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Characteristics of Exceptional or Super Responders to Cancer Drugs

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Abstract

Objective: To summarize case reports of exceptional and super responders already published in the biomedical literature.

Patients and Methods: We searched for published case reports or abstracts of exceptional or super responders to a cancer drug using PubMed and Google Scholar search engines. Pooling such reports is widely considered a promising research strategy and the subject of several ongoing investigations, including the National Cancer Institute's Exceptional Responders Initiative. All articles were read in full, including relevant references. We extracted clinical characteristics of exceptional or super responders, including age, tumor type, drug, genetic mutations, depth of response, duration of response, number of previous lines of therapy, duration of response to a previous line of therapy, and the number of patients treated similarly to identify the exceptional case. This study was performed between March 1, 2015, and April 30, 2015.

Results: Among 489 articles, 32 exceptional responders were identified. The most common malignancies described were renal cell cancer (5 of 32 [16%]) and urothelial carcinoma (4 of 32 [13%]). The use of targeted agents was common in these cases (26 of 32 [81%]), particularly inhibitors of the mTOR pathway (16 of 32 [50%]). The median duration of response among responders was 17.5 months, and 59% (19 of 32) of the patients were last known to be alive with continuing response or stable disease. Notably, 46% (12 of 26) of the patients had received 2 or more previous lines of therapy and 6 of the 32 cases (19%) did not report this information. Few authors report the number of patients treated similarly to observe the super response (12 of 32 [38%]).

Conclusion: Exceptional or super responders to cancer drugs have been described in the literature; however, there is incompleteness in the reporting of relevant data that may help clarify whether such responses are secondary to treatment or reflect underlying biology.

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Enthusiasm for personalized cancer medicine has grown in part because of dramatic reports of exceptional and super responses to cancer drug therapy.[1-8] Even when prospective studies of cancer drugs yield overall null results, many believe that individual patients can achieve meaningful benefit.[2,4] For instance, a case report of a patient with relapsed urothelial cell carcinoma who experienced an exceptional response to everolimus and was later found to have a somatic mutation activating the mammalian target of rapamycin (mTOR) pathway[9] is widely credited as a successful example of this strategy.[2-4]

Based on this and other prominent reports,[10] major cancer centers[5] and the National Cancer Institute (NCI) have begun collecting case reports and tissue samples of exceptional responders in an attempt to identify the underlying genetic changes that predispose particular patients to respond to particular drugs. NCI's Exceptional Responders Initiative seeks to analyze as many as 300 super responses to drug therapy.[4] Its operational definition of such a response is a complete or partial response (lasting at least 6 months) to a therapy in which fewer than 10% of the participants benefit.[1,4] Since its debut in September 2014, the initiative already has assembled 70 cases.[11]

Although a strategy of identifying exceptional responses to cancer drugs has been widely embraced, to date, there has not been an empirical analysis summarizing such cases already published in the biomedical literature. We sought to assemble published reports of exceptional or super

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responders to cancer therapy and describe their characteristics.

PATIENTS AND METHODS

Included Studies and Search Criteria

We searched for case reports or case series in which authors described exceptional or super responses to a cancer medication. Exceptional and super responses were credited as such if the case report authors used these terms to describe or index the case. Because our focus was on medications, we excluded studies of solely surgical or radiation interventions. We included reports of chemotherapy, targeted therapy, immunotherapy, and other drugs or biologics. We included cases using multiple treatment modalities.

We searched MEDLINE for ["exceptional response"] and ["exceptional responder"] and Google Scholar for ["exceptional responder"] and ["exceptional response" cancer] on March 18, 2015. We searched MEDLINE for ["super response"] and ["super responder"] and Google Scholar for ["super response" cancer] and ["super responder" cancer] on April 4, 2015.

Articles were read by the authors. Where relevant, reference lists of the articles were reviewed to identify additional case reports of exceptional or super responders. We included reports filed in meeting abstracts and published articles. We excluded cases described only in brochures or pamphlets. We excluded 1 article that was not in English.[12]

Data Collection

We extracted the following characteristics for exceptional responders: histologic type and stage of cancer, age of patient, drug used, depth of response seen (eg, complete or partial response), duration of response, last known status of the patient (eg, continued responder, progressive disease, deceased, or lost to follow-up), presence of any putative driver genetic mutation, the number of previous lines of therapy, the best duration of response to a previous line of therapy, and the number of similar patients treated to observe the response; for instance, whether 1 exceptional responder was seen in 35 patients treated in a phase I study or 200 consecutive patients were treated at a single outpatient clinic.

Statistical Analyses

Descriptive statistics are reported where appropriate. Waterfall plots were created using Microsoft Excel, and statistical analyses were conducted using STATA version 13.0 (STATA Corp).

RESULTS

Our search strategy yielded 489 articles, which were reviewed in full. A review of these publications and relevant reference lists resulted in 32 case reports of exceptional or super response to an anticancer drug therapy, pertaining to 19 tumor types (Table 1). The most common malignancy described was metastatic renal cell cancer (5 of 32 [16%]), followed by urothelial carcinoma (4 of 32 [13%]) and perivascular epithelioid cell tumor (3 of 32 [9%]).

Among these 32 cases, 21 cases (66%) used a single drug to induce response, 8 cases (25%) used a combination of drugs, 2 cases (6%) used a drug in combination with surgery, and 1 case (3%) used a combination of drugs followed by an allogeneic stem cell transplant. The most common class of drugs used alone or in combination was that of inhibitors of the mTOR pathway, used in 16 of the 32 cases (50%). Inhibitors of the epidermal growth factor receptor were used in 3 of the 32 cases (9%). Twenty-six of the 32 cases (81%) used at least 1 targeted agent.

Depth of response varied among exceptional or super responders. Eleven of the 32 cases (34%) reported a complete response. A partial response was described in 12 cases (37%) and formally reported as such in 7 cases (22%). Some other response was noted in 4 cases (13%), whereas 5 cases (16%) did not describe the response to treatment.

The duration of response (or stable disease) ranged from 2 to 108 months, with a median of 17.5 months. Nineteen of the 32 patients (59%) were last known to be alive with continuing response or stable disease, 10 (31%) had progressive disease, and 3 (9.3%) died. Figure 1 shows a swimmer plot of exceptional responses, depicting the duration of response and ultimate outcome for each patient.

Twenty cases (63%) identified at least 1 potential culprit or driver genetic mutation, which was thought to explain the exceptional

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