responses were seen in five of the 26 subjects enrolled at any dose level (19%) with three (11%) complete responses (CRs). All CRs occurred at the highest dose (84 mg/m²) with 50% (3/6) of subjects at this dose level achieving a CR despite prior doxorubicin and/or mitoxantrone in all subjects [35]. The clinical responses seen in this small Phase I trial were encouraging, particularly in such a heavily pretreated group. This higher dose of 84 mg/m² is the dose that was used in the subsequent Phase II trial performed by the same group and, as reported below, it was relatively well tolerated [36].

Although most Phase I trials of pixantrone administer study drug on days 1, 8 and 15 of a 28-day cycle it can also be given less frequently at a higher dose. Phase I data of an every-3-week schedule in 24 patients with a malignancy for which there was no available effective therapy determined the MTD to be 180 mg/m² every 21 days [37]. As with the other Phase I trials of pixantrone given on a weekly basis, the DLT was neutropenia, which occurred in three out of five patients treated with 240 mg/m².

**Phase II/III trials: clinical efficacy of single-agent pixantrone in aggressive NHL**

Clinical trials of single-agent pixantrone have consistently produced responses in heavily pretreated patients with relapsed/refractory DLBCL, most of who have previously been exposed to an anthracycline.

The initial Phase II trial of 33 patients with relapsed/refractory DLBCL (n = 24), mantle cell lymphoma (n = 7) or other lymphoma (n = 2) administered pixantrone at 85 mg/m² weekly × 3 followed by 1 week off for up to six cycles [38]. Most patients had received a prior anthracycline and 78% had received two or more prior treatment regimens. The CR rate was 19% with an overall response rate (ORR) of 27%.

These encouraging results led to the EXTEND trial, a randomized Phase III trial of pixantrone versus investigator choice in patients with aggressive NHL that had relapsed after at least two prior chemotherapy regimens [39]. All patients had received prior anthracycline at least once, but were not refractory to anthracyclines as indicated by at least a partial response lasting ≥6 months to the last anthracycline received [40]. Patients with a LVEF <50% and those who had received...
a cumulative dose of doxorubicin or equivalent that exceeded 450 mg/m² were excluded [34]. One hundred and forty patients were randomized to receive up to six cycles of pixantrone (85 mg/m²) on days 1, 8 and 15 of a 28-day cycle versus investigator’s choice. Oxaliplatin was the most frequently used comparator (45% of subjects). Following a fosfamide (18%), vincristine (16%), etoposide (13%), mitoxantrone (6%) and gemcitabine (1%) [35]. Accrual to the study was slow so it was closed early after 140 patients were enrolled rather than the planned 300.

CR/complete response unconfirmed (CR/Cru) response was significantly higher in the pixantrone arm with a CR/Cru rate of 24 versus 7% in the comparator arm (p = 0.009) [32]. The ORR was also significantly better at 40 versus 14% (p = 0.001). Although there was a significant improvement in progression-free survival for pixantrone, it was short in both arms at 5.3 versus 4.5 months (p = 0.015). The median overall survival for the pixantrone arm was 10.2 versus 7.6 months in the comparator arm, but this was not statistically significant (p = 0.251). Patients enrolled in this study were heavily pretreated and 57% of patients were considered refractory to most recent treatment regimens. Not surprisingly, the patients with refractory disease had a lower response rate in both arms, although responses were still seen with CR/Cru rates of 15% in refractory patients receiving pixantrone versus 29% of patients with chemosensitive disease [36].

The higher response rate and longer duration of response with pixantrone came at the expense of more toxicity. 76% of patients on the pixantrone arm experienced a grade III/IV toxicity versus 52% in the comparator arm. As a result, withdrawal due to AEs was more common in the pixantrone arm, with 21% of subjects stopping study drug early due to AEs versus only 13% in the comparator arm. AEs were predominantly hematologic with grade III/IV neutropenia in 41% versus 19% and febrile neutropenia in 7 versus 3% of patients in the pixantrone and comparator arms, respectively. In addition, as discussed below, there were more cardiac events (19 vs 10%) in the pixantrone arm [37]. Due to fewer responses to therapy, the rate of withdrawal due to progressive disease was higher in the comparator arm (36% vs 40%). As a result, despite more frequent AEs, patients on the pixantrone arm were able to stay on the study for a longer time, receiving a median of four treatment cycles versus three in the comparator arm [32].

Clinical efficacy of pixantrone drug combinations in relapsed/refractory aggressive NHL

Ultimately, pixantrone will likely be used as part of a multidrug regimen. There is a small Phase I/II trial of pixantrone, methylprednisolone, cisplatin and cyclophosphamide (PSHP) in which pixantrone replaces etoposide in an ESHAP-like regimen. Nineteen patients with relapsed/refractory NHL [38] were enrolled and the MTD of pixantrone was determined to be 80 mg/m² on days 1–5, cisplatin 25 mg/m² days 1–4, and cytarabine 2000 mg/m² on day 5 of a 21-day cycle. All patients had previously received an anthracycline. 63% had refractory disease to their most recent therapeutic regimen. The DLT in the Phase I portion of the trial was bone marrow suppression with grade III/IV anemia in 53% of subjects, grade III/IV neutropenia in 84%, grade III/IV thrombocytopenia in 95% and febrile neutropenia in 26%. These results were similar to those reported with standard ESHAP [39]. The ORR for this Phase I/II trial of PSHP was 58% with a complete remission rate of 37%. 55% of the responders went on to stem cell transplant.

CPOP, a CHOP-like regimen that uses standard doses of cyclophosphamide (750 mg/m²), vincristine (1.4 mg/m²) and prednisone (100 mg days 1–5), but replaces doxorubicin with pixantrone, has been studied in patients with aggressive NHL who have relapsed after one or two prior chemotherapy regimens. Results from a Phase I study evaluating this combination determined the recommended Phase II dose of pixantrone to be 150 mg/m² on day 1 of a 21-day cycle [32]. As with prior Phase I studies, neutropenia was the DLT. A dose expansion Phase II study was performed using the 150 mg/m² dose in 30 patients to determine response rate. The trial had a median age of 61 years (range: 26–76 years) and had DLBCL (67%), mantle cell lymphoma (27%) or grade III follicular lymphoma (7%). All subjects had previously received doxorubicin, 43% had received prior rituximab and 29% had prior stem cell transplant. In this group of patients, all of whom had relapsed after or were refractory to a prior anthracycline regimen, the ORR of 73% and CR/Cru rate of 47% is impressive and compares well with other salvage regimens (Table 1) [32–34]. The median duration of CR was 10.5 months, demonstrating some durability of response even in patients with relapsed/refractory NHL.

Pixantrone in the front-line setting

Pixantrone has the potential to be equally effective and less toxic than doxorubicin, however, before it can become a part of first-line therapy in patients with DLBCL this theoretical benefit needs to be confirmed. An ongoing randomized Phase II study of R-CPOP versus R-CPOP as first-line therapy for DLBCL will help to answer these questions [36]. This study is closed to enrollment and we await final results; however, an interim analysis was presented in abstract form at the American Society of Hematology annual meeting in 2020. All patients with IV thrombocytopenia in 95% and febrile neutropenia in 26% experienced a grade III/IV toxicity versus 52% in the R-CPOP arm [33]. AEs versus only 13% in the comparator arm. A dose expansion Phase II study was performed using the 150 mg/m² dose in 30 patients to determine response rate. The trial had a median age of 61 years (range: 26–76 years) and had DLBCL (67%), mantle cell lymphoma (27%) or grade III follicular lymphoma (7%). All subjects had previously received doxorubicin, 43% had received prior rituximab and 29% had prior stem cell transplant. In this group of patients, all of whom had relapsed after or were refractory to a prior anthracycline regimen, the ORR of 73% and CR/Cru rate of 47% is impressive and compares well with other salvage regimens (Table 1) [32–34]. The median duration of CR was 10.5 months, demonstrating some durability of response even in patients with relapsed/refractory NHL.

Table 1. Response rates of relapsed/refractory lymphoma to salvage regimens.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of prior treatments</th>
<th>CR (%)</th>
<th>Relay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPOP</td>
<td>1 (33%)</td>
<td>73</td>
<td>47</td>
</tr>
<tr>
<td>RICE</td>
<td>1 (25%)</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>RICE vs R-DHAP</td>
<td>2 (5%)</td>
<td>64 vs 64</td>
<td>15 vs 15</td>
</tr>
<tr>
<td>E-RPOCH</td>
<td>Median of 4</td>
<td>68</td>
<td>28</td>
</tr>
</tbody>
</table>

CPOP: Cyclophosphamide, vincristine, prednisone and pixantrone; CR: Complete response; Relay: complete response unconfirmed; ORR: Overall response rate; R-DHAP: Dexamethasone, cytarabine and cisplatin plus rituximab; R-EPOCH: Etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone plus rituximab; RICE: Ixabepilone, carboplatin and etoposide plus rituximab.

Table 2. Adverse events and response rates with R-CPOP versus R-CPOP.

<table>
<thead>
<tr>
<th></th>
<th>R-CPOP (n=39)</th>
<th>R-CPOP (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE attributed to treatment</td>
<td>24 (62%)</td>
<td>21 (54%)</td>
</tr>
<tr>
<td>Grade III/IV AE attributed to</td>
<td>15 (38%)</td>
<td>12 (31%)</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>11 (26%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Grade III/IV neutropenia</td>
<td>10 (26%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Grade III/IV infection</td>
<td>7 (18%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Decline in LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–15%</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>16–20%</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>≥20%</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Death within 30 days of last</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>dose study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal secondary to AE</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td>CR (%)</td>
<td>32</td>
<td>34</td>
</tr>
</tbody>
</table>

Pixantrone: treatment for aggressive non-Hodgkin’s lymphoma

Pixantrone has demonstrated clinical efficacy even in heavily pretreated patients with relapsed/refractory DLBCL. However, this beneficial effect needs to be carefully weighed against the potential toxicities. This was very clearly shown in preliminary data from the EXTEND trial of pixantrone versus investigator’s choice [40]. In this study the dropout rate between the two arms was very similar (71% vs 77%) but the reason for dropout differed with more dropouts due to AEs in the pixantrone arm (21% vs 13%) and more dropouts...
Table 3. Response and grade III/IV hematologic toxicity with single-agent pixantrone in aggressive non-Hodgkin's lymphoma.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Drug dose</th>
<th>Grade III/IV neutropenia (n [%])</th>
<th>Febrile neutropenia (n [%])</th>
<th>ORR (%)</th>
<th>CR/Cu (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Pixantrone 5–84 mg/m² dose, 1, 8 and 15 of 21-day cycle</td>
<td>6/6 (100) 84 mg/m² dose</td>
<td>0/6 (0) 84 mg/m² dose</td>
<td>19 (all dose levels)</td>
<td>11 (all dose levels)</td>
<td>[14]</td>
</tr>
<tr>
<td>Phase II</td>
<td>Pixantrone 85mg/m² days 1, 8 and 15 of 21-day cycle</td>
<td>n/a</td>
<td>27</td>
<td>15</td>
<td>[24]</td>
<td></td>
</tr>
<tr>
<td>EXTEND</td>
<td>Pixantrone 85mg/m² days 1, 8 and 15 of 21-day cycle</td>
<td>28/68 (41.2)</td>
<td>5/68 (7.4)</td>
<td>25.7</td>
<td>15.7</td>
<td>[24]</td>
</tr>
<tr>
<td>Comparator</td>
<td>13/67 (19.4)</td>
<td>2/67 (3.0)</td>
<td>8.6</td>
<td>4.3</td>
<td>[24]</td>
<td></td>
</tr>
</tbody>
</table>

CR: Complete response; Cru: complete response unconfirmed; ORR: Overall response rate.

Pixantrone: treatment for aggressive non-Hodgkin’s lymphoma

Review: Clinical Trial Outcomes

Beaven & Rizzieri

Review: Clinical Trial Outcomes

Pinxantrone has demonstrated efficacy and good tolerability in the treatment of aggressive NHL. Cell Therapeutics, Inc. (CTI) is seeking approval of pixantrone for use in patients with relapsed/refractory DLBCL after at least two prior treatment regimens. If approved this would be the first drug approved specifically for use in multiply relapsed DLBCL. The FDA reviewed pixantrone in 2010 and declined approval for use in the USA, although they did encourage CTI to conduct more trials for possible resubmission. The FDA’s decision was due to concerns about the results and AE profile seen in the EXTEND trial. Although the study failed to meet its non-inferiority endpoints, the trial closed early due to slow enrollment, which changed the preplanned statistical analysis parameters, and since only eight patients were enrolled in the USA there were concerns that results were not representative of the US population. Furthermore, the FDA was concerned about the high rate of AEs seen in the pixantrone arm with 21% of subjects dropping out due to AEs versus only 13% in the control arm. As the data from the EXTEND trial has matured and the R-CHOP versus R-CPOP trial, will further help to define the actual incidence and severity of pixantrone-induced cardiac damage. No in-depth examination has been performed yet to assess which patients are at highest risk of developing cardiac toxicity, but it is likely that factors such as increasing age, male gender, co-morbidities such as hypertension, or prior exposure to an anthracycline will all increase the risk of cardiac toxicity from the pixantrone. Therefore, the pros and cons of pixantrone use should be carefully explored prior to beginning therapy in any high-risk patients.

Conclusion & future perspective

Pixantrone has demonstrated efficacy and good tolerability in the treatment of aggressive NHL. Cell Therapeutics, Inc. (CTI) is seeking approval of pixantrone for use in patients with relapsed/refractory DLBCL after at least two prior treatment regimens. If approved this would be the first drug approved specifically for use in multiply relapsed DLBCL. The FDA reviewed pixantrone in 2010 and declined approval for use in the USA, although they did encourage CTI to conduct more trials for possible resubmission. The FDA’s decision was due to concerns about the results and AE profile seen in the EXTEND trial. Although the study failed to meet its non-inferiority endpoints, the trial closed early due to slow enrollment, which changed the preplanned statistical analysis parameters, and since only eight patients were enrolled in the USA there were concerns that results were not representative of the US population. Furthermore, the FDA was concerned about the high rate of AEs seen in the pixantrone arm with 21% of subjects dropping out due to AEs versus only 13% in the control arm. As the data from the EXTEND trial has matured and the R-CHOP versus R-CPOP trial, will further help to define the actual incidence and severity of pixantrone-induced cardiac damage. No in-depth examination has been performed yet to assess which patients are at highest risk of developing cardiac toxicity, but it is likely that factors such as increasing age, male gender, co-morbidities such as hypertension, or prior exposure to an anthracycline will all increase the risk of cardiac toxicity from the pixantrone. Therefore, the pros and cons of pixantrone use should be carefully explored prior to beginning therapy in any high-risk patients.

Cardiac toxicity of pixantrone

The main goal for the development of the anthracycenediones was to create a clinically active drug with minimal cardiac toxicity. Mitoxantrone was the first drug of this class and it is approved by the US FDA for use in hormone refractory prostate cancer, acute nonlymphocytic leukemia and multiple sclerosis [14]. Unfortunately, research and long-term follow-up have failed to demonstrate an improved side-effect profile. In fact, there is one study in Hodgkin’s lymphoma that found increased delayed cardiotoxicity in the mitoxantrone arm compared with the doxorubicin or epirubicin arms [14]. The cardiotoxic effects of mitoxantrone have been well documented in the literature. In the pixantrone phase II study of NHL previously exposed to an anthracycline enrolled 65 patients with a mean prior doxorubicin-equivalence exposure of approximately 300 mg/m² [14]. A cardiac event occurred in 32% of patients, but these were predominantly decreases in LVEF of 10% although two patients had a grade III decrease in LVEF (20–39%). The multigated acquisition scan performed at the end of the study showed a mean decrease in LVEF of 6% in the Phase I portion and only 1.8% in the Phase II portion. Similarly, when combined with fludarabine, dexamethasone and rituximab in low-grade lymphomas, grade I/II decreases in LVEF occurred in 27% of patients, but were symptomatic in only 7% of patients [14]. The randomized Phase II trial of R-CHOP versus R-CPOP in the first-line setting will provide important data about the cardiac toxicity of the anthracycenedione pixantrone, compared with the anthracydione doxorubicin [14]. Data are not finalized, but an interim analysis after 78 subjects had received at least one dose of study drug reported that no subjects in either arm had symptomatic CHF. However, some cardiotoxicity was seen with asymptomatic decreases in LVEF occurring in eight subjects in each arm with a mean decrease of 1% in the R-CPOP arm and 17% in the R-CHOP arm.

Longer follow-up from clinical trials, in particular due to progressive disease in the comparator arm (40 vs 56%). Neutropenia is the most frequent grade III/IV AE that occurs with single-agent pixantrone (Table 3) [14,15,16,17,18,19,20,21,22,23,24,25]. Fortunately, febrile neutropenia is rare, occurring in only 7.4% of subjects on the pixantrone arm of the Phase III extend trial [27]. The role of granulocyte growth factor has not been explored with the weekly pixantrone doses, but with the low incidence of febrile neutropenia primary prophylaxis is not recommended by the American Society of Clinical Oncology growth factor guidelines [26]. Given that most patients receiving single-agent pixantrone are likely relapsed or refractory to multiple prior therapies, managing neutropenia by dose delays or reductions is a reasonable approach.

The most unusual AE that occurs with pixantrone is a reversible blue discoloration of skin and urine that occurs secondary to the dark blue color of pixantrone itself. Autopsies of animals receiving pixantrone reveal a blue pigmentation of all organs secondary to its wide volume of distribution [24]. In the Phase I trial patients in NHL, all patients had a blue/green tinge to their urine and one out of 26 patients developed a blue discoloration of the skin that resolved after 3 days [24]. In subjects with non-lymphoid solid tumors, weekly doses of 75 mg/m² or higher led to its wide volume of distribution [24]. In the Phase I trial patients in NHL, all patients had a blue/green tinge to their urine and one out of 26 patients developed a blue discoloration of the skin that resolved after 3 days [24]. In subjects with non-lymphoid solid tumors, weekly doses of 75 mg/m² or higher led to...
new data are becoming available from the PX203 trial of R-COP versus R-CHOP, the FDA has agreed to allow CTI to resubmit [32]. It is expected that CTI will likely resubmit the new drug application for pixantrone in late 2011/early 2012.

Pixantrone was developed to provide new data on cyclophosphamide, vincristine, prednisone and doxorubicin plus rituximab versus cycle chemotherapy with or without etoposide in relapsed or refractory aggressive NHL. The primary intention was to determine whether the addition of pixantrone would improve efficacy compared to the CHOP combination chemotherapy regimen.

Toxicity of pixantrone

Neutropenia is the most frequent toxicity that occurs with pixantrone, but febrile neutropenia is uncommon.

Cardiac toxicity of pixantrone

More long-term data are required to fully assess whether pixantrone is less cardiotoxic than doxorubicin.

Conclusion & future perspective

Cell Therapeutics, Inc. will likely resubmit pixantrone to the US FDA for evaluation for new drug approval in late 2011. If approved, pixantrone would be the first drug approved specifically for use in relapsed/refractory DLBCL.

References

Papers of special note have been highlighted as: ■ of considerable interest


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Preplanned interim analysis of results of the PIX203 trial of cyclophosphamide, vincristine, prednisone and doxorubicin plus rituximab versus cyclophosphamide, vincristine, prednisone and pixantrone plus rituximab as first-line therapy in diffuse large B-cell lymphoma.


**Websites**
