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CORR Insights®: Is Chemotherapy Associated with Improved Overall Survival in Patients with Dedifferentiated Chondrosarcoma? A SEER Database Analysis

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Where Are We Now?

Dedifferentiated chondrosarcoma (DDCS) is a relatively rare but aggressive chondrosarcoma subtype with high rates of recurrence and metastasis with a worse overall prognosis than conventional chondrosarcoma [13, 20]. Indeed, the 5-year overall survival rate of DDCS is < 25% with a median survival of < 1 year [5, 16]. The standard treatment for chondrosarcoma is surgical resection [4], and metastatic disease is associated with decreased overall survival [4, 5, 19]. In the past, chondrosarcoma has been considered relatively resistant to chemotherapy, though the evidence base for this has mostly consisted of small retrospective case series without control groups [7, 11, 12], including some that actually found treatment benefits in specific subgroups [6]. The largest study of which I am aware evaluated 337 patients with DDCS at nine European treatment centers from 1975 to 2005 and found that chemotherapy was not associated with improved overall survival, including in a subset of patients with potentially curable disease treated surgically [5].

In the face of the limited evidence suggesting a lack of benefit to chemotherapy, many patients with DDCS nonetheless do receive perioperative chemotherapy. This is consistent with guidelines from the National Comprehensive Cancer Network (NCCN) that primary DDCS treatment follow osteosarcoma protocols that include chemotherapy [11]. However, the question of whether chemotherapy provides a real benefit to patients with DDCS remains unanswered.

The present study by Cranmer et al. [3], the second largest study to date involving chemotherapy in DDCS, attempts to better answer that question. The authors queried the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2016 to identify a sample of 185 patients with local or regional DDCS, 60 of whom (32%) received chemotherapy. After accounting for known confounders, the authors found no overall survival benefit associated with chemotherapy. To validate their analytic approach and test for large-scale treatment misclassification in the SEER database, the authors ran the same analysis in a separate cohort of 2261 patients with osteosarcoma from the SEER database. This parallel analysis showed that chemotherapy was associated with improved overall survival in osteosarcoma, consistent with prior research [1]. Overall, these findings, in conjunction with other research [5], suggest that we should reevaluate current NCCN guidelines that all patients with primary DDCS follow osteosarcoma treatment protocols that involve chemotherapy. More importantly, perhaps we should acknowledge the shortcomings of the existing evidence base, especially related to heterogeneous study populations and treatment regimens, and work to bolster the evidence base in these specific areas.

Where Do We Need To Go?

Although the present study adds to the evidence base showing a lack of

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benefit of chemotherapy in patients with DDCS, several questions remain. The population of patients with DDCS is heterogeneous in terms of clinicopathologic characteristics, so the possibility of subsets of those with DDCS being more sensitive than others to chemotherapy remains to be fully explored. Another area of interest is whether there are differences in treatment effect across chemotherapy regimens. Does medication type, treatment duration, and/or timing of chemotherapy relative to other treatments play a role in treatment efficacy or the lack thereof? Because the SEER database does not provide sufficient detail related to chemotherapy medication, duration, and timing, these questions cannot be explored in the present study but are an important area for further research. Lastly, the development of novel active systemic therapies including immunotherapies is an area requiring further exploration and analysis [18, 20]. Indeed, the limited effect of chemotherapy seen in the present study and similar studies highlights the need for targeted agents with greater efficacy in this patient population.

How Do We Get There?

Filling in these knowledge gaps will be challenging. Fortunately, there are specific steps we can take to address some of the knowledge gaps related to identifying DDCS subpopulations responsive to chemotherapy, assessing whether different chemotherapeutic regimens affect outcomes, and identifying novel systemic therapies with potentially greater efficacy.

One of the important ways we can improve the existing knowledge base is by parsing out heterogeneous populations and assessing chemotherapeutic efficacy within these subpopulations. Are there true benefits in certain subpopulations that we are not seeing because they are washed out by pooled heterogeneous data? One of the steps we can take to address this issue involves improving the existing institutional and national databases from which we collect retrospective data. For example, databases like SEER and the National Cancer Database can benefit from increased granularity related to patient demographics, clinicopathologic characteristics, and treatment regimens. This increased specificity can help to answer questions regarding differences in chemotherapeutic efficacy across subpopulations of patients with DDCS. Other steps include combining institutional datasets to increase sample size, especially with the increased granularity afforded by institutional data.

Another way we can improve the existing knowledge base is by clarifying the role of treatment characteristics (e.g., medication type, mode of delivery, frequency, and timing related to other interventions). Like the populations they treat, chemotherapeutic protocols are heterogeneous, and a catch-all for any chemotherapy may miss true treatment effects of specific therapies or regimens. Do DDCS patients require different regimens than patients with conventional chondrosarcoma or other sarcomas to see a treatment benefit? Accounting for such heterogeneity requires increased granularity and specificity in current and future data.

Immunotherapy has had notable success in other challenging cancers and is an area of current exploration in DDCS [9]. For example, Kostine et al. [8] noted PD-L1 expression in the majority of DDCS tissue specimens, which prompted further investigation into anti-PD-1 and/or PD-L1 antibodies in this patient population. In a study by Paoluzzi et al. [14] in patients with metastatic sarcoma, including only one patient with DDCS, a partial response was noted after six cycles of nivolumab (an anti-PD-1 monoclonal antibody). However, in the SARC028 trial evaluating pembrolizumab, another anti-PD-1 monoclonal antibody, only one of five patients enrolled with DDCS achieved a partial response [17]. In addition to these studies, others are underway evaluating other immunotherapeutic strategies such as Hedgehog signaling pathway inhibition [10] and IDH inhibition [15].

Despite the obvious challenges with conducting prospective research on rare conditions such as DDCS, large prospective studies are indeed possible, especially when coordinated across institutions and populations. For example, the European over 40 Bone Sarcoma Study is a collaborative prospective study jointly run by the Italian Sarcoma Group, the Cooperative Osteosarcoma Study Group, and the Scandinavian Sarcoma Group [6]. Similarly, the recent phase 2 trial of pazopanib in patients with metastatic or unresectable chondrosarcoma is an example of a successful international multicenter prospective study conducted at seven institutions in two countries [2]. International and multicenter collaborative efforts are a powerful tool to help to mitigate the challenges associated with patient recruitment and sample size and can help to address the gaps in our existing knowledge base.

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